SOME ORGANIC ARSENIC COMPOUNDS OF POSSIBLE

THERAPEUTIC ACTIVITY.

by

Joseph Kennedy, B.Sc.

Thesis presented for the Degree of Ph.D.

University of Edinburgh.

Contents.

INTRODUCTION

(1) The nature of chemotherapy.

The large measure of success which has attended
the treatment of those diseases caused by various
classes of protozoal infection followed essentially
from the discovery of the now fundamental organic
arsenic compound, then used in medicine under the
name of "atoxyl".   This compound, prepared in 1863
by Béchamps and which he believed to be an anilide
of arsenic acid, was shown by Ehrlich and Bertheim to
be the sodium salt of p—amino phenylarsinic acid (I).

$$As \underset{\diagdown OH}{\overset{\diagup O\,Na}{=0}}$$
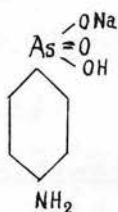
(I)

Marked curative results were then obtained in
the treatment of sleeping sickness with atoxyl.   It
was particularly useful in the first stage of the
disease/

disease, but proved quite valueless in cases with involvement of the cerebro-spinal fluid. The one great disadvantage in the use of atoxyl was the great risk of causing optic atrophy unless care was taken with the dosage.

Concurrently with the acquisition of much important clinical experience, chemists were busily engaged in the preparation of vast numbers of derivatives of this amino arsinic acid with a view to finding that particular modification, in which the curative or therapeutic effect was present in an enhanced degree, and in which the toxic effect was reduced to a minimum. As in the general case, although their ideal remains yet to be attained, the chemical research has been so intense, and the types of disease studied so diversified, that our knowledge, classed under the title of chemotherapy, has been widely advanced and applied to the alleviation of much needless suffering.

The earlier modifications were directed towards the establishment of some relationship between the chemical constitution and physiological action and were chiefly confined to substitution in the benzene nucleus of phenylarsinic acid (E. Fourneau, Ann. de l'Inst./

l'Inst. Past. 1925).   The introduction of an amino group in the para position to the arsenic acid residue was found to diminish the toxicity and bring about a corresponding increase in the therapeutic activity.   The orientation of the amino group was found to be very important.   When the substitution took place in the ortho position to the arsenic group, the compound obtained was very toxic and possessed no therapeutic activity, while the meta substituted compound showed only a slight action. The effect of introducing a second amino group was next investigated.   Starting with p-amino phenyl arsinic acid, a second amino group was introduced in the ortho position to the amino group already present and meta with respect to the arsenic group.   The diamino compound so obtained exhibited a remarkably low toxicity but had very little therapeutic action, presumably on account of the rapidity with which it was found to be eliminated in the urine.

If in place of the amino group a hydroxyl group be introduced into the para position of phenyl arsinic acid, the compound p-hydroxy phenyl arsinic acid was obtained.   It proved less toxic than atoxyl and more active towards the nagana of mice.   As in the case/

case of the amino group the orientation of the
hydroxyl group plays an important part.   The ortho
position is again unfavourable being less active
and more toxic than the para isomer.   The meta
hydroxy acid on the other hand is perhaps more active
than the para hydroxy compound.   In both cases then
the ortho position was definitely shown to be un-
favourable, but no sharp distinction could be drawn
between the meta and para positions.   Since the
m-hydroxy and p-amino phenyl arsinic acids were the
most active of their respective isomers, it was to
be expected that the compound p-amino m-hydroxy phenyl
arsinic acid would possess a high activity and be
more active than the m-amino p-hydroxy acid. Exactly
the reverse order was, however, found to hold, the m-
amino p-hydroxy acid being the more active of the two.
Any attempt then to find a relation between chemical
constitution and physiological action would seem to
be confined to a consideration of the most favourable
groups and their optimum orientation.   On acetylation
of the amino groups Fourneau found that in the para
position the trypanocidal activity was increased or
remained unchanged, whereas when the amino group was
present in the ortho or meta position, the
trypanocidal action was always diminished by
acetylation/

acetylation.   From the behaviour of a substituent
in one compound, however, its influence in another
cannot be predicted with certainty.   It is impossible
to assign a therapeutic value to a group when intro-
duced in a certain position as is well illustrated
by the fact that o-hydroxy phenyl arsinic acid is
highly toxic,but if an amino group be already present
in the para position the introduction of a hydroxyl
group in the ortho position is very favourable.

So far mention has only been made of those
modifications containing pentavalent arsenic.   On
energetic reduction of p-amino phenyl arsinic acid the
compound pp'diamino arsenobenzene (II) was obtained
(Ehrlich and Bertheim, Ber., 1911, 44, 1260).

$$H_2N \bigcirc As = As \bigcirc NH_2 \qquad (II)$$

It was found that the reduction of p-amino
phenyl arsinic acid to diamino arsenobenzene brought
about a great increase in toxic power and also
increased the trypanocidal action.   The belief that
only those compounds containing trivalent arsenic
exerted/

exerted a direct trypanocidal action led to the
examination of other arsenic compounds and the
discovery of salvarsan (III). (Ehrlich and Bertheim,
Ber., 1912, 45, 756).

As $=$ As

HCl, H_2N NH_2, HCl

OH   OH

(III)
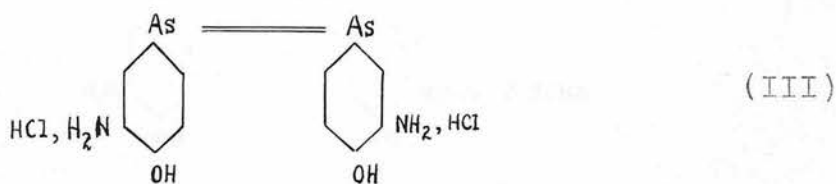
The use of salvarsan "606" is perhaps the
greatest achievement of chemotherapy in the treat-
ment of syphilis and other spirochaetal diseases.
Further advances have, however, been made since the
war.   Bismuth has very largely displaced mercury
and as a supplement to arsenobenzene derivatives,
it is now recognised to be of considerable importance.
Search has been made for more active derivatives of
salvarsan and the most efficient of these, neo-
salvarsan, the sodium salt of 3:3'-diamino-4:4' di-
hydroxy arsenobenzene-N-methylene sulphinic acid (IV)
was made by the introduction of a methylene sulphinic
group into one of the amino groups of salvarsan
using formaldehyde sulphoxylate.   All the other
salvarsan/

salvarsan derivatives showed a marked increase in
toxicity accompanied by a diminution or no change
in the therapeutic activity.

$$As \textemdash\textemdash As \qquad (IV)$$
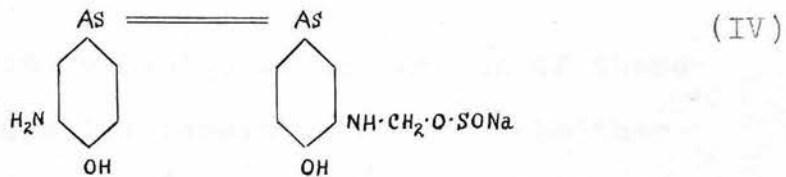
The advantage of neo-salvarsan, apart from its
decreased toxicity, is that it does not require
neutralisation.   On the other hand it is less
stable, oxidising readily on shaking the solution,
and its toxicity is apt to vary in different samples.
There still remains some doubt concerning the exact
nature of its chemical constitution.

Following the introduction of salvarsan into
chemotherapy many toxic effects showing widely
differing symptoms soon became apparent.   After
careful enquiry, it was found possible to avert
entirely or alleviate most of these toxic effects by
careful use of the drug.   The preparation of the
drug and its method of injection have been carefully
standardised/

standardised so that its administration is now
relatively safe. There still remains some doubt
however whether modern methods of treatment
definitely eradicate syphiliticinfection or whether
they merely render the disease latent. Time and
future work will show.

The exact mechanism of the action of these
compounds also still remains obscure. Neither
atoxyl nor salvarsan show any therapeutic activity
in vitro in concentrations much greater than are
possible for bodily administration. If, however,
atoxyl be reduced and salvarsan partially oxidised
to their corresponding arsenoxides, these products
have an intensely lethal action on spirochaetes or
trypanosomes in vitro, which the two initial sub-
stances conspicuously lack. Voegtlin and his co-
workers (U.S. Public Health Service, J. Pharmacol.
1920, 15, 475) strongly support the view, that a
reduction or oxidation effected by contact with the
tissues is the essential preliminary to the curative
action, a supposition which necessarily requires the
cooperation of the host. The fact, that the
administration of these relatively inactive pre-
decessors is therapeutically more effective than the
injection of the, in vitro, active arsenoxides
derived/

derived from them, would then be explained on the
assumption that the slow liberation of the latter
in the body, at a rate which never produces a high
concentration, provides the optimum conditions for
their persistent action on the parasites, without
danger to the host.

More recently Jacobs and Heidelberger (J. Amer.
Chem. Soc., 1919, 41, 1587) have revived interest
in pentavalent arsenical compounds, temporarily
eclipsed by the arsenobenzenes, by preparing
tryparsamide, the monosodium salt of N-(p-phenyl
arsinic acid) glycineamide, which holds out consider-
able prospect of the eventual conquest of African

$$As\underset{OH}{\overset{ONa}{\lessgtr}}O$$

Tryparsamide.

$NH \cdot CH_2 \cdot CONH_2$
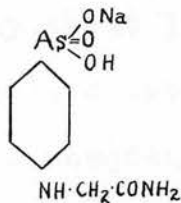
sleeping sickness.   It has also been employed in
neurosyphilis and it is generally agreed that in
early/cases of paresis and tabes, treatment with
tryparsamide is of considerable value, better
results being obtained than with the arsenobenzenes.
Many injections are required and since Moore,
Robinson and Lyman (J. Amer. Med. Assoc. 1924, 83,
888) have shown that it is useless in primary and
secondary/

secondary syphilis its value would seem due, not to direct spirochaeticidal action, but to its tonic action on the tissues. When tested by Ehrlich's therapeutic index — the ratio of the minimum dose C, which will cure a standard infection in an animal without relapse, to the maximum dose T, tolerated by a healthy animal — it gives a relatively unfavourable figure. For this reason Brown and Pearce (J. Exp. Med., 30, 417) preferred to reject the hypothesis of direct attachment to the parasite in the case of tryparsamide, and rather to rely upon the assumption of a more easy diffusibility of the drug into the tissues, thus increasing the internal resistance of the body cells to the parasite.

A further remedy for trypanosomiasis was produced in Germany about 1920. The composition of this compound called Bayer 205 or Germanin was not disclosed, but consequent on the researches of Fourneau, it has been definitely established that the compound Fourneau 309 is identical with Bayer 205.
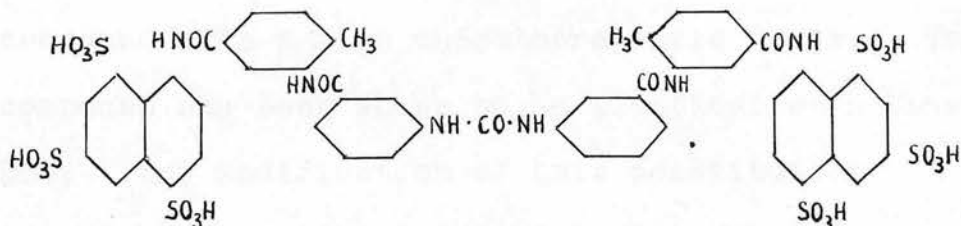
Fourneau 309.

Bayer 205.

The preparation of Bayer 205 was conceived
owing to the discovery in 1906 that the azo dyestuff
afridol violet possessed some trypanocidal activity.
Fourneau then prepared a large number of aminobenzoyl
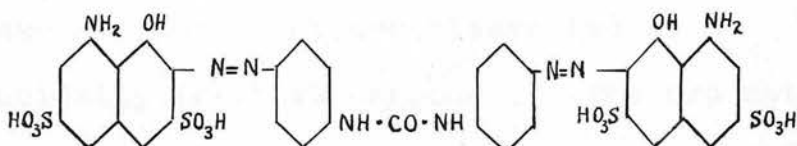
Afridol Violet

derivatives of various naphthalene sulphonic acids.
During the course of the investigation he found that
compounds containing the m-amino benzoyl nuclei were
more effective than those with the p-amino benzoyl
residues.   Further it was found that the partial
replacement of the m-amino benzoyl residues by amino-
tolyl gave more encouraging results and finally, of
the several naphthalene sulphonic acids, the acid 1-
amino-naphthalene-4:6:8-trisulphonic acid gave a
compound with a high chemotherapeutic index.   This
compound has been shown to be identical with Bayer
205.   Any modification of this constitution
invariably resulted in a great diminution of the
trypanocidal activity,   The central substituted urea
residue/

residue seems to form an essential part of the
molecule.   Condensation of the free amine with
various chlorides, e.g. oxalyl, malonyl, diethyl-
malonyl, phthalyl, isophthalyl and terephthalyl
in place of phosgene and the formation of a thio-
urea, azo or azoxy compound always led to a
trypanocidally inactive compound.   The two methyl
groups would also seem to play an important role
since replacement by higher homologous alkyl groups,
by methoxyl or halogens resulted in feeble or in-
active compounds.   The sulphonic groups even seem
to serve a physiological purpose in addition to their
physical solubility function, since of the sulphonic
acids employed in the condensation, only the 4:6:8
acid gave a compound with marked trypanocidal
properties.

Preliminary tests on mice, rats, guinea-pigs
and rabbits infected with Trypanosoma brucei, T.
equiperdum, T. equinum, T. gambiense and T.
rhodesiense showed it to possess definite curative
properties.   It was also found to prevent infection
when administered prophylactically.   Perhaps the
most remarkable feature of Bayer 205 is the duration
of its action in the body.   A case is recorded of

a/

a rabbit infected with T. equiperdum that was, rendered immune for five months to reinoculation. The first attempts to apply the drug to the cure of

human trypanosomiasis met with encouraging results but an intensive study emphasised the fact that its use was not without danger. One of the more serious toxic effects of the drug was the appearance in the urine after the second or third injection of albumin and casts and in some cases blood. Although in fresh cases a peripheral sterilisation of the blood occurs sufficiently prolonged to suggest permanent cure, cases of chronic trypanosomiasis with altered cerebro-spinal fluid show as a rule a slight but only transient improvement. In a few cases a temporary check is effected but in the majority the disease slowly progresses to a fatal issue. Bayer 205 perhaps possesses more value as a prophylactic than as a curative agent. It definitely diminishes the risk of infection of healthy individuals, while infected cases are better treated with arsenicals.
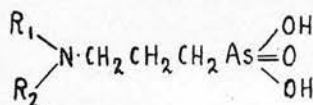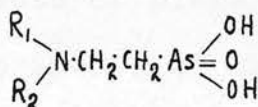
The success which attended the use of Bayer 205 as a trypanocidal agent suggested the interesting possibility/

possibility of preparing a number of complex ureas
containing arsenic, in the hope that these would
have a prolonged trypanocidal action in the body.
Following the general relation between chemical
constitution and physiological action found in the
Bayer compounds, namely that m-aminobenzoyl deri-
vatives were therapeutically most effective King and
Murch (J.C.S., 1924, 125, 2595) aimed at preparing
the following compound which would possess a well
marked resemblance to Bayer 205.   Although they
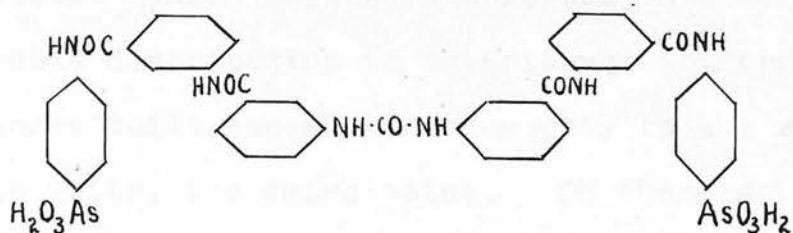
did not succeed in attaining their ultimate aim a
number of intermediates of the above type were
obtained, but they possessed no therapeutic activity.
There is of course a great difference between a
compound of this type and Bayer 205.   The
accumulation of sulphonic acid groups in Bayer 205
renders it very soluble, whereas the arsinic acids
prepared were very sparingly soluble, and for that
reason were perhaps unable to diffuse freely
throughout/

throughout the tissues to exert their influence and
hence were rapidly eliminated.   Further Bayer 205
possesses amphoteric properties having free amino
groups in the molecule,and a number of intermediates
of the above type containing a free amino group
were found to cause a temporary disappearance of
trypanosomes from the blood stream.   Experience
has shown that a more frequent activity occurs in
compounds of an amphoteric nature (King,   J.C.S.
1927, 1049) which may be attributed to a more
favourable distribution in the tissues conferred on
substances built somewhat analogously to the simple
protein units, the amino acids.   On these con-
siderations, Gough and King (J.C.S., 1928, 2426)
prepared a number of amino aliphatic arsinic acids,
derivatives of β-amino ethyl and γ-amino propyl
arsinic acids, which from their similarity to the
amino acids derived from the tissues and their
small molecular weight would possess a greater
power of penetration and a more favourable distri-
bution.

$$\begin{matrix} R_1 \\ \diagdown \\ R_2 \diagup \end{matrix} N\cdot CH_2 CH_2 \cdot As \overset{OH}{\underset{OH}{=\!O}} \qquad \begin{matrix} R_1 \\ \diagdown \\ R_2 \diagup \end{matrix} N\cdot CH_2 CH_2 CH_2 As \overset{OH}{\underset{OH}{=\!O}}$$

These/

These compounds, however, were found to have only a slight or no therapeutic activity. On the theory that activity is due to reduction to the trivalent state by the tissues these acids may be difficult to reduce or alternatively they may be excreted too readily from the system.

A compound which has been instrumental in further developing the field of chemotherapy is the German preparation Plasmoquine, N-diethyl-amino-isopentyl 8-amino 6-methoxy quinoline, which bears a fairly close resemblance to the cinchona

CH_3O

NH N

$CH \cdot CH_3$

CH_2

CH_2

$CH_2 \cdot N(C_2H_5)_2$
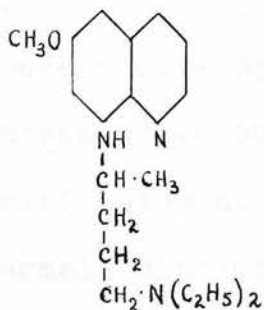
Plasmoquine

alkaloids of which quinine has long been used in the treatment of malaria. The anti-malarial effects of plasmoquine were first demonstrated by experiments on bird malaria. In tertian and quartan/

quartan malarial infections plasmoquine was shown
to be quite as effective as quinine in destroying
both the sexual and asexual forms of the parasites,
but in the treatment of subtertian infections it
proved less efficient.   Relapses were frequent
and therefore in clinical practice quinine was
combined with plasmoquine treatment.   This proved
at least equal, if not superior, to the use of
quinine alone.   Owing to its toxic effects,
however, the use of pure plasmoquine has largely
been abandoned, although it is sometimes employed
in cases of quinine idiosyncrasy, in pregnancy with
risk of abortion and in children by whom it is well
tolerated.

The recent development of anti-malarials has
followed three clues suggested by a consideration
of the constitution of (a) the cinchona alkaloids,
(b) the harmala alkaloids and (c) plasmoquine
(Barger and Robinson, J.C.S., 1929,   2947).   The
harmala analogy is based on the work of Gunn and
Marshall (Proc. Roy. Soc. Edin., 1920, 15, 145)
who advanced evidence to show that harmaline
although inferior to quinine, possessed curative
value/

value in acute malaria, whereas harmine although
valueless in acute malaria prevented the recurrence
of attacks in three cases of relapsing malaria in
which the administration of quinine had been tried
and had failed.   Some harmala analogues have been
prepared (J.C.S., loc. cit.) having the constitution
(I), Seshadri (J.C.S., 1929, 2952) prepared
quinoline and 6-methoxy quinoline derivatives of
type (II) by condensing the appropriate quinoline
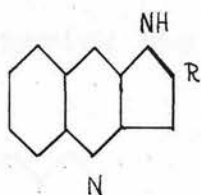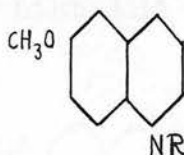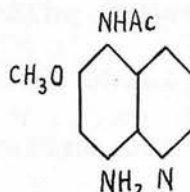

I   II

compound with bromoalkylphthalimides, and Baldwin
(J.C.S., 1929, 2959) obtained a number of substituted
amino 6-methoxy quinoline compounds (III) somewhat
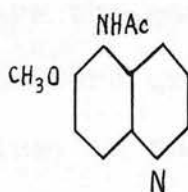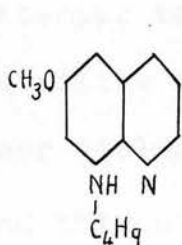
III

analogous/

analogous to plasmoquine.

The compound 8-N-ethyl piperazino quinoline
was prepared in order to obtain a molecule similar
to plasmoquine but containing a piperazine ring
in place of the N-diethylamino-isopentyl chain.
This was prepared by condensing piperazine with 5-
nitro 8-iodo-quinoline, ethylating the free
nitrogen atom of the piperazine ring and subsequently
removing the nitro group from the quinoline ring by
reduction, conversion to the iodo compound and
finally removing the iodine.   Like the compounds
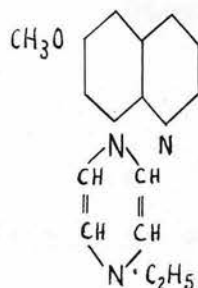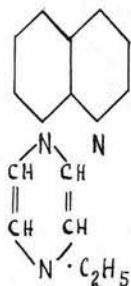
described above 8-N-ethyl piperazino quinoline was
therapeutically inactive towards malaria.   All
attempts to prepare the corresponding 6-methoxy
quinoline compound were unsuccessful owing to the
poor yields obtained in the piperazine condensation,
and this could not be improved on substituting
ethyl/

ethyl piperazine for piperazine.   Similar compounds
with condensed piperidine residues have also been
explored (Kermack and Smith, J.C.S., 1930, 1356) and
found to be inactive.   A recent acridine derivative
however merits further investigation.

The only arsenic compound generally used in
the treatment of malaria is stovarsol, 3-acetyl-
amino 4-hydroxyphenylarsinic acid.   It has been

OH

NHAc   Stovarsol

AsO_3H_2
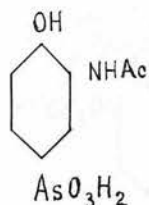
found active to the older parasites on which
quinine had failed, but was unfortunately accompanied
by disturbing effects, the chief of which was a
marked rise in the patient's temperature.   It also
possessed no effect on quartan or malignant in-
fections.   This led Fourneau to prepare the quinine
salt of stovarsol and this he showed better than
stovarsol but very similar to quinine and stovarsol
given separately.

This/

This combined quinine and arsenic therapy
presented the interesting hypothesis that a quinoline
arsenic compound, for example, a substituted quino-
line arsinic acid might be an efficient anti-malarial
or perhaps a trypanocide.   Accordingly Slater (J.C.S.
1930, 1209; 1931, 107, 1938; 1932, 2104, 2196) has
prepared many quinoline arsinic acids.   These
include 6-methoxy quinoline derivatives of amino
phenyl arsinic acids (I) and quinoline 5- and 6-
arsinic acids (II).   None of these is active but the

I.

II.
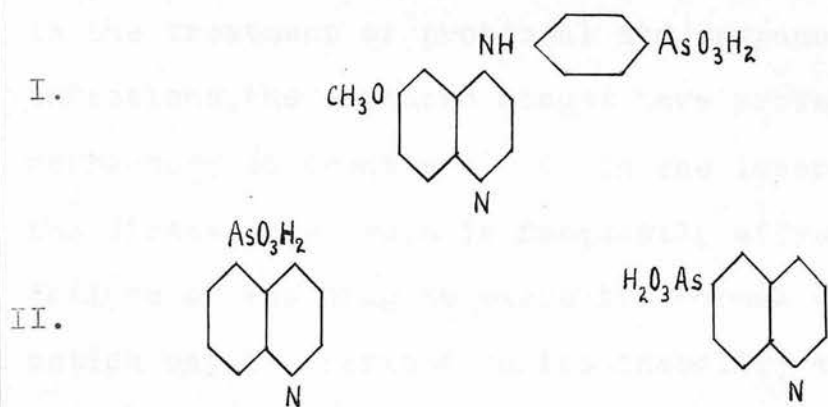
accessibility of the latter compounds and their
derivatives opens the way for the synthesis of
quinoline analogues of stovarsol and salvarsan, and
these should be of considerable interest.

Little is known of the pharmacological action
of quinine or plasmoquine in malaria, whilst in the
case of the arsenic compounds the hypotheses
developed/

developed in the chemotherapy of trypanosome
infections may be generally applied. The inactivity
of the above quinoline arsenic compounds may be
attributed to the size of the molecules rendering
their free diffusion throughout the cells difficult
and their period of action short on account of their
rapid elimination from the system.

How these various theories may have to be
modified rests with the advance of our knowledge and
although several compounds have proved very effective
in the treatment of protozoal and trypanosome
infections,the advanced stages have proved exceedingly
refractory to treatment. In the later stages of
the disease the brain is frequently affected and the
failure of the drug to exert its normal curative
action may be ascribed to its inability to diffuse
freely throughout the brain tissues. With the idea
that a fat soluble compound would be suitable for
this purpose, it was hoped to prepare some compounds
closely related to tryparsamide, used in the treat-
ment of neuro-syphilis, which would also possess a fat
soluble factor.

One attempt to prepare compounds which will
readily pass into the central nervous system has been
made/

made by Stratman-Thomas and Lowenhart (J. Pharm. and
Exp. Therap., 1928, 33, 443, 459), who have prepared
the monosodium salts of p-β-hydroxy ethyl amino
phenyl arsinic acid (Etharsanol) and p-γ-hydroxy
propylamino phenyl arsinic acid (Proparsanol).

$$As \overset{OH}{\underset{ONa, 2H_2O}{\lessgtr O}}$$

NH·CH$_2$·CH$_2$OH

Etharsanol.

$$As \overset{OH}{\underset{ONa, 4H_2O}{\lessgtr O}}$$

NH·CH$_2$·CH$_2$·CH$_2$OH
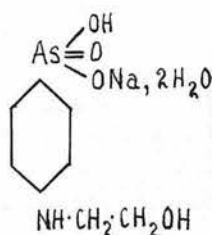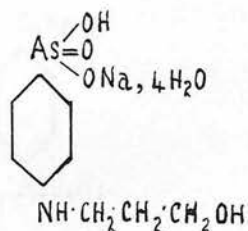
Proparsanol.

These compounds although twice as toxic as
tryparsamide have been used in a few cases of sleep-
ing sickness without the appearance of amblyopia, and
considerable penetration of arsenic into the brain
tissue has been demonstrated.

It was then the object of this research to
attempt to prepare some analogues of tryparsamide
with long aliphatic side chains to render them fat
soluble.   The difficulty of directly introducing
such a chain into tryparsamide itself was realised,
and/

and at the outset the following scheme was pursued.

$$\underset{CO \cdot C_nH_{2n+1}}{\bigcirc} \rightarrow \underset{CH_2 \cdot C_nH_{2n+1}}{\bigcirc} \rightarrow \underset{\underset{NO_2}{C_nH_{2n+1}}}{\bigcirc}$$

$$\rightarrow \underset{\underset{NH_2}{C_nH_{2n+1}}}{\bigcirc} \rightarrow \underset{\underset{AsO_3H_2}{C_nH_{2n+1}}}{\bigcirc}$$
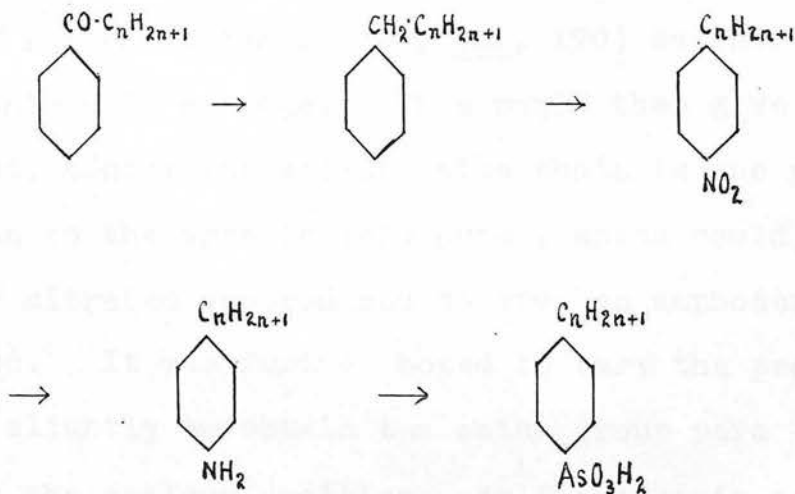
In the particular case investigated the acid
chloride of pelargonic acid was condensed with pure
dry benzene by means of the Friedel Craft reaction
to give the ketone pelargonyl phenone. This ketone
was reduced to a hydrocarbon by the method of
Clemmensen (Ber., 1913, 11, 1837). Nitration of
this hydrocarbon gave as chief product p-nitro
phenyl nonane. The nitro group was assumed to go
chiefly into the para position on account of the
bulky side chain attached to the ring which would
naturally prevent substitution in the ortho position.
The nitro compound was reduced with iron and acetic
acid to give an aliphatic aromatic amine. This
amine/

amine and its acid salts were readily soluble in fat
solvents and it was hoped by means of the Bart-
Schmidt reaction (Ann., 1920, 421, 170) to introduce
an arsenic acid residue.   This would then give a
compound, containing a fatty side chain in the para
position to the arsenic acid group, which could be
further nitrated and reduced to give an amphoteric
compound.   It was further hoped to vary the pro-
cedure slightly to obtain the amino group para -
usually the optimum position - to the arsenic acid
group.   After numerous attempts it was found
impossible to introduce an arsenic acid group in
place of the amino group.   A considerable quantity
of tar was invariably obtained from which no
crystalline compound could be isolated.   Since the
only difference between p-toluidine, in which the
amino group was readily replaced by arsenic in the
Bart reaction, and p-amino pelargonyl benzene was
the length of the side chain, it was decided to try
a compound containing an aliphatic side chain of
intermediate length.   For this purpose p-amino
butyl benzene (Reilly and Hickinbottom, J.C.S., 1920,
117, 103) was prepared and employed in the Bart
reaction.   In this case a few needles of a crystalline
product/

product somewhat contaminated with tar were obtained,
but only in very minute amount insufficient for
purification and analysis.   A similar attempt with
3-nitro-4-amino butyl benzene (Reilly and Hickin-
bottom, loc. cit.) which was prepared in the hope
that the nitro group would increase the aromatic
nature over the aliphatic, also proved unsuccessful.

C_9H_{19} ⬡ NH_2 C_4H_9 ⬡ NH_2 C_4H_9 ⬡ NO_2 NH_2
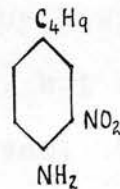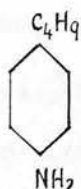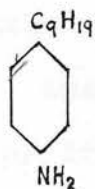
        Since this failure seemed definitely due to
the influence of the long aliphatic side chain, it
was decided to attack the problem in a slightly
different way.   In the preparation of tryparsamide
(Jacobs and Heidelberger, loc. cit.) the mono-
sodium salt of p-amino phenyl arsinic acid is con-
densed with chloroacetamide.   Attempts were then
made to use in place of chloroacetamide, the bromo
fatty acid amides (Fourneau, Bull. Soc. Chim. France
 [4], 43, 1232-64).   Fourneau had already employed
α-brompropionamide in the above condensation
(Fourneau, loc. cit.) and the resultant product had
been/

been resolved.   It was therefore attempted to extend
this condensation to α-bromobutyramide.   This was,
however, unsuccessful, the bromobutyramide being
hydrolysed on prolonged boiling in aqueous solution,
and other solvents and conditions of reaction proved
equally unsuitable.

Attention was next directed toward the
malonamide group.   The compound N-(p-phenyl arsinic
acid) amino malonamide had been prepared by Lewis and
Bent (J. Amer. Chem. Soc., 1926, 48, 949), but no
report of its therapeutic activity was given.   Com-
pounds of type I were then prepared, R being an
alkyl group.

AsO_3H_2

$NH \cdot CH \diagup_{\diagdown}^{CONHR}_{CONHR}$

I.

AsO_3H_2

$NH \cdot CO \cdot CH_2 \cdot CONHR$
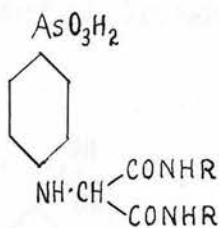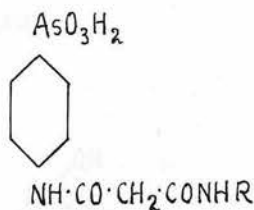
II.

Although not directly attached to the benzene
ring these compounds possessed the advantage that it
was possible to introduce two alkyl groups in one
stage/

stage as against one in the case of the mono-
carboxylic acids.   The compounds having R = methyl,
ethyl, propyl, n-butyl, iso-butyl, amyl and iso-amyl,
have been prepared with a maximum yield in the case
of the propyl compound.   These compounds, closely
analogous to tryparsamide from which they only differ
in the presence of an extra substituted carbamide
group, are also interesting in view of their relation
to some malonamide arsinic acids of type II, prepared
by Morgan and Walton (J.C.S., 1931, 1743-1748) from
arsanilic acid and carbethoxy acetyl chloride and
subsequent treatment with ammonia or alkylamines.
The compounds of type I were prepared by condensing
the monosodium salt of arsanilic acid with N-
substituted bromomalonamides thus:
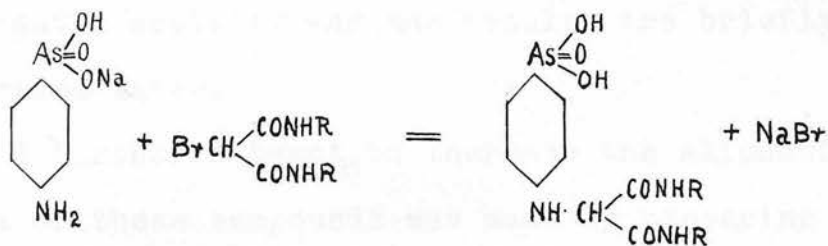
The N-substituted bromomalonamides were obtained by
treatment of malonic acid diethyl ester with the
corresponding/

corresponding amine and subsequent bromination
according to the method of Backes, West and Whiteley
(J.C.S., 1921, 119, 359).

These malonamide arsinic acids were well
defined crystalline compounds becoming less soluble
in 50 per cent. alcohol and insoluble in cold and
hot water with increasing length of R.   The calcium,
barium and magnesium salts also became more insoluble
with the introduction of the more fatty substituents
and in many cases showed a characteristic crystalline
form.   The acids, however, remained insoluble in
ether.   A further acid prepared by condensing bromo-
malonic acid diethyl ester with arsanilic acid was
obtained but only in small yield, insufficient for
testing in cases of experimental trypanosome infection
in mice.   The other acids have been tested for
therapeutic activity and the results are briefly
summarised later.

A further attempt to increase the aliphatic
nature of these compounds was made by preparing some
alkyl bromomalonamides (III), in which the central
carbon atom of the malonyl group had an alkyl group
attached/

attached.   The alkyl group was introduced into

$$\begin{array}{c} CONHR \\ | \\ Br-C-Alkyl \\ | \\ CONHR \end{array}$$

III.

$$\begin{array}{c} Br \cdot CH \cdot COOH \\ | \\ CH_2 \cdot CONH_2 \end{array}$$
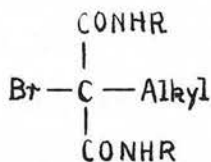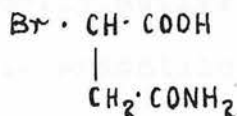
IV.

malonic acid diethyl ester by means of the sodio-
malonic ester synthesis.   This alkyl ester was then
treated with ammonia or other primary amine and the
resultant alkyl malonamide was then brominated in a
manner similar to the malonamides cited above.
Those prepared are described but they failed to con-
dense with arsanilic acid.   The number of large
groups around the central carbon atom may have
prevented the introduction of the larger arsanilino
group.

Attempts to extend this condensation reaction
to the succinamide series were next considered.   A
succinamide series has already been obtained by
Morgan and Walton (loc. cit.) by condensing arsanilic
acid with succinic anhydride.   Since the optically
active/

active compound bromosuccinamide (IV) was described
in the literature and further this introduced the
interesting possibility of an optically active arsonic
acid, attempts were made to condense arsanilic acid
with bromosuccinamide.   All attempts, however, were
unsuccessful.   In addition a number of attempts to
utilise o-arsanilic acid in the general condensation
also met with failure.

Following the rather disappointing results of
the investigation of tryparsamide analogues in the
malonamide series, it was decided to explore a
somewhat different type of compound.   For this
purpose the diphenyl ether molecule was chosen as
one about which very little seemed to be known.
Roberts and Turner (J.C.S., 1925, 127, 2009) have
prepared o-phenoxy phenyl arsinic acid from o-phenoxy
aniline by means of the Bart reaction.   Starting
from chloro substituted phenols and o-chloronitro-
benzene a few chloro derivatives of o-phenoxy phenyl
arsinic acid have also been obtained.   It was
therefore resolved to extend this field by preparing
various/

various halogen and amino substitution products of
p-diphenyl ether arsinic acid.   p-Diphenyl ether
arsinic acid was prepared according to the scheme:

$$\text{C}_6\text{H}_5\text{OK} + \text{Cl-C}_6\text{H}_4\text{-NO}_2 = \text{C}_6\text{H}_5\text{-O-C}_6\text{H}_4\text{-NO}_2$$

$$\text{C}_6\text{H}_5\text{-O-C}_6\text{H}_4\text{-NH}_2 = \text{C}_6\text{H}_5\text{-O-C}_6\text{H}_4\text{-AsO}_3\text{H}_2$$
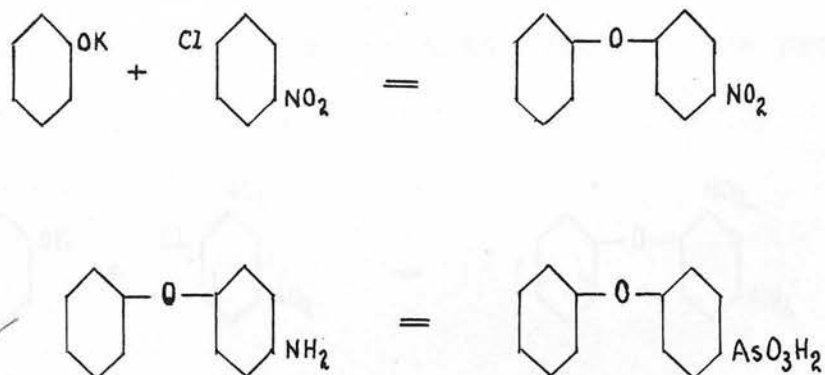
Potassium phenate and p-chloronitrobenzene were
heated together in phenol solution and the resultant
p-nitro diphenyl ether was reduced with tin and
hydrochloric acid.   Then by means of the Bart-
Schmidt reaction an arsenic acid residue was intro-
duced in place of the amino group to give p-diphenyl
ether arsinic acid.   On nitration according to the
method of Michaelis (Ann., 320, 321) three nitro
groups were introduced into the molecule in place of
one as was the case in the nitration of p-methyl
phenyl arsinic acid.   It was impossible to predict
the orientation of the three nitro groups.   In
order that the positions of the final nitro and
arsenic/

arsenic acid groups might be previously fixed 2:4-
dinitro diphenyl ether was prepared by condensing
potassium phenate with 2:4-dinitro chlorobenzene.
Attempts to reduce one of these nitro groups and
subsequently introduce an arsenic acid residue proved
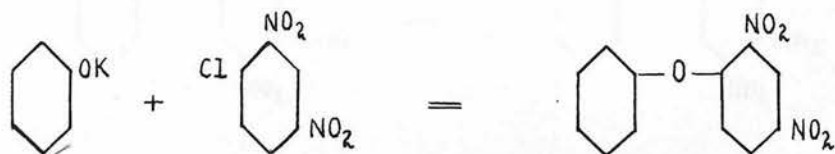
unsuccessful.   The dinitro compound was insoluble
in cold alcohol and the method of half reduction
with ammonia and sulphuretted hydrogen was thus
upset.   When solution was brought about by heating
tars invariably resulted.

The next step started from the p-amino diphenyl
ether obtained above.   After acetylation, the p-
acetylamino diphenyl ether was nitrated with nitric
acid in glacial acetic acid solution.   The nitro
acetylamino compound was then hydrolysed on boiling
with alcoholic hydrochloric acid and a small
quantity/
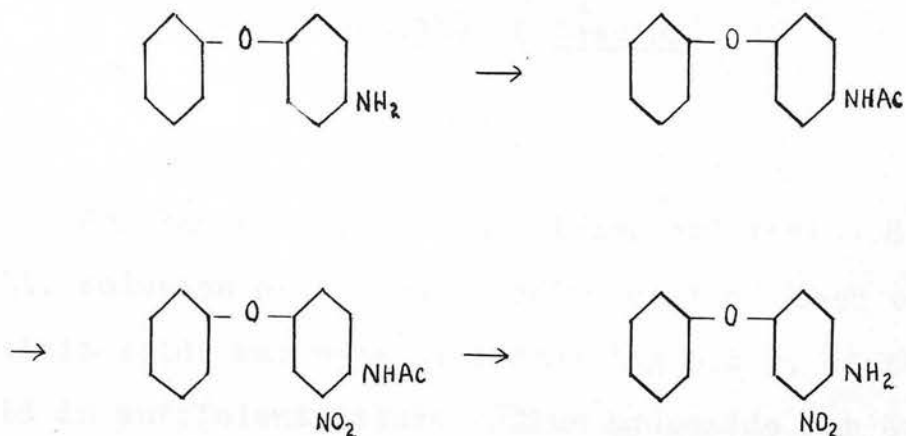
quantity of a red oil was obtained which formed a

crystalline picrate.   It was hoped after the

preparation of a quantity of this amine to obtain

a nitro arsinic acid by the Bart reaction and

finally an amino arsinic acid.   By starting with

differently substituted phenols and chlorobenzenes,

it should be possible to obtain a wider variety of

products in which the orientation of the various

substituent groups is definitely fixed.

(2) /

(2) Results of Testing.

For the purposes of physiological test a 5 per cent. solution of the mono-sodium salt of each of the arsinic acids was made by dissolving 0.5 g. of the acid in sufficient dilute sodium hydroxide for exact neutralisation and making the volume up to 10 c.c.

These solutions have been tested by Professor Warrington Yorke on an experimental trypanosome infection in mice,and a brief summary of the results is given below.

Sodium salt of N-(p-phenyl arsinic acid)	Maximum lethal dose per 20 g. mouse.	Therapeutic Action.
Amino malonamide	50-75 mg.	Curative in large doses
Amino-malon-dimethylamide	50 mg.	nil
Amino-malon-diethylamide	25 mg.	Very slight
Amino-malon-di-n-propyl-amide	10 mg.	nil
Amino-malondi-n-butylamide	5 mg.	nil
Amino-malondi-iso-butylamide	10 mg.	nil

The malonamide was curative in large doses
comparable with the maximum lethal dose.   With
increasing length of the alkyl chain, the toxicity
showed a marked steady increase.   The ethylamide
was the only other member of the series to show a
slight therapeutic effect.   These compounds then
are highly toxic and possess, except in two cases,
no therapeutic action.   In this respect they are
inferior to the malonamide arsinic acids of Morgan
and Walton (loc. cit.) who find that the most
active member of the series is the ethylamide.   The
outstanding difference between the two types of
compounds is the presence in those of Morgan and
Walton of a -CO-NH- grouping directly attached to
the benzene ring, a factor which has been found
repeatedly favourable to therapeutic activity.

(3) /

(3) Methods of Analysis.

Arsenic.

The following method for the estimation of
arsenic was given in the Pharmacopoeia Germanica.

The arsenic compound (0.2 g.) is oxidised by
means of 10 c.c. of concentrated sulphuric acid and
1 c.c. of fuming nitric acid in a long necked 100 c.c.
Jena flask. After boiling for 1 hour, the cooled
mixture is treated with 50 c.c. of water, evaporated
and the process repeated. To the cold solution
after the second evaporation are now added
successively 10 c.c. of water, 2 g. of potassium
iodide in 5 c.c. of water, and sufficient water to
dissolve the precipitate. After standing for 30
minutes, the liberated iodine is titrated without
an indicator. A slight modification was made in
this method owing to the relatively small amounts of
the compounds obtained. In place of 0.2 g. only
0.1 g. was taken and for the titration twentieth
normal sodium thiosulphate was used. This
method although fairly convenient gave consistently
high/

high results.   Blank estimations on pure p-arsanilic
acid and tryparsamide also gave high values, but in
blank experiments using only the reagents, this
discrepancy could not be accounted for.   In the
case of arsanilic acid it was found As 35.2:
$C_6H_8O_3NAs$ requires As 34.6%, and for tryparsamide
found As 28.2: $C_8H_{11}N_2As$ requires As 27.4%,
whereas blank experiments with the reagents alone
could justify these figures being diminished only
to the extent of 0.1%.   This discrepancy has not
been thoroughly investigated, but it would seem
due perhaps to some occlusion of nitric acid by
the arsenic acid produced.

The gravimetric magnesium pyroarsenate method
was also employed for a very few estimations and
was abandoned because it gave exceedingly low
results. This was especially noticeable in the
diphenyl ether arsinic acids while carbon and
hydrogen estimations gave good results with these
compounds.

Nitrogen.

All amino nitrogen estimations were done by the
micro-Kjeldahl method following the instructions as
given/

given in Die Qualitative Organische Mikroanalyse,
Pregl.   This method proved quite satisfactory and
gave reliable results.   Other nitrogen estimations
were carried out by the Dumas combustion method.

Bromine.

In addition to the usual method of Carius an
interesting method applicable to bromomalonamides
(Backes, West and Whiteley, loc. cit.) was also
employed.   This method consisted in mixing a
weighed quantity of the bromo compound with glacial
acetic acid and potassium iodide, and after standing
for 2 hours, titrating the liberated iodine with
sodium thiosulphate.   It was found possible to
extend this method to the determination of bromine
in the alkyl bromomalonamides prepared.

EXPERIMENTAL /

EXPERIMENTAL

Pelargonyl chloride.

Pelargonic acid (158 g.) and thionyl chloride
(150 g.) were mixed together and allowed to stand
overnight in a flask closed with a calcium chloride
tube.　The reaction proceeded smoothly at room
temperature and in the morning the flask was warmed
under an air condenser on the steam bath for 1-2
hours.　It was then connected with a vacuum pump
and the mixture was distilled.　Some thionyl
chloride came over first and pure pelargonyl chloride
distilled at $97°/13$ mm. as a colourless liquid with
a pungent odour.　The yield from 90 g. of acid was
91 g.　92% of theory.

Pelargonyl phenone.

According to the Friedel Craft reaction
pelargonyl chloride (176.5 g.) and pure dry benzene
(98 g.) were mixed together in a flask and anhydrous
aluminium/

aluminium chloride (267 g.) was added in one portion.
A vigorous evolution of hydrochloric acid fumes soon
commenced and the flask was allowed to stand under a
reflux water condenser for half an hour until the
reaction had subsided.   It was then heated on the
water bath for 2 hours, allowed to cool and the
aluminium chloride addition compound decomposed by
pouring the mixture in a thin stream on to crushed
ice.   The ketone separated as a brown upper layer
which was extracted with ether.   The ether extract
was washed first with water, then with dilute sodium
hydroxide, with water again and finally dried by
shaking with anhydrous potassium carbonate.   The
ether was removed and the ketone distilled in vacuo
when it passed over at 168°/13 mm. as a colourless
liquid which crystallised about 15°.   Yield 80% of
theory.

Analysis:

4.330 mg. substance gave 13.210 mg. CO_2 and 3.940 mg. H_2O

Found   83.2% C;   10.1% H.

$C_{15}H_{22}O$ requires   82.6% C;   10.1% H.

The/

The pelargonyl phenone was immiscible with water
but freely soluble in all the organic solvents.

Caproyl phenone.

According to the method used for the prepar-
ation of pelargonyl phenone 67 g. of caproyl chloride
and 50 g. of benzene were mixed in a flask and 135 g.
of fused anhydrous aluminium chloride were added in
one portion.   After the reaction had subsided the
mixture was heated on the water bath for 2 hours.
Then after cooling, the mixture was poured in a thin
stream on to crushed ice, the phenone which separated
was shaken out with ether, the ether layer washed,
dried and the ether removed.   The residue was
distilled in vacuo and the caproyl phenone distilled
as a colourless oil at 137°/15 mm.   On standing it
crystallised in long plates, m.p. about 30°.   Yield
80% of theory.

Analysis:

4.850 mg. substance gave 14.550 mg. CO_2 and 3.960 mg. H_2O

Found. 81.8% C; 9.1% H.

$C_{12}H_{16}O$ requires   81.8% C; 9.1% H.

a/

α-phenyl n-nonane.

According to the method of Clemmensen (Ber.,
1913, 11, 1837) granulated zinc (4-5 parts) was
placed in a large flask and covered with a 5%
solution of mercuric chloride and allowed to stand
for 1 hour.   The zinc was in this way amalgamated.
The solution was poured off and pelargonyl phenone
(1 part) added, then a portion of 50% (by volume)
hydrochloric acid and the flask was heated under a
reflux water condenser for 5-6 hours during which
period the remainder of the hydrochloric acid (4-5
parts) was added gradually.   The hydrocarbon mixed
with some unchanged ketone formed the upper layer
which, when cold, was extracted with ether.   The
ether extract was washed with sodium hydroxide, then
with water and finally dried with anhydrous
potassium carbonate.   The ether was removed on
the water bath and the residue was distilled in vacuo.
Two fractions were collected, the lower fraction
being redistilled and the higher fraction, consisting
chiefly of unchanged ketone, was reduced again.
Owing to the formation of a very high boiling pro-
duct, probably a secondary alcohol, it was not
found/

found advantageous to repeat the reduction of the
unchanged ketone more than once.   On redistilling
the lower fraction α-phenyl n-nonane passed over at
137°/13 mm. as a colourless highly refracting liquid.
Yield based on the first reduction 65% of theory,
or based on the first and second reductions 85% of
theory.

<u>Analysis</u>:

  5.059 mg. substance gave 16.310 mg. CO_2 and 5.260 mg. H_2O

<u>Found</u>: 88.0% C; 11.6% H.

$C_{15}H_{24}$ requires   88.2% C; 11.8% H.

<u>p-Nitro α-phenyl n-nonane.</u>

  The hydrocarbon was stirred in a beaker and
the nitrating acid run in slowly.   Different
strengths of nitrating acids were used and different
temperatures.   With weaker nitrating acids and lower
temperatures very little hydrocarbon was nitrated.
The following conditions were found to be the most
suitable.

  α-Phenyl n-nonane (10 g.) was stirred
vigorously in a beaker cooled in an ice-salt bath
to 0°C., and during 2 hours 10 g. of fuming nitric
acid/

acid (density 1.5) and 15 g. of 100% sulphuric acid
were dropped in.   After all the acid had been
added the mixture was stirred for 1 hour at room
temperature to complete the reaction.   The reaction
mixture was then poured into several times its
volume of water and the lower aqueous layer run off.
The nitro compound was taken up in ether, washed
well with sodium hydroxide, then with water, and
finally dried with anhydrous potassium carbonate.
The ether was removed and the residue distilled in
vacuo when the nitro phenyl nonane came over at
195-197°/15 mm.   A small amount of a higher boiling
fraction was also obtained but was not purified.
The nitro phenyl nonane was a clear, pale yellow
liquid, lighter than water and having a slightly
predominating fatty odour.   Yield 50% of theory.

Analysis:

   4.670 mg. substance gave 12.420 mg. CO_2 and 3.840 mg. H_2O

   3.324 mg.   "   "   0.168 c.c. N_2 at 23.5° and
                                                                    752 mm.

                  Found. 72.5% C;   9.2% H;   5.8% N.

   $C_{15}H_{23}O_2N$ requires   72.3% C;   9.2% H;   5.6% N.

p/

<u>p-Amino α-phenyl n-nonane.</u>

p-Nitro α-phenyl n-nonane (20 g.) was mixed in
a flask, fitted with a mercury seal stirrer and reflux
water condenser, with reduced iron powder (12 g.) and
heated to 90° on a water bath with continual stirring.
150 c.c. of 50% acetic acid were run in during 5 hours.
The contents of the flask were filtered while still
hot and the residue was washed with ether.   The
filtrate was extracted with ether and the amine
acetate passed into the ether layer.   The ether
extract was made strongly alkaline with sodium
hydroxide and the free amine remained in the ether
layer.   The ether extract was separated, washed,
dried and the ether removed in the usual way.   The
amine distilled in vacuo as a very pale greenish yellow
oil at 174-175°/15 mm.   Yield 75% of theory.   A
small amount of a higher boiling fraction was also
obtained.   It crystallised on standing in the ice
chest but was not purified.

<u>Analysis</u>:

5.159 mg. substance gave 15.555 mg. CO_2 and 5.250 mg. H_2O

3.023 mg.   "   " 0.164 c.c. N_2 at 23.5° and
                                         752 mm.

<u>Found</u>. 82.3% C;   11.4% H;   6.2% N.

$C_{15}H_{25}N$ requires 82.2% C;   11.4% H;   6.4% N.

With/

With hydrochloric and sulphuric acids the amine gave
white crystalline salts insoluble in water but
readily soluble in ether.

p-Acetyl amino α-phenyl n-nonane.

Amino phenyl nonane (2.2 g.) was mixed with
acetic anhydride (2 c.c.) and heated under an air
condenser for 1 hour.   The hot solution was poured
into cold water, the excess acetic anhydride decomposed
with sodium hydroxide and the solid mass filtered off
and recrystallised from aqueous alcohol.   The
acetyl compound separated as a felted mass of long
thin colourless needles. m.p. 93°.

Analysis:

2.977 mg. substance gave 0.146 c.c. N_2 at 21° and
751 mm.

Found.   5.4% N.

$C_{17}H_{27}ON$ requires   5.6% N.

The acetyl compound was insoluble in water
but readily soluble in most organic solvents.   It
could also be conveniently crystallised from acetone.

Behaviour/

Behaviour of p-amino α-phenyl n-nonane to the Bart Reaction.

p-Amino α-phenyl n-nonane (5.5 g.) was suspended in water (25 c.c.), hydrochloric acid (9 c.c. of s.g. 1.126) added and cooled to -5°C. For the diazotisation 25 c.c. of n-sodium nitrite were used. After the diazotisation was complete 5 g. of sodium arsenite in 25 c.c. of water were added and during 3-4 hours with stirring 32 c.c. of n- sodium hydroxide were dropped in. After the addition of most of the sodium hydroxide a separation of tar took place from which no crystals could be isolated after extraction with alkali and acidification with hydrochloric acid. The same experiment was repeated several times and the order of addition of ~~of~~ the sodium arsenite and sodium hydroxide was reversed but without any success.

p-Amino n-butyl benzene.

According to the method of Reilly and Hickinbottom J.C.S., 1920, 117, 103) molecular quantities of aniline and butyl alcohol were mixed with fused zinc chloride/

chloride ($\frac{1}{2}$ mol.) and heated to 240° in a sealed
tube for 24 hours. A solid but somewhat soapy
crystalline mass resulted. This was washed with
water to remove free zinc chloride, then with
petrol ether (b.p. 80-100°) to remove secondary amines.
The remaining zincichlorides of the primary amines
were then warmed with concentrated sodium hydroxide
on the steam bath. The free bases separated as a
dark brown upper layer. These were taken up with
ether, dried with anhydrous potassium carbonate, the
ether removed and the remaining bases fractionated.
The fraction distilling from 245-260° was almost
pure p-amino n-butyl benzene. The yield was
about 20% of theory.

Behaviour of p-amino n-butyl benzene to the Bart
    reaction.

7.5 G. of the amino butyl benzene were
diazotised at -10° with 50 c.c. of n-sodium nitrite
in the presence of 50 c.c. of water and 18 c.c.
of concentrated hydrochloric acid. The diazotisation
proceeded/

proceeded normally. 10 G. of sodium arsenite in
50 c.c. of water were then run in,followed by 60 c.c.
of n-sodium hydroxide. A large separation of tar
took place together with considerable frothing and
the evolution of nitrogen. After filtration to
remove the tar the filtrate was acidified with
hydrochloric acid and the solution became turbid.
On standing some long needles formed which were some-
what contaminated with tar. Numerous attempts were
made to prepare larger quantities of this product
without success, insufficient material being
obtained for purification and analysis. The
crystals on combustion had a garlic-like odour.

p-Acetyl amino n-butyl benzene.

According to the method of Reilly and Hickin-
bottom (J.C.S., loc. cit.) 7.5 g. of amino butyl
benzene were mixed with 5 c.c. of acetic anhydride
and heated under reflux for 1 hour. The mixture
was then poured into cold water when the solid
acetyl compound soon separated. The solid was
filtered off and crystallised from alcohol in white
plates/

plates.　m.p. 105°.　　Yield 90% of theory.

3:nitro 4: acetylamino 1:n-butyl benzene.

2 G. of the preceding compound were dissolved
in 10 c.c. of glacial acetic acid and 0.6 c.c. of con-
centrated nitric acid were added.　　The whole was
then heated on the steam bath or gently under reflux
for 1 hour.　The mixture was then poured into water
when the nitro compound settled to the bottom as a
heavy oil.　This was taken up in ether, the ether
extract dried and the ether evaporated off.　　The
residue crystallised and it was purified by re-
crystallisation from alcohol, when it separated
in fine yellow needles, m.p. 76°.

3: nitro 4: amino 1: n- butyl benzene.

The nitro acetylamino compound was dissolved
in 10 times its weight of alcohol and then an amount
of concentrated hydrochloric acid added and the whole
refluxed until there was no precipitate on pouring
into dilute hydrochloric acid.　　The solution was
then poured into water and the base shaken out with
ether/

ether.   The ether was evaporated off and the
residue on standing in the ice-chest crystallised
in reddish yellow needles.   The base was purified by
conversion to the hydrochloride.   Alcoholic hydro-
chloric acid was added to the base and the hydrochlor-
ide precipitated in white shining plates by the
addition of ether.   It was filtered off and de-
composed by the addition of water, the free base
being taken up with ether and separated.   The
ether was evaporated off and the base set in the
ice-chest to a mass of reddish yellow needles, m.p.
about 13°.

Behaviour of 3: nitro 4: amino 1-n-butyl benzene to the Bart reaction.

Only a small quantity of this compound was
available, but attempts were made to introduce an
arsenic acid group by means of the Bart reaction in
a similar manner to that described for p-amino butyl
benzene.   With the additional nitro group it was
anticipated that the diazotisation would be more
difficult but in addition the hydrochloride was
decomposed/

decomposed to the free amine in the presence of
water.   It was impossible to overcome this
difficulty by the addition of alcohol owing to
the formation of phenol and subsequent tarring of
the reaction product.

Preparation of p-arsanilic acid.

According to the method given in Organic
Syntheses, vol. 3, p. 13, to 1035 g. of syrupy
arsenic acid (80-85%) in a 12 inch evaporating dish,
were added 828 g. (800 c.c.) of aniline in 100 c.c.
portions;   meanwhile the lumps of aniline arsenate
which formed were broken up by rapid stirring with
a porcelain spatula.   When all the aniline had
been added, the powdered solid was transferred to
a 3 litre round bottomed flask fitted with a
mechanical stirrer, a thermometer reaching to the
lower part of the vessel, and a condenser arranged
for downward distillation, an additional 800 c.c.
of aniline were added and the flask was slowly
heated on an oil bath.   The bath may be kept at a
temperature of 170-175° as long as there is any
considerable/

considerable amount of unmelted material in the
flask.   When the contents of the flask had become
liquid the temperature of the bath was dropped and
the mixture was held at 155-160° (inside temperature)
with continual stirring for at least 4-5 hours.   The
mass assumed an intense violet colour.   The reaction
mixture was poured into 700 c.c. of water and the
flask washed out with a portion of a previously
prepared solution of 350 g. of sodium hydroxide in
1400 c.c. of water, the washings being added to the
reaction mixture.   The remainder of the alkali was
then added and the mixture agitated and cooled under
the tap.   At this point two distinct layers were
present, a lower pink coloured alkaline water layer,
and an upper strongly coloured aniline layer.   The
water layer was while warm carefully separated from
the purple coloured oil by means of a separating
funnel (heated to prevent separation of sodium
arsanilate), and after treatment with 15 g. of
animal charcoal, filtered through paper.   The
arsanilic acid can be obtained from the aqueous
alkaline solution either as the free acid or as the
sodium salt.   To obtain the free acid the solution
was acidified with concentrated hydrochloric acid
until/

until the purple colour of bromphenol blue changed
to faint yellow; care should be taken in the
addition of the acid not to overstep the end point.
Crystallisation was stimulated by scratching and
the flask was allowed to stand overnight to complete
the precipitation. The crystals were filtered off
and recrystallised once from water (about 2500 c.c.)
in order to obtain a white product. If the initial
crystals obtained have an appreciable pink tinge,
it is advisable to remove most of the colour by
digesting with a small volume of warm alcohol before
crystallisation from water is attempted. The
yield of pure acid was 230 g.

Bromo ethyl malonic ester.

According to the method of Knoevenagel (Ber.,
1888, __21__, 1356) bromine (1 mol.) was gradually
added to malonic ester (1 mol.). The reaction was
started by gentle warming,then it proceeded by itself
at the ordinary temperature. When all the bromine
was added the product was fractionated and the
portion distilling at 230-236° collected. The
greatest/

greatest part distilled at 233-235°. As slight
decomposition took place it was distilled in vacuo
when it came over at 137°/11 mm. The distillate
was washed with sodium carbonate, then with water,
dried over calcium chloride and finally redistilled.
It is a colourless oil. Yield 75% of theory.

N-(p-phenyl arsinic acid) aminomalondiethyl ester.

A solution of 1.74 g. of p-arsanilic acid in
7.75 c.c. of n-sodium hydroxide was heated under a
reflux water condenser with 3.6 g. of bromomalonic
ester and sufficient rectified spirit to render
solution complete. After boiling for several
hours the solution was evaporated. It separated into
two layers, the lower of which on cooling almost
wholly solidified. The solid was separated off and
washed with dilute hydrochloric acid. It
crystallised from a small volume of hot water in
small white needles, m.p. 230° (decomp.). Yield
poor.

Analysis/

Analysis:

   0.1053 g. substance gave a titration of 11.39 c.c.
                      of 0.0498 N $Na_2S_2O_3$.

   7.667 g. substance gave a titration of 2.16 c.c.
                      of 0.01 N HCl.

                 Found. 20.2% As;   3.9% N.

      $C_{13}H_{18}O_7NAs$ requires 20.0% As;   3.7% N.

      The arsinic acid was soluble in dilute sodium
hydroxide and alcohol but insoluble in small amounts
of dilute hydrochloric acid.

Monobromomalonamide.

      According to the method of Backes, West and
Whiteley (J.C.S., 1921, 119, 359), 5 g. of malonamide
(1 mol.) (Freund, Ber., 1884, 17(1), 133) dissolved
in 400 c.c. of glacial acetic acid were heated on
the steam bath, 25 c.c. of a 10% (by volume)
solution of bromine in acetic acid (1 mol.) were
added/

added slowly, and the mixture was constantly shaken.
The bromine was absorbed rapidly and the reaction
completed without the precipitation of any solid
matter.   After spontaneous evaporation of the
solvent, slightly impure bromomalonamide was
obtained in hard cubes which crystallised from
ethyl alcohol in hard colourless prisms, melting
and decomposing at 181°.

N-(p-phenyl arsinic acid) aminomalonamide.

According to the method of Lewis and Bent
(J. Amer. Chem. Soc. 1926, 48, 949) 0.32 mol. of
arsanilic acid were dissolved in 0.31 mol. of N
sodium hydroxide and the solution filtered.   To
the filtrate was added 0.62 mol. of monobromo-
malonamide and the mixture was refluxed on an air
bath under a reflux water condenser until a heavy
white precipitate separated.   This took at least
2 hours and depended on the pH of the solution.
This precipitate was filtered off and washed with
small quantities of dilute hydrochloric acid.   It
was /

was then dissolved in the minimum amount of cold 2 N
sodium hydroxide and then sufficient 50% hydrochloric
acid was added to precipitate the arsinic acid. The
further purification was effected by repeating this
process.   It crystallised from a mixture of alcohol
and dilute acetic acid.   After three crystallisations
it melted with decomposition at 226°.   Lewis and
Bent record no change at 260°.   Yield 40% of theory.

Analysis:

   0.1232 g. substance gave a titration of 16.24 c.c.
                           of 0.0498 N $Na_2S_2O_3$.
   6.900 mg. substance gave a titration of 6.23 c.c.
                           of 0.01 N HCl.

               Found. 24.6% As: 12.7% N.

   $C_9H_{12}O_3N_3As$ requires   23.7% As: 13.3% N.

      R- salt showed the presence of a trace of
arsanilic acid which was very difficult to remove
without considerable loss, the malonamide arsinic
acid being appreciably soluble in dilute hydrochloric
acid.   This and subsequent arsenic estimations
were done by a convenient iodine thiosulphate
titration/

titration method which gave high results.

The arsinic acid gave an insoluble calcium salt which crystallised in bunches of small needles and a pale yellow crystalline copper salt soluble in excess of ammonium hydroxide. The barium and magnesium salts were readily soluble.

N-(p-phenyl arsinic acid) aminomalondimethylamide.

According to the above method 1.74 g. of p-arsanilic acid dissolved in 7.75 c.c. of N sodium hydroxide and 3.24 g. of bromomalondimethylamide (Backes, West and Whiteley, loc. cit.) were heated together until a separation of solid occurred. In this case the optimum pH appeared to be reached more rapidly since the separation of the arsinic acid occurred after/about 15 minutes. On purification by precipitation with 50% hydrochloric acid the arsinic acid became gelatinous rendering filtration excessively slow. The arsinic acid, however, crystallised from a mixture of alcohol and dilute acetic acid in small white shining plates.
On/

On heating the crystals darkened at 295° but did not melt.   Yield 50% of theory.

Analysis:

0.1527 g. gave a titration of 18.48 c.c. of 0.0498 N. $Na_2S_2O_3$.

7.083 mg. gave a titration of 6.07 c.c. of 0.01 N HCl.

Found   22.6% As: 12.0% N.

$C_{11}H_{16}O_5N_3As$ requires 21.7% As: 12.2% N.

The white copper salt of the arsinic acid crystallised in small detached needles and the fairly soluble calcium and barium salts in small cubes.   The magnesium salt was soluble.

N-(p-phenyl arsinic acid)aminomalondiethylamide.

The above quantity of sodium arsanilate solution was heated with 3.67 g. of bromomalondiethylamide (Backes, West and Whiteley, J.C.S. loc. cit.).   As soon as the bromo compound had passed into solution the arsinic acid immediately began to/

to separate out.   The heating was continued for 20
minutes.   The solid was filtered off and well washed
with dilute hydrochloric acid.   On purification by
reprecipitation with 50% hydrochloric acid this
compound showed no gelatinous properties like its
preceding homologue.   It crystallised from a
mixture of alcohol and dilute acetic acid in
beautiful lustrous plates which remained unchanged
on heating to 300°.   Yield 60% of theory.

Analysis:

   0.0997 g. substance gave a titration of 11.16 c.c.
                              of 0.0498 N $Na_2S_2O_3$.
   0.079 mg. substance gave a titration of 4.825 c.c.
                              of 0.01 N   HCl.

                  Found   20.9% As;   11.1% N.

   $C_{13}H_{20}O_5N_3As$ requires 20.1% As;   11.3% N.

   It formed a pale yellow crystalline copper
salt.   The calcium salt crystallised in small cubes
but was comparatively soluble.   The barium and
magnesium salts were soluble.

N-/

N-(p-phenyl arsinic acid) aminomalondi-n-propylamide.

The sodium arsanilate solution was heated with
4.11 g. of bromomalondi-n-propylamide (Backes, West
and Whiteley, J.C.S., loc. cit.) and 5 c.c. of
alcohol.   The bromo amide passed slowly into
solution and then after 10 minutes the arsinic acid
began to separate.   The heating was continued for
20 minutes.   The solid was filtered off, washed well
with dilute hydrochloric acid and recrystallised
from 50% alcohol.   It formed lustrous platelets
which on rapid heating gradually darkened above 265°.
Yield 70% of theory.

Analysis:

0.1068 g. substance gave a titration of 10.86 c.c.
of 0.0498 N. $Na_2S_2O_3$.

6.029 mg. substance gave a titration of 4.34 c.c.
of 0.01 N HCl.

Found.   19.0% As;   10.1% N.

$C_{15}H_{24}O_5N_3As$ requires   18.7% As;   10.5% N.

It gave an insoluble barium salt which formed
clusters of needles. The calcium and magnesium salts
were soluble.

N/

N-(p-phenyl arsinic acid) aminomalondi-n-butylamide.

The sodium arsanilate solution was heated with
4.54 g. of bromomalondi-n-butylamide (Backes, West
and Whiteley, loc. cit.) and 10 c.c. of alcohol to
complete solution of the bromoamide.   The arsinic
acid separated out after 20 minutes.   After boiling
for a further 30 minutes the solid was filtered off,
washed as above and recrystallised from a consider-
able volume of 50% alcohol.   It formed small
glistening plates which darkened above 270° and
melted with decomposition at 293°.   Yield 55% of
theory.

Analysis:

0.1725 g. substance gave a titration of 16.47 c.c.
of 0.0498 N. $Na_2S_2O_3$.

5.382 mg. substance gave a titration of 3.64 c.c.
of 0.01 N. HCl.

Found.   18.2% As;   9.5% N.

$C_{17}H_{28}O_5N_3As$ requires   17.5% As;   9.8% N.

It gave an insoluble barium salt which
crystallised/

crystallised in large prismatic needles.   The more
soluble calcium salt crystallised in small needles
and the magnesium salt was soluble.

N-(p-phenyl arsinic acid)aminomalondi-iso-butylamide

The sodium arsanilate solution was heated with
4.54 g. of bromomalondi-iso-butylamide (Backes,
West and Whiteley,loc. cit.) and 10 c.c. of alcohol.
The arsinic acid separated after 1 hour.   It was
filtered off, washed well with dilute hydrochloric
acid and recrystallised from 50% alcohol.   It
formed close set clusters which remained unchanged
on heating to 260°.   Yield 45% of theory.

Analysis:

0.1308 g. substance gave a titration of 12.79 c.c.
of 0.0498 N. $Na_2S_2O_3$.

6.636 mg. substance gave a titration of 4.50 c.c.
of 0.01 N. HCl.

	Found.	18.2% As;	9.5% N.
$C_{17}H_{28}O_5N_3As$ requires		17.5% As;	9.8% N.

The insoluble barium salt crystallised in
beautiful stellate clusters of needles. The calcium and
magnesium salts were soluble.

Malondi-n-amylamide.

10.4 g. of ethyl malonate and 10 g. of n-
amylamine on standing in a sealed tube formed a
solid crystalline mass overnight.   The tube was then
heated in a furnace at 120° for 5 hours.   The solid
compound was dissolved out with methyl alcohol and
from the solution 10.5 g. of pure malondi-n-amylamide
were obtained.   It crystallised from petrol ether
(b.p. 100-120°) in white plates, m.p. 128°.

Analysis:

6.491 mg. substance gave a titration of 5.30 c.c.

of 0.01 N. HCl.

Found.   11.4% N.

$C_{13}H_{26}O_2N_2$ requires   11.6% N.

It is readily soluble in methyl and ethyl
alcohol, acetone, chloroform and acetic acid, less
soluble in light petroleum and insoluble in water.

Mono/

Monobromomalondi-n-amylamide.

7.5 g. of the preceding compound were
dissolved in 25 c.c. of chloroform and warmed to
40-50°.   15 c.c. of a 10% (by volume) solution of
bromine in chloroform were added.   The bromine was
rapidly absorbed.   After evaporation of the chloro-
form the semi-crystalline residue was dissolved in ·
ethyl alcohol and on slight dilution with water the
bromomalondi-n-amylamide separated in long prismatic
needles, m.p. 98°.

Analysis:

3.420 mg. substance gave 1.983 mg. AgBr.

5.169 mg. substance gave a titration of 3.29 c.c.
of 0.01 N. HCl.

Found.   8.9% N;   24.7% Br.

$C_{13}H_{25}O_2N_2Br$ requires 8.7% N; 24.9% Br.

It is readily soluble in all the organic solvents
and insoluble in water.

N-/

N-(p-phenyl arsinic acid)aminomalondi-n-amylamide.

The sodium arsanilate solution was heated with
4.97 g. of the preceding compound and 15 c.c. of
alcohol. A solid compound began to separate after
30 minutes and the heating was continued for a further
30 minutes.   The solid was filtered off, washed well
with dilute hydrochloric acid and recrystallised from
a large volume of 50% alcohol. It formed beautiful
small glistening plates which darkened at 275° and
melted with decomposition at 297°.   Yield 40% of
theory.

Analysis:

   0.1106 g. substance gave a titration of 9.82 c.c.

                                   of 0.0498 N. $Na_2S_2O_3$.

   6.927 mg. substance gave a titration of 4.40 c.c.

                                   of 0.01 N. HCl.

                  Found.   16.7% As;   8.9% N.

   $C_{19}H_{32}O_5N_3As$ requires 16.4% As; 9.2% N.

The arsinic acid gave thick clusters of needles
of the insoluble barium, calcium and magnesium salts.
The magnesium salt was slightly soluble.

Malondi-/

Malondi-iso-amylamide.

10.4 G. of ethyl malonate and 10 g. of iso-
amylamine were allowed to stand in a sealed tube
overnight.   Unlike the n-amylamide no crystallis-
ation took place. The tube was then heated in a
hot air furnace at 120° for 6 hours.   On evapor-
ation of the solution a paste was obtained which
after pressing on porous tile could be crystallised
from diluted alcohol or petroleum ether (b.p. 100-
120°), from which it separated in clusters of fine
needles, m.p. 74°.   Yield 50% of theory.

Analysis:

6.501 mg. substance gave a titration of 5.23 c.c.

of 0.01 N. HCl.

Found. 11.3% N.

$C_{13}H_{26}O_2N_2$ requires   11.6% N.

It is readily soluble in all the organic
solvents with the exception of petroleum ether
from which it crystallises and is insoluble in water.

Mono-/

Monobromomalondi-iso-amylamide.

To a solution of 2 g. of malondi-iso-amylamide in 10 c.c. of warm glacial acetic acid were slowly added 4.2 c.c. of a 10% (by volume) solution of bromine in acetic acid. The bromine was rapidly absorbed. After remaining for 10 minutes the solution was poured into a beaker containing 200 c.c. of ice cold water. The precipitated monobromo-malondi-iso-amylamide was filtered off, washed with water, dried and recrystallised from diluted alcohol. It formed fine prismatic needles, m.p. 110°.

Analysis:

3.500 mg. substance gave 2.023 mg. AgBr.

7.349 mg. substance gave a titration of 4.49 c.c.
of 0.01 N. HCl.

Found. 24.7% Br; 8.6% N.

$C_{13}H_{25}O_2N_2Br$ requires 24.9% Br; 8.7% N.

It is readily soluble in all the common organic solvents and insoluble in water.

N-/

N-(p-phenyl arsinic acid) aminomalondi-iso-amylamide.

The sodium arsanilate solution was heated with
4.97 g. of the preceding compound and 15 c.c. of
alcohol.   The arsinic acid separated after boiling
for 1 hour.   It was filtered off, washed well with
dilute hydrochloric acid and purified by solution
in N sodium hydroxide and reprecipitation with 50%
hydrochloric acid.   It was recrystallised from a
large volume of 50% alcohol.   It formed thick clusters
of needles which remained unchanged on heating to 260°.
Yield 40% of theory.

Analysis:

0.0767 g. substance gave a titration of 6.91 c.c.
of 0.0498 N. $Na_2S_2O_3$.

7.245 mg. substance gave a titration of 4.58 c.c.
of 0.01 N. HCl.

Found.   16.8% As;   8.9% N.

$C_{19}H_{32}O_5N_3As$ requires 16.4% As;   9.2% N.

The calcium salt formed hay like bunches of
needles/

needles, the barium salt bundles of small stout prisms and the magnesium salt stellate clusters of needles.   The magnesium salt is very slightly soluble compared with the insoluble calcium and barium salts.

Methyl bromomalonamide.

Methyl malondiamide (Meyer and Bock, Annalen, 1906, 347, 98) was brominated in acetic acid solution in a manner similar to malondi-iso-amylamide. The solution was concentrated considerably by distilling off the acetic acid in vacuo, and on cooling, the methyl bromomalonamide crystallised out. The solid was filtered off, washed with alcohol and ether and recrystallised from hot alcohol.   It formed small needles, m.p. 165°.   Yield 50% of theory.

Analysis:

0.1027 g. substance gave a titration of 20.87 c.c.
of 0.0503 N. $Na_2S_2O_3$.

5.820 mg. substance gave a titration of 5.93 c.c.
of 0.01 N. HCl.

Found/

<u>Found</u>.   40.9% Br;   14.3% N.

$C_4H_7O_2N_2Br$ requires 41.0% Br; 14.4% N.

It is readily soluble in alcohol and acetic acid, less in chloroform, ether, benzene and light petroleum, and insoluble in water.

Ethyl bromomalonamide.

This was prepared from ethyl malondiamide (Freund and Goldsmith, Ber., 1888, <u>21</u>, 1245) in a manner similar to its homologue methyl bromomalonamide.   After concentration of the acetic acid solution in vacuo, it was found convenient to precipitate the ethyl bromomalonamide by the addition of ether.   It crystallised from absolute alcohol in fine needles, m.p. 160°.

Analysis:

3.149 mg. substance gave 2.816 mg. AgBr.

6.102 mg. substance gave a titration of 5.81 c.c. of
0.01 N. HCl.

<u>Found</u>.   38.1% Br;   13.3% N.

$C_5H_9O_2N_2Br$ requires   38.2% Br;   13.4% N.

It/

It is readily soluble in alcohol and acetic acid, less in the other organic solvents and insoluble in water.

Ethyl malondimethylamide.

Diethyl ethyl malonate (Gattermann, Die Praxis des Organisches Chemikers, 12, Aufl. [Leipzig 1914] , s.177) was shaken with 33% aqueous methylamine until the mixture became homogeneous. After standing for a short time long white needles separated. These were filtered off and recrystallised from petroleum ether (b.p. 100-120°), m.p. 177°.

Analysis:

5.110 mg. substance gave a titration of 6.42 c.c.
of 0.01 N. HCl.

Found. 17.6% N.

$C_7H_{14}O_2N_2$ requires 17.7% N.

It is readily soluble in alcohol, chloroform and acetic acid and less in petroleum ether and water.

Ethyl/

Ethyl bromomalondimethylamide.

This was prepared by bromination of the
preceding compound in acetic acid solution like
malondi-iso-amylamide.   The acetic acid was
distilled off in vacuo and the solid residue
recrystallised from benzene.   It formed fine
needles, m.p. 130°.

Analysis:

3.000 mg. substance gave 2.362 mg. AgBr.

7.766 mg. substance gave a titration of 6.59 c.c.
of 0.01 N. HCl.

$$\underline{\text{Found}}.\quad 33.5\% \text{ Br};\quad 11.9\% \text{ N}.$$

$$C_7H_{13}O_2N_2Br \text{ requires}\quad 33.7\% \text{ Br};\quad 11.8\% \text{ N}.$$

It is readily soluble in alcohol and acetic
acid, less in benzene and light petroleum, and
insoluble in water.

Behaviour/

Behaviour of alkyl bromomalonamides with p-arsanilic acid.

Several of the alkyl bromomalonamides prepared
were heated with sodium arsanilate solution as in
the case of the bromomalonamides.   After continued
boiling, however, no separation of solid occurred.
On cooling, the alkyl bromomalonamides crystallised
out and on acidification with hydrochloric acid
some unchanged arsanilic acid was obtained.   No
better success was obtained by the addition of one
molecular quantity of potassium iodide in the hope
that the bromine atom would be replaced by the
iodine and render the compound more active.   After
boiling for some time the solution became dark with
the separation of free iodine which could be
decolourised with sodium thiosulphate.   Following
this interesting observation it was found possible
to extend the method of bromine estimation given
by Backes, West and Whiteley, J.C.S., loc. cit.) to
include the alkyl bromomalonamides.

Behaviour/

Behaviour of bromomalonamides with o-arsanilic acid.

A solution of o-arsanilic acid was made by
dissolving a weighed quantity in sufficient N sodium
hydroxide to make the monosodium salt.   Bromo-
malonamide and bromomalondi-n-propylamide were
separately heated with a quantity of the arsanilate
solution.   After prolonged boiling no separation of
solid took place in either case.   The bromomalonamide
and bromomalondi-n-propylamide crystallised out on
cooling the mixture.   These were filtered off and
the filtrate was acidified with dilute hydrochloric
acid.   The o-arsanilic acid in each case was
recovered unchanged.   Modification of the conditions
by the addition of sodium iodide was also unsuccess-
ful.   Perhaps owing to the proximity of the large
arsenic acid residue it was impossible to introduce
further groups in the ortho position.

p-Nitro diphenyl ether.

According to the method of Haeussermann and
Teichmann (Ber., 1896, 29, 1446) p-chloronitro-
benzene (31.5 g.), phenol (31.5 g.) and potassium
phenate/

phenate (31.5 g.) were mixed in a flask and heated
in a castor oil bath under a reflux water condenser
for 5-6 hours at 150°.   The dark brown melt was
treated with sufficient 2N sodium hydroxide to
render it strongly alkaline.   The solid was
filtered off and washed well with sodium hydroxide
to remove any unchanged phenol.   The reddish brown
solid was then mixed with some water and steam
distilled to remove any unchanged chloronitrobenzene
which is volatile in steam.   The residue was first
crystallised from rectified spirit, but subsequently
it was found more convenient to prepare a super-
saturated glacial acetic acid solution, to
inoculate this solution with a crystal of the
compound, then to filter off the crystals and wash
out the acetic acid with alcohol.   In this way
white shining plates were obtained, m.p. 61°.
It is easily soluble in ether, benzene and glacial
acetic acid and less soluble in cold alcohol.
Yield 20% of theory.

p-Amino/

p-Aminodiphenyl ether.

According to the method of Haeussermann and
Teichmann (Ber.,loc. cit.) 21.5 g. of the preceding
compound were dissolved in 200 c.c. of 90% alcohol.
35.4 G. of granulated tin were added and then
gradually an amount of concentrated hydrochloric
acid.   The solution rapidly became darker in colour
and heating was continued until the solution again
became clear.   The solution was diluted with water
and the alcohol removed in vacuo.   Sulphuretted
hydrogen was then passed through the hot solution
to decompose the stannochloride.   The stannous
sulphide was filtered off while hot and the filtrate
was concentrated somewhat and allowed to cool.
White needles of the amine hydrochloride separated.
These were filtered off and decomposed with sodium
hydroxide.   The free amine was then extracted with
ether.   During the extraction the aqueous layer
exhibited a blue colour and the ethereal layer a
pink colour.   The ether layer was removed, washed
with sodium carbonate and dried with anhydrous
potassium carbonate.   The ether was evaporated off
and the residue crystallised on standing.   It
crystallised/

crystallised from hot water with difficulty in fine
white needles, m.p. 84°.   Yield 30% of theory.   A
method of reduction employing iron and hydrochloric
acid gives much better yields of similar amines
(Roberts and Turner, J.C.S., 1925, 127, 2009).

The amine sulphate was prepared by heating
5.6 g. of p-aminodiphenyl ether with 18 c.c. of 5N
sulphuric acid and sufficient water to render
solution complete.   The solution was filtered
rapidly, using a hot water funnel, and the amine
sulphate crystallised from the filtrate on cooling
in a mass of white needles.   Larger   crystals
formed long plates felted together.   On heating
they darkened above 230°.

Analysis:

4.466 mg. substance gave 10.125 mg. CO_2 and 2.040
mg. H_2O.

Found.   61.8% C;   5.1% H.

$C_{12}H_{12}O_3NS_{\frac{1}{2}}$ requires   61.6% C ;   5.1% H.

Diphenyl/

Diphenyl ether p-arsinic acid.

According to the method of Schmidt (Annalen, 1920, 421, 170) 11 g. of p-amino diphenyl ether. were converted to the amine sulphate as in the previous experiment. This step was merely to ensure purification of the amine. The amine sulphate with the slight excess of sulphuric acid was diazotised at 0° with 60 c.c. of N sodium nitrite in presence of 120 c.c. of water. The solution was then cooled to -5°C. and with strong stirring 12 c.c. of 5N potassium hydroxide were run in and then very gradually 36 c.c. of potassium arsenite solution to which had been added 2.4 c.c. of 5 N sulphuric acid. This addition took place with evolution of nitrogen and frothing which arose to the rim of the beaker. The reaction mixture was allowed to stand overnight. The solution was then made alkaline with sodium hydroxide and filtered from a considerable amount of tar. The filtrate was then acidified with 50% hydrochloric acid and the free arsinic acid crystallised in clusters of needles on stirring. It was purified by solution in the minimum amount of/

of N sodium hydroxide and reprecipitation with 50%
hydrochloric acid after stirring in the cold with
animal charcoal.   Finally it crystallised from hot
water in small glistening plates which remained un-
changed on heating to 260°.   Yield 6% of theory.

Analysis:

   4.532 mg. substance gave 8.155 mg. CO_2 and 1.520
                                            mg. H_2O.

                        Found.   49.1% C;   3.73% H.

   $C_{12}H_{11}O_4As$ requires   49.0% C;   3.77% H.

     The calcium salt crystallised in clusters
of small prisms.   The barium salt is more soluble
and the magnesium salt readily soluble.

Nitration of diphenyl ether arsinic acid.

     According to the method of Michaelis (Annalen,
320, 321) 1 g. of diphenyl ether arsinic acid was
added in small portions with continual shaking to a
mixture of 5 g. of concentrated sulphuric acid and
4 g. of fuming nitric acid at room temperature. The
yellow/

yellow coloured clear solution was then poured into
about ten times its volume of cold water and after
stirring for a short time the nitro acid separated
in very beautiful shining needles.   The yield was
almost quantitative on working with small quantities.
The acid was purified by recrystallisation from hot
water to which a little alcohol had been added when
it formed beautiful clusters of small needles.

Analysis:

4.711 mg. substance gave 5.835 mg. CO_2 and 0.740 mg. H_2O.
3.398 mg. substance gave 0.276 c.c. N_2 at 21° and 760 mm.

	C	H	N
Found.	33.8%	1.8%	9.4%
$C_{12}H_{10}O_4As.NO_2$ requires	42.5%	3.0%	4.1%
$C_{12}H_9O_4As(NO_2)_2$ "	37.5%	2.4%	7.3%
$C_{12}H_8O_4As(NO_2)_3$ "	33.6%	1.9%	9.8%

The nitro compound obtained was therefore a tri-
nitrodiphenyl ether arsinic acid.   It was impossible
to fix definitely without hydrolysis the orientation
of the three nitro groups.

2/

2:4 dinitro diphenyl ether.

1:2:4 Chlorodinitrobenzene (20.25 g.) were
placed in a flask and a hot solution of 15 g. of
potassium phenate in 15 g. of phenol was poured in.
A vigorous reaction took place with a separation of
solid.   The mixture was heated in an oil bath at
150° for 5-6 hours.   The solution was allowed to
cool and made alkaline with sodium hydroxide.   The
solid present passed into solution and the aqueous
layer gave a strong test for chloride.   The brown
oil which separated was steam distilled to remove
any chloronitrobenzene.   It was then extracted
with ether, washed well with sodium carbonate and
dried with anhydrous potassium carbonate.   The
ether was removed on the water bath and a yellow
oil remained which on standing slowly crystallised.
It was pressed on porous tile to remove the adherent
oily material.   It crystallised from rectified
spirit in long thin prisms, m.p. 69°.   Yield 14 g.,
50% of theory.

Analysis /

Analysis.

4.909 mg. substance gave 9.965 mg. CO_2 and 1.380 mg. H_2O.

3.590 mg. substance gave 0.331 c.c. N_2 at 22.5° and
757 mm.

Found. 55.4% C; 3.12% H; 10.6% N.

$C_{12}H_8O_5N_2$ requires 55.4% C; 3.08% H; 10.8% N.

It is non-volatile in steam, soluble in most
organic solvents, easily crystallised from alcohol
in pale yellow needles or prisms and insoluble in
water.

Attempted reduction of 2:4 dinitro diphenyl ether.

To reduce one nitro group only the method of
reduction with concentrated ammonia and sulphuretted
hydrogen in alcoholic solution was employed. The
chief trouble was the insolubility of the dinitro
compound in cold alcohol, and it failed to pass into
solution on treatment with ammonia and sulphuretted
hydrogen. When a warm alcohol solution was used
tar formation invariably occurred and no crystalline
product/

product could be isolated from the mixture after
several attempts.

p-Acetylamino diphenyl ether.

p-Amino diphenyl ether (1 mol.) was boiled
under a reflux water condenser with acetic anhydride
(1 mol.) for 30 minutes.   The solution was allowed
to cool, poured into a considerable volume of water
and any unchanged acetic anhydride decomposed with
sodium hydroxide.   The oil which settled at the
bottom of the beaker soon solidified.   The solid
was filtered off, washed well with water and re-
crystallised from diluted alcohol.   It formed
lustrous plates, m.p. 107-108°.   Yield almost
theoretical.

Analysis:

4.928 mg. substance gave 13.330 mg. CO_2 and 2.540 mg. H_2O.

3.164 mg. substance gave 0.174 c.c. N_2 at 24° and
758 mm.

Found.   73.8% C; 5.73% H; 6.30% N.

$C_{14}H_{13}O_2N$ requires   74.0% C; 5.73% H; 6.17% N.

It/

It is soluble in most of the common organic solvents and insoluble in water.

Nitro p-acetylamino diphenyl ether.

2.27 G. of the preceding acetylamino compound were mixed with 2 c.c. of glacial acetic acid and 0.9 c.c. of concentrated nitric acid were added with shaking. All the solid passed into solution. The mixture was boiled under reflux for 1 hour. It was then allowed to cool but did not crystallise. A fairly large volume of water was added and the nitro compound was extracted with ether. The ether layer was separated off, washed with sodium carbonate and dried with anhydrous potassium carbonate. The ether was removed on the water bath leaving a red oil which crystallised on standing. The crystals were somewhat contaminated with tarry matter, but after pressing on porous tile, a quantity of yellow crystals was obtained. The nitro compound crystallised from rectified spirit in beautiful pale yellow needles, m.p. 101°.

Analysis/

Analysis:

5.011 mg. substance gave 11.385 mg. CO_2 and 1.900 mg. H_2O.

2.820 mg. substance gave 0.254 c.c. N_2 at 22.5° and
754 mm.

Found.   62.0% C; 4.2% H; 10.3% N.

$C_{14}H_{12}O_4N_2$ requires   61.8% C; 4.4% H; 10.3% N.

It is readily soluble in the common organic
solvents and insoluble in water.

Hydrolysis of nitro p-acetylamino diphenyl ether.

The above nitro acetylamino diphenyl ether was
boiled with ten times its weight of alcoholic
hydrochloric acid until on pouring into dilute
hydrochloric acid no precipitation or turbidity
occurred.   The solution was then poured into a
large volume of water and the nitroamine extracted
with ether.   The ether layer was removed, washed
with sodium carbonate and dried with anhydrous
potassium/

potassium carbonate. The ether was removed and a
red somewhat tarry oil remained which did not
crystallise on standing in the ice-chest. Attempts
to prepare the hydrochloride by the addition of a
small quantity of alcoholic hydrochloric acid only
resulted in the formation of a thick tarry substance
which could not be crystallised.

By the addition of picric acid solution, a
yellow crystalline picrate was obtained insoluble in
cold alcohol, but insufficient of this material was
obtained in the first trial for purification and
analysis. Further experiments would have yielded
sufficient material for the application of the Bart
reaction.

SUMMARY/

SUMMARY

1. Some benzene derivatives containing long aliphatic
    side chains have been prepared.   Such amino
    compounds did not take part in the Bart reaction.

2. A series of N-substituted aminomalonamide phenyl
    arsinic acids have been prepared and their
    therapeutic activity tested on an experimental
    trypanosome infection in mice.

3. Several alkyl bromomalonamides have been pre-
    pared but these would not condense with p-
    arsanilic acid.

4. Attempts to prepare succinamide arsinic acids
    and the utilisation of o-arsanilic acid in the
    general condensation met with failure.

5. A short study has been commenced in the diphenyl
    ether series and a few new compounds prepared.

In conclusion the author wishes to express
his thanks to Professor Barger for his continued
interest and for much helpful advice and encourage-
ment during the course of the investigation.