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Organolead compounds

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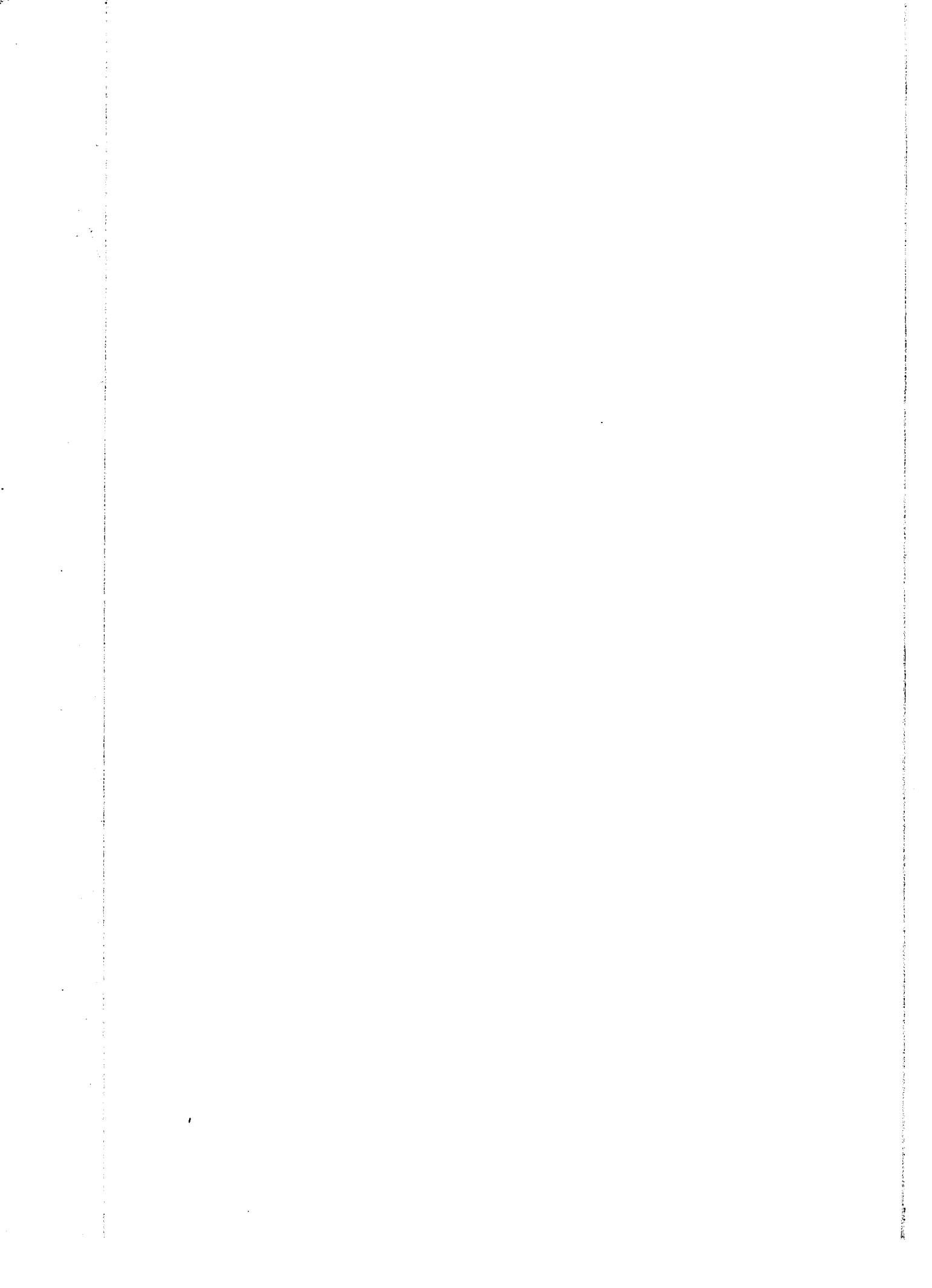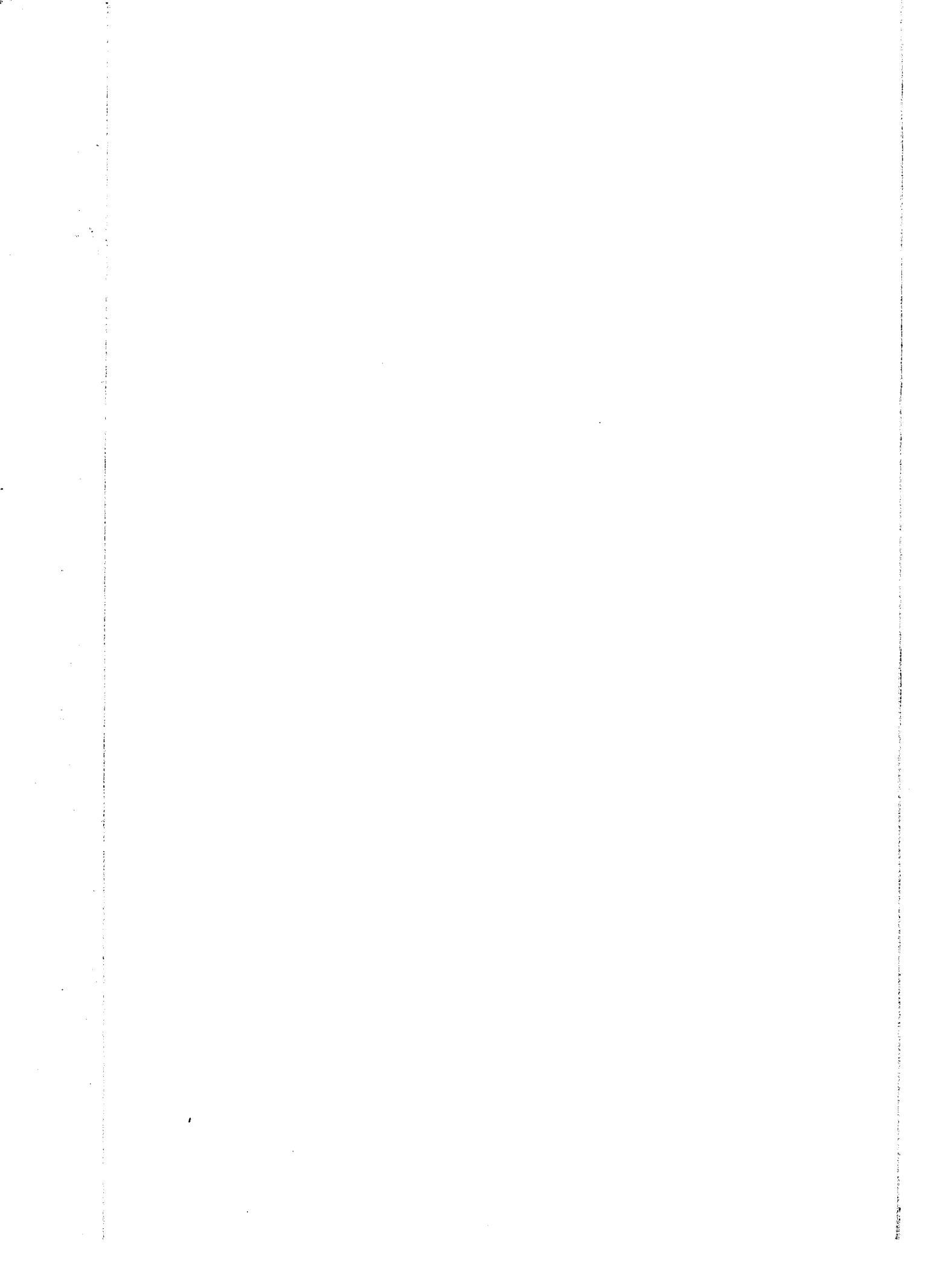
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ORGANOLEAD COMPOUNDS

BY

Jack D. Robinson

A Thesis Submitted to the Graduate Faculty
for the Degree of

DOCTOR OF PHILOSOPHY

Major Subject   Organic Chemistry

Approved

In charge of Major work

Head of Major Department

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A. ORGANOLEAD COMPOUNDS IN CANCER THERAPY

INTRODUCTION

Compounds of lead offer a promising field for research. During the past few years, special attention has been paid to their use as anti-knock reagents in internal combustion engines, as fungicides in the treatment of plant diseases and as compounds which may be of possible use in cancer therapy. This work was undertaken to study organolead compounds with reference to their possible use in these fields.

Cancer is probably one of the most dreadful diseases from which man suffers. While tuberculosis causes more deaths, the methods of treatment are fairly well known. During the years between 1870 and 1880 the death rate in cancer was 40 per hundred thousand in Liverpool. In 1924 the rate was 112 per hundred thousand, an increase of 280 per cent. One of the largest life insurance companies on the Pacific Coast places cancer fourth as the cause of death. In New Zealand, cancer is responsible for more deaths than any one other cause except organic heart disease. In 1922 it was 85.2 per hundred thousand and in 1925 it had risen to 90.8.

The reported increase in prevalence of disease, however, may be explained in two ways. In the first place, cancer is essentially an ailment of the elderly individual and so the increased life that we may expect gives cancer a chance to develop. Then, as is well known, diagnosis of disease in past

years has not always been accurate and it is highly probable
that many persons have died of cancer without knowing it. But
there is no doubt at all of the seriousness of cancer and its
prevalence.

The sad part of the matter is that at present there are
only so few instruments that may be used in the treatment of
cancer and that they result in such a high percentage of
failures. Any method which will reduce this percentage will
be of tremendous assistance to the medical profession and to
the public suffering from this disease. This work was under-
taken to study the preparation of organolead compounds which
might be used in cancer therapy.

Metals were first used in the treatment of malignant
diseases by Torres in 1904 but there was little interest at-
tached to this type of material until the work of Wassermann
and Keysser (1), who in 1911 used compounds of selenium and
tellurium. These compounds were found to be effective when
used to treat animal tumors, but when used on man the effective
dose was found to coincide with the lethal dose. Neuberg (2)
was influenced by Wassermann's results to test other metals
which he used in the colloidal state. Some of the metals used
were lead, copper, silver, and cobalt. He had excellent suc-
cess with animals but could not treat humans without poisoning

(1) Wassermann and Keysser, Deutsche med. Wchnschr., 37:2389
     (1911).
(2) Neuberg, Deutsche med. Wchnschr., 38:375(1912).

them. Caspari (3) was the first to report a slight improvement in one case of carcinoma of the tongue when treated with an aniline-silver compound. Izar (4) and Basile (5) were able to cure rat sarcomas with colloidal sulfur but had no success with man, when afflicted with this disease.

Colloidal silver was used by Kausch (6) but he had to abandon its use because of severe reactions which occurred, while Rohdenburg (7) obtained no therapeutic results from a commercial preparation of colloidal silver.

Among other copper preparations tried by Loeb (8) and Gaube (9) was cuprase which is colloidal copper hydrate. Although Loeb could obtain no permanent results Gaube noticed considerable improvement in patients, but his observations were over too short a time to be of value. Richard Weil (10) studied the problem in considerable detail and came to the conclusion that colloidal copper compounds did as much damage as they did good in the treatment of malignant disease. Colloidal gold has been used by Carl Lewin (11) who found that he could treat transplanted mouse tumor successfully but had no

(3) Neuberg, Caspari, and Löhe, Berl. klin. Wchnschr., 49:1405 (1912).
(4) Izar, Ztchr. f. Immunitätsforsch. u. exper. Therap.(1)15:238 (1912).
(5) Izar and Basile, ibid., 18:64(1912).
(6) Kausch, Arch. f. klin. Chir., 102:159(1913).
(7) Rohdenburg, J. Med. Research, 26:331(1915).
(8) Loeb, Interstate Med. J., 19:1015(1912).
(9) Gaube, La Cuprase et le Cancer, Paris, (1913).
(10) Weil, J. Am. Med. Assoc., 61:1034(1913).
(11) Lewin, Berl. klin. Wchnschr., 50:541 (1913).

success with human patients. Gudzent (12) found that treatment with silver compounds did not enhance the effectiveness of radium or the roentgen ray.

This was the situation in 1920 when W. Blair Bell (13) started treatment of human cancer with colloidal lead. The reasoning that led him to the choice of lead rather than some other metal is worthy of consideration at this time. The use of lead as a specific reagent was first called to his attention by the abortions induced by lead poisoning. He had observed that among people working in lead mines, cancer was singularly rare and abortions unusually frequent. Bell was not satisfied with the theories that have been advanced to account for abortions but believed that this was due to some specific action upon the cells of the chorionic villi. These cells are young, rapid growing and in many ways similar to carcinoma cells. He spent considerable time analyzing the foetus for the material that was responsible for inhibition of these chorionic cells. He reports a complete failure in this direction.

Bell's theory of abortions was that the cells of the chorionic villi were responsible for the nourishment which the foetus receives and that abortion resulted from the lack of nourishment of the foetus due to the suppression of the activ-

(12) Gudzent, Strahlentherapie, 11:277(1920).
(13) W. B. Bell, Lancet, 206:267(1924).

ities of these cells (13). He believes that in the case of
lead poisoning the action of these cells is inhibited by the
action of lead upon them specifically. With this hypothesis
he began the series of experiments which led him ultimately to
the use of colloidal metallic lead in the treatment of cancer.

His next experiments were carried out to see what cells
were especially affected by lead. He found that the injection
of lead in a rabbit caused the gradual but complete disappear-
ance of the spermatozoa from the testis. He was able to show
rather conclusively that lead had a specific effect upon a
certain type of cells. Lead and the compounds of lead were ef-
fective in retarding the growth of tadpoles when quite young,
germination of seeds, growth of hyacinth bulbs and all young
growing cells in general. Lead was found to affect blood
cells and nerve cells as well and was found to be much more ef-
fective on young cells than on old ones.

Since there is a certain type of cell that is affected by
lead, it is probable that there is something in common to them
all that is attracted by lead. Blair Bell found that in all
the cells considered there was a high phosphatid content (14)
and he assumed that this was the reason that lead was attracted
by them. He proved very clearly that the lead combined with
these phosphatids in a chemical combination (14). Besides this
factor which makes them all susceptible to the influence of

(14) Bell, Lancet, 203:1005(1922).

lead, all these cells are physiologically malignant. They are all young, rapidly growing vigorous cells expressing a sort of biological avatism. They are engaged primarily in the business of growing and gathering food for this growth. They know nothing of the niceties of behavior which govern the action of the "normal" cell, and are utterly ruthless in the means by which they gain their ends. Their life is a strenuous struggle for existence and everything must be sacrificed for this purpose. In this respect they are exactly like cancer cells as well as in their high lipin content (15). It was for this reason that Blair Bell began his research on the action of lead upon malignant tumor.

Bell (15,14) soon had an opportunity to test his theory on a human patient for in November, 1920, a young woman came to him with an inoperable, essentially hopeless tumor of the breast. He considered it legitimate to try the effect of lead. He injected a preparation of colloidal lead beginning with small amounts and gradually increasing the dose. The result was startling for the tumor began to shrink and in the course of a few weeks the breast had regained its normal size and appearance. The patient improved steadily and in a little more than a year was nursing a child at the breast which had apparently been utterly destroyed by cancer.

Bell did not publish this work but immediately started

(15) Bell, Lancet, 209:1003(1925).

intensive research along this line. When he did publish his results they made it very evident that many apparently hopeless cases of cancer could be quite successfully treated with colloidal lead. Another interesting discovery that he made was that patients who had become radio-resistant due to long treatment, became susceptible after treatment with lead. It must not be imagined that the treatment of cancer by lead had been worked out for there were many serious dangers and complications resulting from the use of this material. It is scarcely necessary to state that the line between the effective dose and the lethal dose was very narrow. Bell reported on 227 cases of cancer, most of which had been hopeless inoperable ones. From this number he returned 30 to their avocations, while the life of others was extended tremendously (16).

These results are all the more remarkable when one considers that Bell excluded no patient from this treatment because of the hopelessness of the case. As a matter of fact, he would not use the lead treatment in those cases which offered any hope of surgery or treatment with rays unless it was specifically asked for. While treatment with rays was found to be very effective in connection with the use of lead, the patient must first be activated by lead in order for the rays to be effective.

The reagent used in this work was a colloidal preparation

(16) Bell, Woolfenden, Cunningham and Herd, Lancet, <u>210</u>:537 (1926).

of lead (16,13) made by the method of Bredig and centrifuged
to remove large particles. This material did not keep more
than 48 hours and became more toxic with age. It is only
available to physicians having at their disposal rather exten-
sive laboratory equipment. For this reason, it has been dif-
ficult for this method to be tested out widely.

F. C. Wood (17) visited Dr. Bell and on his return tested
out his preparation on cancer animals. He found that this col-
loidal lead produced marked injury to the tumors. This report
was made in 1926 at Dallas and to Wood belongs the credit of
bringing the method to this country. One of the results of
this report was to interest Ullmann in the work and he has
done considerable along this line.

Ullmann (18) began his work by slightly modifying the
preparation of colloidal lead in such a way as to make it more
stable. He was able to ship his preparation short distances
and found that it could be used within a reasonable length of
time. He found, however, that the complications arising from
the use of this reagent were so alarming that he felt it ab-
solutely necessary to find some preparation less toxic. He
found this in colloidal lead orthophosphate.   This com-
pound was chosen for various definite reasons. In the first
place, (19) it is much less toxic to the patient as a whole and ap-

(17) Wood, J. Am. Med. Assoc., 87:717(1926).
(18) Ullmann, Radiology, 8:461(1927).
(19) Bischoff and Blatherwick, J. Pharmacol., 31:361(1927).

parently does not grow more toxic with age. It is quite stable and appears to have much the same effect upon tumor as the colloidal preparation of metallic lead. This is explained by the assumption that all lead taken into the body is converted almost immediately into the insoluble lead orthophosphate. This salt is very slightly soluble while the acid salt is one hundred times as soluble. Malignant tumors contain a definite amount of lactic acid and are more acid than normal tissue. It would be expected, therefore, that the malignant tumors would be more susceptible to the lead in this form than the normal tissues. This was found to be the case.

Before lead orthophosphate had been decided upon as the reagent to be used in Ullmann's work, a group of chemists, Bischoff, Maxwell, Evans, and Nuzum (20), made a study of the toxicity of various lead compounds given intravenously. They found that the compounds of lead could be divided into four general classes depending upon their action upon the blood. The most toxic group was composed of such compounds as ionic lead compounds, colloidal lead hydroxide, metallic lead, lead glycerophosphate, oleate and stearate. The next most toxic group includes colloidal lead oxychloride, oxycarbonate, and carbonate. The third group is made up of tetraethyl lead and triethyl lead chloride. These compounds bring about only a slight drop in hemoglobin even when the lethal dose is ap-

(20) Bischoff, Maxwell, Evans and Nuzum, J. Pharmacol., 34:85 (1928).

proached. Group four is the least toxic and consists of tri-lead phosphate, dilead phosphate and lead sulfide. These compounds are all very insoluble and produce no noticeable effect upon the red cells of the blood at all.

With the preparation finally decided upon, colloidal lead orthophosphate, Ullmann (21,22) was able to do remarkable things in the treatment of human cancer. He has given a report of his results and as he admits, they are not good statistics but are very encouraging nevertheless. The point to be borne in mind when considering them is that he did not refuse the treatment to any one regardless of how complicated the other organs had become with metastases.

He found in his work that treatment by means of lead compounds could be materially augmented by the use of X-rays. In all the patients treated by him lead was used in connection with X-rays. He found that patients, who had received treatment with X-rays until they would show no more reaction to this form of treatment, could be irradiated quite effectively after injection of the colloidal lead phosphate. He gives as his very definite impression the idea that patients who have been treated with lead require much less morphine than untreated ones in the same condition.

An interesting question is when the irradiation should be

(21) Ullmann, J. Am. Med. Assoc., 92:18(1929).
(22) Ullmann, Surgery, Gynecology and Obstetrics, 46:119(1928).

given after lead treatment. Ullmann (21) has followed the recommendations of Mottram (23) that irradiation should be given on the third and fourth day following lead treatment.

The treatment of cancer by lead is not simply a matter of injecting a specified amount of a prepared reagent and then waiting for results. Rather the patient must be watched very carefully and given special care. It is safe to say that each patient requires a specific kind of management. Ullmann (24) has published a paper in which he gives some very good suggestions for the care of the inoperable cancer patient when under treatment. He finds that these patients should be made to exist upon a basic diet or a diet which results in basic reactions.

Ullmann (21) feels that the problem of lead therapy in the treatment of cancer is by no means solved although he looks forward to startling results by means of such treatment. He is very optimistic which is refreshing when the seriousness of the problem is considered. In this optimism, he is not joined by all physicians. This can be explained, however, when one considers the technique that must be developed before results may be expected.

Drs. Colston, Waters and Gay (25) of Baltimore are decidedly discouraging in their report of the treatment of cancer

(23) Mottram, Brit. Med. J., 1:132(1928).
(24) Ullmann, Reprinted from Radiology, 3:497(1924).
(25) Waters, Colston and Gay, J. Am. Med. Assoc., 92:14(1929).

with colloidal metallic lead. They were not at all convinced
that the effect upon the tumors they treated was due to lead
but believed that the results were due to the high voltage
roentgen therapy. This feeling is shared by Drs. Soiland,
Costolow and Meland (26) of Los Angeles. They make the state-
ment that they do not believe that lead therapy is the solution
to the cancer problem.

Knox (27) of New York has treated cancer after the method
of Blair Bell and finds it to be quite effective. She agrees
with Bell that in a few persons with advanced inoperable can-
cer definite arrest of the disease may be obtained by the com-
bination of lead and roentgen therapy.

And so the matter stands. It is very evident that there
is much to be done on this problem. Even the most skeptical
of the critics of this treatment of cancer admit that lead and
its compounds are powerful agents in the destruction of tumor
tissue. The problem then becomes one of synthesizing the
proper compound and administering it in the proper manner. The
proper compound will be undoubtedly found by a chemist but he
must appreciate the properties that an ideal compound should
have. The advise of the medical profession will prove invalu-
able in this work.

Bell (13,14) insists that a compound to be effective
should be injected into the blood stream in order to arrest

(26) Soiland, Costolow and Meland, J. Am. Med. Assoc., 92:104
     (1929).
(27) Knox, ibid., 92:106(1929).

metastases. He points out that a compound cannot be specific for one class of cells or one kind of one class but this difficulty is overcome by using lead and its compounds since they are attracted by the malignant cells because of their high phospholipin content. He proposes as the ideal compound one which will deliver lead slowly to the highest bidder, which in this case is the cancer cells rich in phospholipins. This points to a compound of lead soluble in water or blood serum which will ionize quite slowly.

Bischoff, Maxwell, Evans and Nuzum (20) give a very good discussion of the properties an ideal lead compound should have. They claim that the ideal lead combination should be low in toxicity or the same order as the phosphate used by Ullmann. Besides this it should be able to ionize at a very low acidity such as is found in the cancer cell. Most important of all this compound should concentrate in the tumor itself. They recommend fat-soluble lead compounds such as an organolead compound. They mention as being of this class, tetraethyl lead and triethyl lead chloride.

The material given in the following pages is a description of the various attempts that have been made to prepare derivatives of tetraethyl lead that are water soluble.

EXPERIMENTAL

Series of Triethyl Lead Salts

Historical

The materials used in cancer therapy have been used in a colloidal state which rather limits their use to institutions having a highly technical laboratory. Even then, as is well known, it is quite possible that experiments in this field cannot be duplicated by different laboratories or even by the same laboratory. Also, a colloidal system is very sensitive to factors not easily controlled and is quite unstable at all times. The properties of colloidal lead are variable with time and so there can be no such thing as a stock reagent. Altogether a compound forming a solution with all its inherent virtues seems preferable.

A series of compounds having the type formula $(C_2H_5)_3PbO\overset{O}{\overset{\|}{C}}R$, where R represents the group of any acid, has been prepared. The methods of Browne and Reid (28) were followed in the preparation of these compounds using silica gel as a catalyst in the reaction of tetraethyl lead and an acid

$$(C_2H_5)_4Pb + RCOOH \longrightarrow (C_2H_5)_3OOCR + C_2H_6 \ldots \ldots (I)$$

where possible, and the double decomposition in aqueous solution of triethyl lead acetate with the sodium salt of the acid

$$(C_2H_5)_3PbOOCCH_3 + NaOOCR \longrightarrow (C_2H_5)_3PbOOCR + NaOOCCH_3 \ldots (II)$$
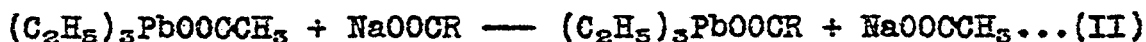
when necessary. These compounds were all crystalline

(28) Browne and Reid, J. Am. Chem. Soc., 49:830(1927). These authors make proper acknowledgment of previous work.

but with a range of melting temperatures which varies with the
rate of heating. This verifies the description of this type
of compound given by Browne and Reid (28). These compounds are
very disagreeable to work with since in the form of dust or
volatilization products they induce sneezing, nasal secretion
and tears.

Six representative compounds of this type have been tested
for toxicity and reaction of rats. The results are not en-
couraging but do not preclude the use of these compounds in
cancer therapy. They are not especially soluble in water;
their solubilities range from 0.25% to 1.0%, and only two pre-
cipitate serum. They are quite toxic and when injected intra-
venously, induced considerable pain while the animals used (rats)
become very quarrelsome. When injected intramuscularly, they
produce sterile abscesses and great local irritation. The
animals dying soon after injection show a black precipitate in
the blood stream of all organs, the nature of which was not
ascertained. The lead, however, appears to be precipitated to
an insoluble form from the solution. These compounds have not
been tested on experimental rat carcinoma and will be withheld
until less toxic compounds now in course of preparation become
available.

The compounds are all so very similar that no differentia-
tion is possible. They are much more like salts than like true
esters. They react ionically in water solution and so their
effect is probably due to the triethyl lead ion which is common

to them all rather than to the molecule as a whole. The results are not sufficiently encouraging to warrant more work on this particular type of compound.

Experimental

The majority of these compounds was prepared by the reaction of an acid on tetraethyl lead, but in one case (p-aminobenzoate) no reaction took place. When the acid was sparingly soluble in tetraethyl lead a little benzene was added to form a solution of the two in benzene, whereupon the reaction proceeded smoothly. In the case of triethyl lead p-aminobenzoate, the compound was prepared by treating the sodium salt of the acid with an aqueous solution of triethyl lead acetate. There was a reaction between tetraethyl lead and oleic and stearic acids but the products were waxes and could not be purified readily. It was not possible to prepare a triethyl lead salt of glycollic, thioglycollic, sulfanilic, anthranilic, p-chloromercuribenzoic or phthalic acids.

As we have mentioned before, the melting points of these compounds depend upon the rate of heating. The constants that are given here were taken as the bath was being heated at the rate of about $7 - 10^{\circ}$ per minute. In the purification of these compounds the suggestion of Browne and Reid (28) was followed and a sample of each crystallization was placed in separate capillary tubes and their behavior compared on the same thermometer at the same time during a melting point determination.

The preparation of triethyl ~~Lead~~ p-toluenesulfonate is typical and represents the procedure used in preparing all of the compounds. Any deviation from this procedure is indicated in the proper place.

Twenty-four grams (0.075 mole) of tetraethyl lead was mixed with 12 g. (0.070 mole) of p-toluenesulfonic acid in a 200 cc. balloon flask under a reflux condenser. A few crystals of silica gel were added and the mixture was heated on a boiling water bath. A smooth, vigorous reaction developed and gas was evolved in quantities. The rate of evolution of this gas was watched by bubbling it through water. After about twenty minutes the mass solidified and the evolution of gas almost ceased. The material was then dissolved in benzene, in which it is very soluble, and the filtered solution treated with 10 cc. of petroleum ether (B.P.40-60°). The crystals that formed were very pure and melted at 167-8°. The mother liquor was treated with more petroleum ether to obtain a second crop of equally pure crystals. The melting point of these crystals was unchanged after a second crystallization from a benzene-petroleum ether solution. The yield of pure material was 23 g. (71%). This compound as well as all others in this work, was analyzed for lead by the method of Gilman and Robinson (29).

Analysis: Calc. for $C_{13}H_{22}O_3SPb$: Pb, 44.52%. Found: Pb, 44.45 and 44.46%.

(29) Gilman and Robinson, J. Am. Chem. Soc., 50:1714(1928).

The constants, yields and analysis of the compounds prepared are given in the following table.

Table I

Compound	m.p.	Yield %	Analysis for lead Calc.%	Found %
Salicylate	83-91°	55	48.03	47.51-47.47
Furoate	153-4	68	51.11	50.97-50.87
Phenylacetate	101-6	65	48.25	47.73-47.72
Furylacrylate	119-21	58	48.05	47.63-47.67
Thiosalicylate (30)	97-99	27	46.30	45.73-45.70
Monophosphate (33) $[(C_2H_5)_3PbOPO(OH)_2]$	not at 250°	77	52.93	52.73-52.51

Triethyl Lead p-Aminobenzoate (31): 5 g. (0.014 mole) of triethyl lead acetate (28) was dissolved in 63 cc. of water and the filtered solution added to a filtered solution of 6 g. (0.036 mole) of sodium p-aminobenzoate. A granular precipitate formed slowly which melted at 84-86° when crystallized from a benzene-petroleum ether solution. This melting point was unchanged by further crystallization. The yield of pure product was 3 g. (49%).

Analysis: Calc. for $C_{13}H_{22}O_2NPb$: Pb, 48.13%. Found: Pb, 48.00 and 47.90%.

(30) This reaction becomes violent unless diluted with 50 cc. of benzene.
(31) There is no reaction between p-aminobenzoic acid and tetraethyl lead in the presence of silica gel.

Several attempts were made to prepare triethyl lead salts
of glycollic, thioglycollic, sulfanilic, anthranilic, p-chloro-
mercuribenzoic and phthalic acids. None of these acids except
thioglycollic acid reacts with tetraethyl lead in the presence
of silica gel. Thioglycollic acid reacts explosively unless
benzene is added as a solvent and then the product of the
smooth reaction is a yellow solid, insoluble in organic sol-
vents with a melting point over 300°. When the sodium salts
of thioglycollic, sulfanilic, anthranilic, p-chloromercuri-
benzoic, and phthalic acids are dissolved in water and the
solution added to a solution of triethyl lead acetate in water,
the products are amorphous precipitates which are insoluble
in all organic solvents and which do not melt at 300°. In the
case of glycollic acid such treatment results in no precipi-
tate although the solution was held at -10° for a day. These
intractable precipitates all contain lead and are soluble in
sodium hydroxide and slightly soluble in water. They are
probably the lead salts of the acids although they were not
analyzed for lead.

Six representatives of this series of triethyl lead salts
were tested for toxicity and solubility in water and the re-
sults are given in Table II.

Table II

Compound	Solubility	M.T.D. (32)	M.L.D. (32)
p-Toluenesulfonate	0.5-1.0%	12-15 mgs.	15 mgs.
Salicylate	0.25	15-18	18-20
Phenylacetate	0.3	12-15	15
Furoate	0.3-0.4	12-15	15
p-Aminobenzoate	0.5-1.0	12-15	15
Furylacrylate	0.3-0.5	12-15	15-18

Conclusion

A series of triethyl lead salts of various organic acids has been prepared and their properties studied with a view to their possible use in cancer therapy.

(32) These values are given as mgs. per kg. of body weight of rats when injected in water solution intravenously.
(33) This compound was purified by washing with water to remove any phosphoric acid and with ether to remove any unreacted tetraethyl lead. This compound was prepared too recently to be tested which is unfortunate in view of Ullmann's (21) work on colloidal ortho lead phosphate. The compound is to be tested.

Compounds of Lead Containing the p-Bromophenyl Groups

Historical

In this work an attempt has been made to prepare compounds of lead containing a solubilizing group of such a nature that the compound could be dissolved in water and used for therapeutic purposes. There are various groups which could be used such as the sulfonic acid group, the amino and substituted amino groups, the hydroxyl group and the carboxyl group. Of these the carboxyl group was chosen.

One of the methods for preparing compounds with a carboxyl group is to pass dry carbon dioxide into a solution of the appropriate Grignard reagent. If a compound containing lead and a halogen which reacts with magnesium to form an RMgX compound could be synthesized, the preparation of the acid might be possible in this way. Various compounds containing the p-bromophenyl group have been prepared but the halogens do not react with magnesium to form an active RMgX compound.

The compounds, triphenyl p-bromophenyl lead, diphenyl di p-bromophenyl lead, tetra p-bromophenyl lead and triethyl p-bromophenyl lead, have been prepared by treating the appropriate organolead halide with a solution of p-bromophenylmagnesium bromide. The tetraphenyl lead used was prepared according to the directions of Gilman and Robinson (34). They also give methods for the preparation of triphenyl lead chloride, di-

(34) Gilman and Robinson, J. Am. Chem. Soc., 49:2315(1927).

phenyl lead dichloride, triethyl lead chloride and diethyl lead dichloride in excellent yields (35). The yield of the p-bromophenyl lead compounds was good as a general rule although in the case of tetra p-bromophenyl lead the yield was poor. This verifies the observation of Krause and Schmitz (36); that higher homologs of tetraphenyl lead cannot be prepared from lead chloride and the Grignard reagent in satisfactory yields (38). Krause (37) maintains that the formation of tervalent lead depends upon the molecular volume rather than upon the nature of the group.

Experimental

Triphenyl p-Bromophenyl Lead: 51.8 g. (0.10 mole) of solid triphenyl lead bromide was added to a solution of p-bromophenylmagnesium bromide prepared from 47 g. (0.2 mole) of p-dibromobenzene and 4.8 g. (0.2 mole) of magnesium in 150 cc. of dry ether. There was a smooth reaction and after refluxing and stirring the solution for one hour, it was poured on iced hydrochloric acid and the ether layer was separated and dried. The oil remaining after the ether had been removed crystallized from alcohol to give a pure product melting at 115°. There were 41 g. of crude material or 69%.

→ 51, 3112 (1929)

(35) Gilman and Robinson, J. Am. Chem. Soc., 1919. 1930
(36) Krause and Schmitz, Ber., 52:2165(1919).
(37) Krause, ibid., 54:2060(1921).
(38) Pfeiffer and Truskier, ibid., 37:1125(1904).

Analysis(29): Calc. for $C_{24}H_{19}BrPb$; Pb, 34.92%. Found: Pb, 34.33 and 34.47%.

This material was very carefully purified, freed from alcohol and used in several experiments to form, if possible, an RMgX compound. There was no color test (39) when it was refluxed for 60 hours in toluene-ether mixture with magnesium. When heated in a sealed tube at about 135° with activated magnesium (40) and ether; there was no color test. When triphenyl p-bromophenyl lead was mixed in ether with magnesium and a solution of ethylmagnesium bromide added to remove any impurities, there was no reaction with the magnesium. When carbon dioxide was added to this mixture, propionic acid was the only acid material isolated while about 75% of the triphenyl p-bromophenyl lead was recovered unchanged.

Diphenyl Di p-Bromophenyl Lead: There was a smooth reaction when 21 g. (0.04 mole) of solid diphenyl lead dibromide was added to an excess (0.1 mole) of p-bromophenylmagnesium bromide stock solution. The mixture was refluxed for one-half hour and poured on iced hydrochloric acid to hydrolyze. The ether layer was separated and the ether evaporated. The residual oil was crystallized from alcohol and 17 g. (63%) of a crude crystalline product was obtained m.p.111-113°. When recrystallized from alcohol this compound melted sharply at 123°.

(39) Gilman and Schulze, J. Am. Chem. Soc., 47:2002(1925) give a qualitative color test for the Grignard reagent which has been used throughout this work.
(40) Gilman, Peterson and Schulze, Rec. trav. chim., 47:19(1928).

Analysis: Calc. for $C_{24}H_{18}Br_2Pb$; Pb, 30.76%. Found: Pb, 30.65 and 30.80%.

This material was carefully purified and subjected to the same treatment as triphenyl p-bromophenyl lead but there was no evidence of the formation of a Grignard reagent in any experiment.

Tetra p-Bromophenyl Lead: This compound was prepared after the same general procedure as Gilman and Robinson (34) give for tetraphenyl lead. Fifty grams (0.18 mole) of lead chloride was added to a solution of p-bromophenylmagnesium bromide prepared from 118 g. (0.5 mole) of p-dibromobenzene and 12.2 g. (0.5 atom) of magnesium. To this solution, 250 cc. of benzene were added and the mixture, from which no ether had been removed, was refluxed for eight hours at 65°. The characteristic precipitate of lead formed and after hydrolysis with iced hydrochloric acid this sludge was extracted with hot benzene. The ether-benzene layer was separated and the solvent evaporated. The oily residue was a mixture which when crystallized from alcohol, yielded 8 g. (10.7%) of crude material m.p. 162-5°. When this material was purified from alcohol, it melted sharply at 187°.

Analysis: Calc. for $C_{24}H_{16}Br_4Pb$; Pb, 24.91%. Found: Pb, 24.68 and 24.38%.

This compound did not form a Grignard reagent when treated in the same way as the two previously described compounds.

Triethyl p-Bromophenyl Lead: 20 g. (0.06 mole) of solid

triethyl lead chloride was added to a solution of p-bromophenyl-
magnesium bromide prepared from 24 g. (0.1 mole) of p-dibromo-
benzene and 2.4 g. (0.1 atom) of magnesium. The reaction was
smooth and there was no evidence of the formation of unsaturat-
ed lead compounds. The solution was refluxed in ether for one-
half hour and then hydrolyzed with iced ammonium chloride solu-
tion. The ether layer was separated, dried with calcium chlor-
ide and evaporated. When the residual oil was heated under
3 mm. pressure in an atmosphere of nitrogen it decomposed
rather violently at an oil bath temperature of about 210° just
as a few drops had started to distill. There is little doubt
that the oil is largely triethyl p-bromophenyl lead but as yet
we have been unable to distill it. The attempts to distill
this compound were not made at very high vacuums. The lowest
pressure used was 3 mm. which was the best the system used
would produce. It is entirely possible that at very high
vacuums the oil could be distilled.

The oil from a second similar run was dissolved in dry
ether and the impurities destroyed with an excess of p-bromo-
phenylmagnesium bromide. The solution was then refluxed with
magnesium for four hours with no noticeable result. When car-
bon dioxide was led into the solution, the only acidic material
isolated was p-bromobenzoic acid. There was an appreciable
quantity of triethyl lead chloride formed from splitting the
triethyl p-bromophenyl lead with hydrochloric acid while the
reaction was being worked up. Hydrochloric acid will split

the lead-carbon linkage with ease. If the linkage is quite weak, dilute acid is sufficient while for a stable linkage like the one in a compound like tetraethyl lead, more concentrated acid is necessary (28).

Summary

Tetra p-bromophenyl lead, triphenyl p-bromophenyl lead and diphenyl di p-bromophenyl lead have been prepared and the compounds treated with magnesium. There is no evidence of the formation of a Grignard reagent even under rather strenuous conditions. Triethyl p-bromophenyl lead decomposed without distilling and did not react with magnesium to form a Grignard reagent.

Reformatsky Reaction

Introduction

In this work on water soluble lead compounds, one of the first classes of compounds to be considered was the group of acids. Such compounds are valuable in therapeutics because they may be injected intravenously in the form of their sodium salts. A reaction rather widely used in the preparation of organic acids and esters is the Reformatsky reaction. This reaction was originally used to condense α-bromoesters with a carbonyl group by means of zinc (41). Later magnesium was used as the condensing agent and the formation of an intermediate RMgX compound was postulated (42). Since organolead halides react with RMgX compounds it seemed entirely reasonable to expect them to condense with the α-bromoesters in the presence of a metal like zinc or magnesium. The product in case this reasoning is correct would be an organolead ester which should yield the acid easily on hydrolysis. In this way it would be possible to prepare a series of acids and study the effect of various configurations upon any therapeutic problem. Unfortunately, all attempts to prepare compounds of this nature resulted in failure. The magnesium was attacked and there was undoubtedly a reaction for there was sufficient heat evolved to cause the benzene-ether solution to boil. The product of

(41) Reformatsky, Ber., 20:1210(1887).
(42) Zeltner, ibid., 41:589(1908).

the reaction, however, in the case of triethyl lead chloride, was tetraethyl lead and some degradation product such as divalent lead and metallic lead.

The ester used in the greater part of this work was ethyl bromoacetate although ethyl α-bromopropionate was also used. The bromoacetate offers the most promise because in case there is a normal reaction the product will be a compound that has the lead linked to a primary carbon atom while in the case of the bromopropionic ester, the lead will be linked to a secondary carbon. Compounds containing a lead atom attached to a secondary carbon atom are very much less stable than in the case of a primary carbon-lead linkage.

Triethyl lead chloride was the organolead halide used most extensively in this work although one experiment was performed using triphenyl lead bromide. There was no more success attending this experiment than in the cases where triethyl lead chloride was used. The products were the same regardless of which bromoester was used and so it seems reasonable to assume that the lead ester was formed and then decomposed for each compound would have that one part of its molecule the same.

This reaction offered so much promise that a total of seven experiments were performed in an attempt to isolate the lead ester. They are so similar that only the results from one experiment will be given here and this may be considered typical of all the work.

Experimental

Twenty-five grams (0.077 mole) of triethyl lead chloride was dissolved in 150 cc. of benzene and 50 cc. of dry ether. The ether was added to facilitate the formation of the RMgX compound. Two and four-tenths grams (0.1 atom) of magnesium was added to the triethyl lead chloride solution and then 14.5 g. (0.08 mole) of ethyl bromoacetate was poured into the mixture. The magnesium became tarnished and in the course of one-half hour heat was evolved at an accelerating rate until the reaction had to be cooled to prevent it from becoming too vigorous. The magnesium was almost completely dissolved where-upon the heat of reaction died down and after the mixture was stirred and refluxed for one hour the solution was filtered from the magnesium and lead salts and the ether and benzene distilled off. No water was used to hydrolyze the mixture. The residual oil from the ether-benzene solution was vacuum distilled and 13 g. (53%) of tetraethyl lead B.P.82°/13 mm. was collected with no lower boiling fraction. This material was analyzed for lead by the method of Calingaert (43).

Analysis: Calc. for $C_8H_{20}Pb$; Pb, 64.08%. Found: Pb, 63.56 and 63.42%.

Dry hydrogen chloride was bubbled through a solution of 1.330 g. of this material dissolved in ether. The gas evolved was collected and the volume measured. A sample was exploded with oxygen and shown to be ethane. There was 94.5 cc. (cor-

(43) Private communication. See p.113, Part B, THIS THESIS.

rected)of this gas collected while the theoretical for tetra-ethyl lead, providing one ethyl group was removed by the hydrogen chloride, is 92.5 cc. This proves rather conclusively that the material is tetraethyl lead.

The benzene-ether distillate was redistilled using a Glinsky column in a search for ethyl acetate. No such fraction could be obtained and the vacuum distillation of the residual oil gave no fraction that might have been the unchanged ester. There was no residue after the tetraethyl lead had been distilled except a small amount of tar which contained lead. It is possible that during the decomposition of the lead ester, the ester fragments polmerized to form tar.

The salts were next examined to determine what part of the magnesium had been used and left in the form of compounds. All of the material that was filtered from the ether-benzene solution, was soluble in water except a small amount of metallic lead and magnesium. This water solution was treated with a stock ammonium acetate solution (44) and then with potassium dichromate to precipitate the divalent lead. The precipitated lead chromate weighed 2.1 g. (equivalent to 3 g. of triethyl lead chloride or 8%). The filtrate from the lead chromate was made alkaline with ammonium hydroxide and sodium phosphate was added to precipitate the magnesium as magnesium ammonium phosphate. This precipitate weighed 11.8 g. which is equiva-

(44) A stock ammonium acetate solution which is used throughout
this work is made up from 20 cc. of concentrated ammonium
hydroxide (sp.gr.0.9) and 50 cc. of 50% acetic acid.

lent to a large part of the magnesium added originally. The metallic residue was dissolved in dilute nitric acid. The nitric acid was neutralized with ammonium hydroxide and the solution then made acid with acetic acid. A solution of potassium dichromate was then added to precipitate the lead as lead chromate. The precipitate weighed 3 g. and is equivalent to 3 g. of triethyl lead chloride (12%).

The tar left from the distillation of the tetraethyl lead was extracted with ether and a solid infusible portion was left which was insoluble in all organic solvents and water (about 2 g.). The ether extraction was evaporated and an oil remained which crystallized from petroleum ether to form very pretty long needles. These needles decomposed about 125° and when dissolved in sodium hydroxide and reprecipitated with hydrobromic acid formed triethyl lead bromide m.p. 104° mixed melting point 103°. The yield was 5 g. (20%) of triethyl lead chloride. There was no evidence of any other product in this ether soluble oil.

In an effort to account for the formation of the tetraethyl lead, several critical experiments were carried out. These show that tetraethyl lead is not formed from the decomposition of triethyl lead chloride at high temperatures or from any reaction of triethyl lead chloride with the magnesium.

Twelve grams (0.036 mole) of triethyl lead chloride was heated in an oil bath under an atmosphere of nitrogen at 5 mm. pressure up to 160°. This condition was kept constant for

thirty minutes and in that time no tetraethyl lead distilled (45).

Twenty-four grams (0.073 mole) of triethyl lead chloride was dissolved in 100 cc. of benzene and 25 cc. of ether and 2.4 g. (0.1 mole) of magnesium was added. The mixture was stirred and refluxed for three hours. At the end of that time there was a little black residue which may have been metallic lead and the solution was turbid while the magnesium was slightly etched. The benzene layer was filtered and distilled. The residue was heated in an effort to distill any tetraethyl lead formed but there was none. It appears then that the tetraethyl lead is formed from the decomposition of the lead ester rather than from the decomposition of the triethyl lead chloride.

Conclusion

An equivalent quantity of magnesium reacted with ethyl bromoacetate and triethyl lead chloride and was largely recovered as magnesium ammonium phosphate.

Ninety-two per cent of the lead used in the reaction may be accounted for as tetraethyl lead, divalent lead, metallic lead, and unchanged triethyl lead chloride.

There was no compound isolated which would indicate what happened to the bromoester during the reaction.

(45) Calingaert, Chem. Reviews, 2:43(1925), describes the reaction of triethyl lead bromide during steam distillation. He says that this material decomposes to form tetraethyl lead under these conditions.

Malonic Ester Condensation

The malonic ester condensation has been much used for the preparation of organic acids because of the reactivity of the sodium derivative of the ester with organic halides. Since the halogen of an alkyl lead halide is very reactive, it would appear that a compound could be prepared by condensing the sodium derivative of malonic ester with triethyl lead chloride. Such a compound should give the dibasic acid readily on hydrolysis and by gentle heating be made to lose one carboxyl group and form the monobasic straight chain acid. This compound would be of very great importance for use in experiments on the treatment of cancer with organolead compounds. Unfortunately, triethyl lead chloride could not be made to condense with sodium malonic ester in any of the experiments tried. The results from a typical experiment will be given here.

The general procedure is the same as that recommended in "Organic Syntheses" (46). The absolute alcohol was prepared from reagent absolute alcohol and sodium. About 300 cc. of absolute alcohol was used to dissolve 3.45 g. (0.15 atom) of sodium. To this solution, 24 g. (0.15 mole) of ethyl malonate was added directly with stirring. A milky precipitate formed which might possibly have been the disodium derivative. After 50 g. (0.15 mole) of triethyl lead chloride had been added, the solution was stirred and refluxed for sixteen hours. At

(46) "Organic Syntheses", John Wiley and Sons, Inc., New York, 1925, Vol.IV, p.11.

the end of that time the solution was poured into 500 cc. of cold water and a solid which formed was filtered out. This solid, of which there was 7.5 g. (17%), was shown to be lead chloride by dissolving it in a stock ammonium acetate solution (42) and precipitating the lead as lead chromate by means of potassium dichromate. The alcohol-water solution was extracted repeatedly with ether while still alkaline and later when it had been made acid with hydrobromic acid. By distilling these various ether washings, the equivalent of 36 g. (72%) of triethyl lead chloride was recovered. The material was all identified by converting it to the bromide and taking mixed melting points with known triethyl lead bromide. From this distillation 9 g. of an oil was obtained which boiled 75-80°/9 mm. which contained lead and had an odor of ethyl malonate. It is probably a mixture of tetraethyl lead and ethyl malonate, the separation of which is not feasible because of the slight difference in boiling points. A lead analysis of this oil gave an average of 46.72% lead while the theoretical value for tetraethyl lead is 64.08%. It is apparent from these results that there is very little reaction between triethyl lead chloride and sodium malonic ester. The lead chloride may have been formed by the thermal decomposition of triethyl lead chloride.

Calingaert (47) reports that triethyl lead halides de-

(47) Calingaert, Chem. Reviews, 2:43(1925).

compose when heated in the presence of water to form tetraethyl lead, diethyl lead dihalide and lead halide. He gives as examples of this reaction triethyl lead bromide. In an effort to extend this generalization to triethyl lead chloride and triethyl lead hydroxide, a sample of each was subjected to steam distillation. It was found that there was no tetraethyl lead formed although Calingaert reports the reaction as being quantitative.

A sample of 10 g. of triethyl lead chloride was steam distilled from 100 cc. of water and 200 cc. of distillate was collected. There was no oil present or any material insoluble in water. This indicates that there is no decomposition of triethyl lead chloride to tetraethyl lead and also that triethyl lead chloride is not volatile in steam.

A similar experiment was performed on 10 g. of triethyl lead chloride dissolved in 25 cc. of 10% sodium hydroxide solution to form triethyl lead hydroxide. The distillate gave a neutral reaction to litmus paper and there was no insoluble matter present. This also proves that triethyl lead hydroxide is neither volatile in steam nor decomposed by it to tetraethyl lead.

In view of these results it is difficult to explain the presence of lead chloride formed during the malonic ester condensation.

Miscellany

Diethyl Cyclopentamethylene Lead $(C_2H_5)_2Pb\overset{CH_2-CH_2}{\underset{CH_2-CH_2}{\diagup}}CH_2$:
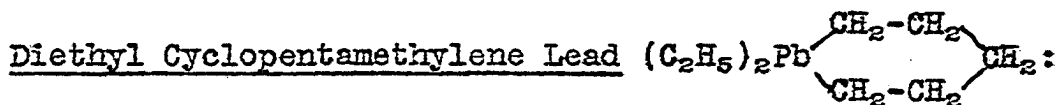
Grüttner and Krause (48) give directions for the preparation of this compound and give as its boiling point 111°/13 mm. A solution of Grignard reagent was prepared from 25 g. (0.175 mole) of pentamethylene chloride in 200 cc. of ether and 7.8 g. (0.32 mole) of magnesium according to the directions of Hilpert and Grüttner(49). The reaction was smooth and slow and the yield was probably in the neighborhood of 85%. To this solution which had been refluxed for six hours, 47.5 g. (0.14 mole) of diethyl lead dichloride was slowly added. This caused the following reaction to take place.

$$(C_2H_5)_2PbCl_2 + C_5H_{10}(MgCl)_2 \longrightarrow (C_2H_5)_2Pb\overset{CH_2-CH_2}{\underset{CH_2-CH_2}{\diagup}}CH_2\ldots\ldots III$$
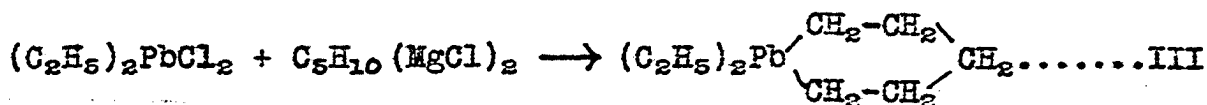
The mixture was refluxed for some time after the rather vigorous reaction had abated and was then hydrolyzed with iced ammonium chloride. The ether layer was fractionated and 9 g. (19%) of diethyl cyclopentamethylene boiling at 96°/7 mm. was collected. This material was used in the preparation of triethyl ε-bromoamyl lead.
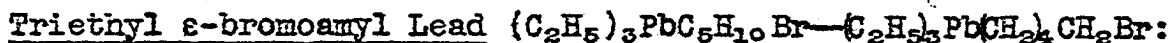
Triethyl ε-bromoamyl Lead $(C_2H_5)_3PbC_5H_{10}Br$—$(C_2H_5)_3Pb(CH_2)_4CH_2Br$: This compound was also prepared according to the directions of

(48) Grüttner and Krause, Ber., 49:2666(1916).
(49) Hilpert and Grüttner, ibid., 47:177(1914).

Grüttner and Krause (48) who give as the boiling point, 167°/13mm.
A solution of 30 g. (0.09 mole) of diethyl cyclopentamethylene
lead in 300 cc. of absolute ether was prepared and cooled with
an excess of carbon dioxide snow. A solution of 16 g. (2 equi-
valents) of bromine in ether was similarly cooled and added to
the first solution with rapid stirring until the color of bro-
mine just persisted. The solution was allowed to come to room
temperature and was then filtered. After the ether solution
had been concentrated to about 100 cc., an excess of stock
solution of ethylmagnesium bromide was added. The equations
for these reactions are given below.

$$(C_2H_5)_2Pb \overset{CH_2-CH_2}{\underset{CH_2-CH_2}{\diagup\diagdown}} CH_2 + Br_2 \longrightarrow (C_2H_5)_2Pb \overset{C_5H_{10}Br}{\underset{Br}{\diagup}} \quad \ldots\ldots IV$$

$$(C_2H_5)_2Pb \overset{C_5H_{10}Br}{\underset{Br}{\diagup}} + C_2H_5MgBr \longrightarrow (C_2H_5)_3Pb(CH_2)_4CH_2Br \ldots V$$
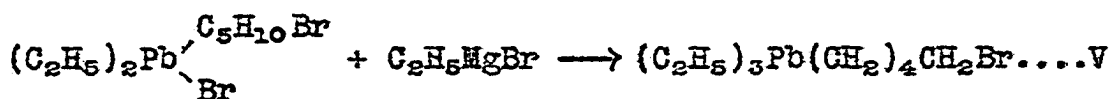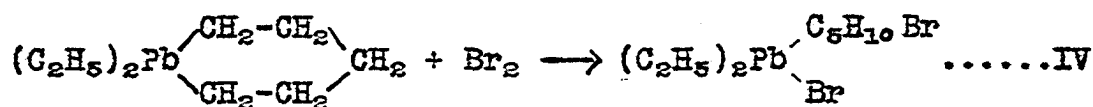
The reaction mixture was hydrolyzed with iced ammonium chlor-
ide and the ether layer separated and fractionated. There was
collected in this way, 15 g. (38%) of triethyl ε-bromoamyl lead
boiling at 147°/5 mm.

Triethyl ε-bromoamyl Lead with Magnesium and Carbon Dioxide:
A solution of 15 g. (0.034 mole) of triethyl ε-bromoamyl lead
in 100 cc. of dry ether was added to 1.4 g. (0.061 atom) of mag-
nesium. There was a gentle reaction and the mixture was reflux-
ed and stirred for one hour. The excess of magnesium was then
filtered from the solution and dry carbon dioxide was added un-

til there was no more color test for RMgX compound. The mixture was poured on ice and a precipitate formed which quickly dissolved. When the water layer was acidified with dilute formic acid (50) and extracted with ether and the ether washings evaporated, there was no residue. The ether layer from the reaction was fractionated and 2 g. (13%) of triethyl ε-bromoamyl lead was recovered. Besides this fraction there was 2 g. (16%) of a compound boiling at 100°/5 mm. which was probably triethyl n-amyl lead for it boils at 120°/13 mm. (51). There was no evidence of any acidic material. The equations for the reactions that were expected are given below.

$$(C_2H_5)_3PbC_5H_{10}Br + Mg \longrightarrow (C_2H_5)_3PbC_5H_{10}MgBr \ldots \ldots VI$$

$$(C_2H_5)_3PbC_5H_{10}MgBr + CO_2 \longrightarrow (C_2H_5)_3PbC_5H_{10}C\overset{OMgBr}{\underset{O}{\diagup}} \ldots VII$$

$$(C_2H_5)_3PbC_5H_{10}\underset{O}{C}-OMgBr + H_2O \longrightarrow (C_2H_5)_3PbC_5H_{10}\underset{O}{C}-OH + MgBrOH \ldots VIII$$
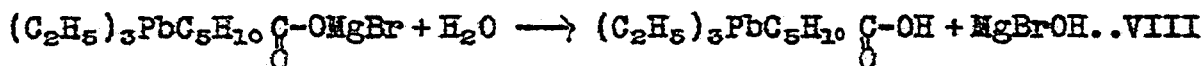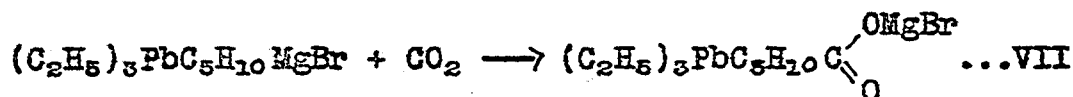
<u>Diphenylaminomagnesium Bromide, $(C_6H_5)_2NMgBr$, with Triethyl Lead Chloride</u>: A solution of diphenylamine was prepared from 3.4 g. (0.02 mole) and 75 cc. of dry ether. A stock solution of ethylmagnesium bromide was added to this until there was a positive color test. To this solution 7.5 g. (0.023 mole) of tri-

(50) Formic acid was used here because it is a rather weak acid and will not readily split a lead-carbon linkage. Also, its extreme solubility in water precludes the possibility of interference in an ether extraction.
(51) Grüttner and Krause, Ann., <u>415</u>:338(1918).

ethyl lead chloride was added and the mixture was stirred for one hour at room temperature. The solution was then hydrolyzed with iced ammonium chloride and the ether layer washed with dilute sulfuric acid. The acid washings were neutralized with ammonium hydroxide but there was no precipitate of an amino compound. The ether layer was evaporated and the oil crystallized from petroleum ether. In this way 2.5 g. (73%) of the diphenylamine was recovered melting at 54° (mixed melting point 54°). From this it may be concluded that there was very little reaction, or the lead molecule if formed was unstable, decomposing to give the original diphenylamine.

Oxidation of Triethyl Allyl Lead: It is possible to oxidize an allyl group quite easily to the acid. This experiment was carried out in an attempt to prepare an organolead acid by oxidizing triethyl allyl lead to triethyl plumbyl acetic acid, $(C_2H_5)_3PbCH_2COOH$, which should be water soluble or at least form a sodium salt which is water soluble. A 2% solution of potassium permanganate was prepared from 14.2 g. (0.09 mole) of potassium permanganate and 700 cc. of water. This solution was added to 10 g. (0.03 mole) of triethyl allyl lead suspended in 200 cc. of water. The addition was made slowly with a dropping funnel while the water was being stirred rapidly, and was well cooled in an ice bath. The solution was filtered and acidified and extracted with ether. This ether solution was extracted with sodium hydroxide and the washings acidified. There was no material formed which was insoluble in water and

when this water solution was extracted with ether and the ether evaporated, there was no residue. Accordingly there was no evidence for the formation of a carboxylic compound. The original ether layer that had been extracted with sodium hydroxide was evaporated and the residue was an oil which was not identified. It is very probable that this oil was the original lead compound. These results were duplicated in another experiment.

Diphenyl Lead Salts: Polis (52) as well as Goddard and Goddard (53) have prepared various salts of diphenyl lead oxide of the general formula, $(C_6H_5)_2PbO-\overset{O}{\underset{}{C}}-R)_2$. It was thought possible to prepare such salts from the various halogenated aliphatic acids and by treatment with a base such as diethylamine, to prepare salts of amino-acids which would be water soluble in the form of their hydrochlorides. The general procedure used was to heat 10 g. (0.02 mole) of tetraphenyl lead with a slight excess of the acid dissolved in xylene for about six hours under a reflux condenser. This is the procedure recommended by Goddard and Goddard (53) but in the experiments performed the desired compounds were not formed. The acids used were chloroacetic, bromoacetic, β-chloropropionic, α-bromopropionic, phthalic and thioacetic acids. The product appeared to be a complex between the tetraphenyl lead and the acid which would not readily be decomposed with solvents.

(52) Polis, Ber., 20:3331(1887).
(53) Goddard and Goddard, J. Chem. Soc., 121:978(1922).

SUMMARY

Attempts have been made to prepare water soluble organolead compounds by means of the malonic ester condensation, the Reformatsky reaction and by the action of carbon dioxide upon Grignard reagents. These efforts were not entirely successful although a series of triethyl lead salts has been prepared which may prove very valuable in the treatment of malignant tumor.

B. ANTI-KNOCK STUDIES

INTRODUCTION

The cheapest way to improve the efficiency of a standard engine is to increase the compression ratio of the engine. The limiting factors in high compression work are briefly as follows: The difficulty of procuring the proper fuel which will not detonate; the general design of the cylinder head, valves and inlet manifolds; the strength of materials used in the engine to withstand the stresses set up by the increased pressure. Detonation is one of the chief stumbling blocks in the line of progress.

The term detonation is apt to be confusing for knocking may be either mechanical or the result of using improper fuel. The knock may be due to some inherent fault of the fuel or the result of auto-ignition or pre-ignition. Auto-ignition occurs when a hot spot develops in the combustion chamber such as is the case when the plug points become red hot and ignite the charge without the use of the ignition apparatus. Pre-ignition is auto-ignition occurring before the passage of the spark. This improper ignition results in severe detonation which develops hot spots. Experiments have been carried out where these hot spots were the only means of ignition by which the engine was run.

There have been many theories advanced to account for the detonation in an internal combustion engine but the one postu-

lated by Ricardo is perhaps the best (1). He believes that as the fuel is introduced into the cylinder as an air-gasoline mixture, it burns so rapidly, if the fuel is unsuitable, that the flame front forces ahead of itself a pocket of unburned gas. The heat developed from this pressure is sufficient to raise the gas to its ignition temperature, whereupon, it auto-ignites and subjects the cylinder walls to a tremendous stress. The result is a peculiar pinking sound or knock which indicates what is taking place.

In 1915, (2) the General Motors Research Laboratories found that it was difficult to install Delco lighting engines in a great many homes because of the regulations that a number of states imposed upon the storage of gasoline in houses. They attempted to solve this problem by designing their engines to use kerosene as a fuel. They were prevented from doing this because of the severe detonation which kerosene induces. Thomas Midgley and T. A. Boyd were set to work investigating this problem at Dayton, Ohio.

These two men tried some 33,000 different chemicals to determine their effect upon knocking in internal combustion engines. Iodine was one of the first substances tried and proved very effective in suppressing the knock. Midgley then

(1) Ricardo, Automotive Industries, 44:856(1921); Callendar, Engineering, 121:509(1926).
(2) An excellent review of the development of anti-knock compounds is given by Tenger, Chem. Age, 18:388(1928); Chem. Trade J., 82:427(1928).

got the idea that the color of the substance used had some effect upon the knock and so tried several aniline dyes. These also were successful up to a certain point. But while aniline and iodine may both be considered anti-knocks, they have serious drawbacks. For example, iodine is costly and the use of it in the necessary quantities would have made the price of the fuel prohibitive. Aniline and its derivatives have a tendency to gum the moving parts of an engine and after using these materials in a fuel the engine must be completely dismantled and cleaned. So the use of these reagents is not feasible at present except in very special cases.

Midgley and Boyd eventually tried the effect of organometallic compounds upon detonation and found that tetraethyl tin, diethyl selenide, diethyl telluride, iron carbonyl, nickel carbonyl and tetraethyl lead were very effective, with ability to suppress detonation increasing in the order given. Tetraethyl lead was by far the most effective of the list given with an effectiveness about twice as great as nickel carbonyl. So it was decided that this compound should be used as an anti-knock reagent.

The chief difficulty that these men encountered at first was the burning of the tetraethyl lead to litharge which collected on the moving parts and caused the valves to stick and the plugs to short. This trouble was overcome by introducing an organic halogen compound with the tetraethyl lead which during combustion formed a lead halide which was volatile and

so could be ejected through the exhaust. Various halogen compounds were tried but the one finally decided upon was ethylene dibromide. It is claimed that the deposition of lead bromide occurs only on the cavities in the cylinder walls and so forms a smoother surface such as is obtained with a graphite lubricant.

After the war, the Standard Oil Company of New Jersey realized the importance of lead tetraethyl as an anti-knock and entered into negotiations with the General Motors Corporation which led, in 1924, to the formation of the Ethyl Gasoline Corporation which was to market the Ethyl Fluid used now to prepare Ethyl gasoline.

The Ethyl Fluid as it is sold today consists of a mixture of 54.5% tetraethyl lead, 36.4% ethylene dibromide and 9.0% Halowax oil in which there is a distinctive aniline dye. The material is sealed in 50 gallon steel drums and shipped to the refineries where it is mixed with the gasoline in a special blender whereby the concentrated Ethyl Fluid never comes in contact with the air. The maximum quantity of Ethyl Fluid in a gallon of gasoline sold to the public is 5.5 cc., or approximately 3.0 cc. of tetraethyl lead per gallon. This fuel has been used successfully in high compression engines. A compression ratio as high as 10:1 has been used in some cases. Each winner in the Memorial Day Races at Indianapolis since 1924 has used Ethyl gasoline. In 1927, the three first cars all used this fuel. The "Shenandoah" and the "Los Angeles"

both used gasoline containing 8 and 11 cc. respectively of
Ethyl Fluid for a gallon of gasoline.

The Standard Oil Company of New Jersey prepared the first
tetraethyl lead used in this kind of fuel, at their Bayway re-
finery. While attempting to use the process now in use with
ethyl chloride and sodium-lead alloy, there was an explosion
of two autoclaves which caused the death of four workmen. The
non-technical press immediately spread a scare which was
sponsored by a group of men led by Prof. Henderson of Yale.
The Ethyl Gasoline Corporation shut down the sale of Ethyl
Fluid, pending a thorough examination by the U. S. Health
authorities, in May 1925. The result of the investigation was
that the Ethyl Gasoline Corporation was allowed to continue
the sale of Ethyl Fluid. This sale re-commenced in February
1926 and has been continued. The tetraethyl lead is now being
made by the DuPont Corporation by the method in which ethyl
chloride reacts upon a sodium-lead alloy. They manufacture
this material in such a way that there is very little danger
to the employees.

There is very little doubt that tetraethyl lead is toxic
but there is also very little doubt that the quantities that
are available to the public are not sufficient to form a very
serious hazard. One of the men working for Midgley and Boyd
in their early experiments was in the habit of syphoning tetra-
ethyl lead by mouth from one container to another. This man's
hands were in contact with this liquid for eight hours daily

and he suffered only superficial injury.

One of the chief competitors of tetraethyl lead as an anti-knock is nickel carbonyl. It is effective but it requires twice as much by volume to produce the same effect as tetraethyl lead. It has several disadvantages for it decomposes rapidly and when burned in an internal combustion engine deposits a hard, gritty material which is detrimental to the engine. It is quite expensive and its decomposition products short the spark plugs.

Another good anti-knock is iron carbonyl. There was a great deal of trouble in getting a method of producing it commercially but a method was finally worked out by the Badisch Aniline and Soda Fabrik who have had a great deal of experience in high pressure work with the Haber-Bosch process. When this material is mixed with gasoline the fuel is known as "Motalin". The chief objection to this material is that the iron oxide formed during the combustion collects on the spark plugs and shorts them. Dr. Kehoe, who has done considerable work on the toxicity of these organometallic anti-knock materials, gives the order of decreasing toxicity of these three as nickel carbonyl, iron carbonyl, and tetraethyl lead.

There are a number of theories which have been advanced to account for the phenomenon known as detonation and they have been admirably reviewed by Dr. Clark (3) of the University of

(3) Clark, J. Soc. Automotive Eng., 23:167(1928).

Illinois. He is not convinced that any one theory so far pro-
pounded is satisfactory for explaining detonation. He gives
evidence for three different kinds of detonation which of course
complicates the problem.

One of the earlier theories to account for the action of
organometallic compounds as anti-knock materials was that dur-
ing the explosion the metal was released and formed a deposit
on sharp corners which diminished the knocking of the fuel. It
is true that sharp points such as sand will produce, do seem to
induce knocking but this theory does not account for the action
of materials containing no metal such as aniline. Neither does
it explain why organic valences are absolutely essential. It
is also well known that knocking starts instantly upon a
change to an improper fuel before the sharp corners have had a
chance to become exposed.

Another theory is that the metallic particles formed act
as miniature spark plugs. It is known that increasing the
number of spark plugs does decrease the tendency of a fuel to
knock. Experiments have been carried out which indicate that
colloidal metal particles act as anti-knock materials but such
results could only be obtained from colloidal metals prepared
from tetraethyl lead, iron carbonyl, or nickel carbonyl (4).
It is possible that some of these compounds may have been
present in the preparation which would explain the action of

(4) Sims and Mardles, Trans. Faraday Soc., 22:363(1926).

the colloidal material.

It is possible that heavy metals would absorb electrons formed in this system of high energy both from thermal and chemical reactions. It has been shown experimentally that both ionization and conductivity are decreased by the presence of tetraethyl lead. But this theory does not account for the action of inducers or for those anti-knock reagents which do not contain a metal such as iodine and aniline. There is good evidence to believe that the action of tetraethyl lead in suppressing ionization is due to its action in suppressing detonation.

Then there is the theory of simple, positive catalysis which postulates that the anti-knock material acts in some way upon the fuel in a wave ahead of the flame so that there will be no detonation. This is a theory hard to prove or disprove but it is unsatisfactory for the reason that it avoids the issue and postulates no mechanism.

Callendar (5) has a most interesting theory in which he assumes that the anti-knock reagent has an action on the droplets of higher boiling materials of a fuel which prevent their pre-igniting. It is known that these droplets have a lower ignition temperature than the vapors of more volatile liquids. When the pressure is increased the heat developed is sufficient to pre-ignite these drops if they were not poisoned

(5) Callendar, Engineering, 121:475, 509, 542, 576, 605(1926); 123:147(1927).

by adsorption of the "dope". This is a promising theory although it is not easy to relate pre-ignition with detonation.

Since there is a theory of positive catalysis, there may equally well be a theory of negative catalysis. The anti-knock reagents may decrease the reaction velocity of the burning fuel and so decrease detonation. This is open to the same objections as the theory of positive catalysis; that it avoids the issue of a mechanism.

There is also a theory which postulates that the "dope" changes the reaction route of oxidation to one involving hydroxyl compounds as intermediate compounds. There is evidence that this is true for fuels form different final products in the presence of the anti-knock compound than they do in its absence. This theory is difficult to extend to knock inducers and like so many theories it does not give any mechanism.

Another theory is one involving the idea of catalytic poisoning. The theory is that the walls of the combustion chamber act as positive catalysts for the reaction velocity and that these are poisoned by the anti-knock compound. It has been found, however, that known catalyst poisons such as mercury and sulfur, actually tend to induce detonation. Also there is no lag in the appearance of the knock when a poor fuel is introduced. It is not necessary to have metal walls to induce detonation for the knock is observed in glass reaction vessels.

A rather unique theory for the suppression of the knock

is the one which postulates that the suppressors absorb radiant energy from the flame which would otherwise activate the fuel ahead of the flame and increase the reaction velocity of the combustion. There is considerable evidence in favor of this theory resulting from the study of fuels with a spectroscope (3). It has been shown that the reaction rate is greatly increased when infra-red radiation is absorbed which corresponds to an absorption band of a fuel spectrum. Ultraviolet light of strong intensity has been found to induce knocking. Detonation suppressors will destroy the fluorescence of substances which have been irradiated with ultraviolet rays. With knock suppressors, the radiation from the flame is uniform throughout the cycle while it is irregular without them. Anti-knock compounds absorb ultraviolet light during detonation while knock inducers increase the intensity of this form of radiant energy. Finally, the lines for lead appear only during the first quarter of the stroke which indicates that if the pyrophoric lead particles are formed they do not persist.

It is possible that during combustion of the fuel, peroxides (5) are formed which are known to be very explosive and these could detonate the mixture of fuel gas. The anti-knock compound might act as a catalyst to destroy these peroxides as they are formed. It is known that the formation of peroxides is absolutely inhibited by anti-knock compounds.

The free radical theory has been put forward to explain what happens to the anti-knock compound while suppressing de-

tonation. This theory assumes that there are free radicals formed, intermediately, which results in the liberation of radiant energy. This may account, in part, for the necessity of having organic valences in the molecule.

There is a theory of reactions which postulates that a product of a reaction may activate the reactant in such a way as to accelerate the velocity of reaction. In the case of combustion, this would result in detonation and it has been suggested that the anti-knock compound may act in some way to break up the reaction. This is very hard to verify experimentally because of the difficulty in measuring minute changes in reaction velocities.

Clark (3) believes that of this list of twelve theories, the ones which offer the most promise are the radiation theory, the peroxide theory, and the chain reaction theory. He points out that there is considerable work to be done on all these theories and outlines some of the difficulties.

There have been many and varied methods of measuring detonation and the effect of knock suppressors upon detonation. Dr. Graham Edgar (6) of the Ethyl Gasoline Corporation, has given a description of various methods used and pointed out the necessity for some standardization. At present it is very difficult to compare the results of different laboratories. Those people using the Midgley bouncing pin method have more

(6) Edgar, J. Soc. Automotive Eng., 22:41(1928); See also Cummings, ibid., 20:599(1927).

success than others in comparing results.

This method was developed by Midgley and Boyd (7) and is used in various modified forms by many experimentors. The engine used is a small Delco light engine operating a bank of electric lamps. The instrument used for measuring detonation is a small steel needle resting upon the piston of a modified optical-indicator pressure-element. The mirror is removed from the original pressure-element along with the mechanism which attaches it to the piston. The piston is held by a spring of such strength that ordinary pressure changes in the engine will cause no effect. When there is detonation, the bouncing pin is thrown upward and strikes a pair of spring contacts which close an electric circuit. This electric circuit contains a 100-watt lamp in series with a water voltameter actuated by a source of 110 volt direct current. When the circuit is closed, water is decomposed and the gas is collected in a graduated U-tube. The volume of gas generated in a given time interval depends upon the number and intensity of the impulses given to the bouncing pin. Detonation is measured by comparing the unknown fuel with two reference fuels, one of which detonates slightly less and the other slightly greater than the unknown. This method is used by the Ethyl Gasoline Corporation.

The Armour Institute of Technology (8) uses a method in which

(7) Midgley and Boyd, J. Soc. Automotive Eng., 10:7(1922).
(8) Roesch, ibid., 19:17(1926).

a four cylinder engine is employed. The spark is advanced until detonation occurs, the intensity of which is measured by ear. The variables are held as constant as is possible and the fuels are compared by plotting the spark advance necessary to produce a knock of a given intensity against the volume in cubic centimeters of tetraethyl lead used. The curves are compared by interpolation.

The Atlantic Refining Company uses a one cylinder engine with a Prony brake. They have a specially constructed carburetor making it possible to get the same fuel mixtures at different throttle openings at constant speed. The throttle is equipped with a recording needle which slides over a graduated scale. The knock of the fuel is measured by the throttle opening necessary to produce a certain detonation. Comparison is made between fuels by means of a standard reference fuel containing benzene.

Ricardo, (9) who is one of the pioneers in this work on detonation and its suppression, developed an interesting method of measuring the knock values of a fuel for the Asiatic Petroleum Company. This method consists of using the fuel in an engine of special design which has an adjustable cylinder head by means of which the compression ratio of the engine can be varied at will over a rather wide range. The compression ratio at which a fuel begins to detonate, as determined by ear, is

(9) Ricardo, Automotive Industries, 44:804, 856, 1003(1921).

characteristic of the fuel and is called the highest useful compression ratio or simply H. U. C. R. This is a rather general way of expressing the knock characteristics of any fuel. This method is also in use by the British Air Ministry Laboratory and the Kansas City Testing Laboratory.

At the Ohio State University Laboratories, (10) a device has been used for measuring detonation dependent upon the ionization of the gas in a cylinder during an explosion. There appears to be a direct relation between the electrical conductivity of the gas and detonation. The conductivity is greater when the detonation is more evident.

The University of Michigan (11) uses a bomb equipped with a recording pressure-indicator. The fuel is rated by determining how much nitrogen must be added to the gasoline-oxygen mixture to prevent peaks on the time-pressure diagram. One of the objections to this method is the difficulty of distinguishing between the vibrations due to the pressure-indicator and pressure peaks due to detonation.

It is quite evident that with so many methods available for measuring detonation, it is not always possible to compare the results of different workers (6). It is earnestly hoped that a method will be developed of such value that it will become standardized in order that there will not be so much confusion in the literature of this field.

(10) Charch, Boord and Mack, Ind. Eng. Chem., 18:334(1926).
(11) Leslie, Brown and Hunn, ibid., 17:597(1925).

There are a number of excellent bibliographies on detonation which should be mentioned here. There are ninety references to articles in this field given by Berl and Fischer (12) while Clark and Thee (13) have published sixty more. The combination of the two compilations covers nearly all the important literature to July, 1925.

Because of the tremendous success which tetraethyl lead has had as an anti-knock compound, much experimental work has been done in testing various compounds for their effectiveness. It is by no means easy to obtain all the values because of the secretive nature of the work. A few tables are given here of compounds which have been tested and the results of which have been published by the different experimentors.

(12) Berl and Fischer, Z. Elektrochem., 30:29(1924).
(13) Clark and Thee, Ind. Eng. Chem., 17:1219(1925).

Table I

Compound	Anti-knock Effectiveness (2) (by volume)
Aniline	11.45
Benzene	1.0
Toluene	1.093
Xylene	1.20
Alcohol	1.85
Ethyl iodide	13.87
Xylidine	12.03
Toluidine	11.86
Tetraethyl tin	20.4
Diethyl selenide	62.5
Diethyl telluride	250.0
Iron carbonyl	250.0
Nickel carbonyl	277.0
Tetraethyl lead	528.0

Table II

Compound	Percentage effect on H.U.C.R.(14) (by weight)
Benzene	1.0
Toluene	2.0
o-Xylene	0.6
pseudo Cymene	-0.4
Turpentine	-0.9
Pyridine	1.2
Aniline	21.7
Methylaniline	22.2
Dimethylaniline	1.7
Diethylaniline	0.0
Benzylaniline	9.5
Toluidine	18.3
m-Xylidine	22.3
Phenylhydrazine	-5.9
Ethylaniline	10.4
Anisole	1.1
Phenetole	1.3
Benzyl alcohol	0.4
Cresol	5.8
Phenol	4.4

(14) These values were obtained by Callendar (5) using Ricardo's (1) method of variable compression ratios.

Table II (continued)

Compound	Percentage effect on H.U.C.R. (by weight)
Terpineol	0.0
Thymol	-1.9
Eugenol	1.3
Benzaldehyde	0.0
Paraldehyde	-0.8
Furfural	-0.8
Ethyl salicylate	-1.1
iso-Butyric acid	0.0
Bromobenzene	-1.7
Ethylene bromide	0.6

Table III

Compound	Grams to produce the same effect as 1 gr. of aniline(15)
Cumidine	0.96
Diphenylamine	1.21
Amylaminobenzene	1.53
Ethylaminobenzene	1.14
Aminodiphenyl	1.60
o-Methyltoluidine	1.15
n-Butylaminobenzene	1.44
n-Propylaminobenzene	1.32
n-Propylaniline	1.95
Ethyldiphenylamine	3.65
Butylaniline	3.10
Diethylamine	1.59
Di n-propylaniline	7.15
iso-Amylaniline	7.10
Ethylamine	2.40
Triethylamine	7.95
Triphenylamine	30.00
Ammonia	2.0(-)
iso-Propyl nitrite	0.085(-)

(15) Midgley's (7) bouncing pin apparatus was used to obtain
, these values.

Table IV

Compound	Anti-knock Coefficient (16)
Tetraethyl lead	100.0
Tetraphenyl lead	59.0
Diethyl lead dichloride	67.0
Diphenyl dimethyl lead	97.0
Diphenyl diethyl lead	93.5
Diphenyl lead dichloride	72.0
Diphenyl lead dibromide	60.0
Diphenyl lead diiodide	80.0
Tri p-xylyl lead	64.7
Lead ethylxanthogenate	7.1
Lead thiolacetate	8.4
Bismuth triphenyl	18.2
Bismuth trimethyl	20.2
Bismuth triethyl	20.2
Stannic chloride	3.5
Stannic iodide	12.8
Diethyl tin diiodide	12.3
Cadmium dimethyl	1.05
Titanium tetrachloride	2.7
Titanium tetraiodide	2.7

(16) The anti-knock coefficient is the ratio between an arbitrary molecular quantity of tetraethyl lead and the molecular quantity of compound necessary to produce the same effect. This fraction is then multiplied by 100 and called the anti-knock coefficient (10). Midgley's bouncing pin method was used in the study of these materials.

Table IV (continued)

Compound	Anti-knock Coefficient
Triphenyl antimony diiodide	4.0
Phenylarsine	1.0-2.0
Triphenylarsine	1.4
Triphenyl methyl arsonium iodide	0.7-1.0
Triethyl dialuminium triiodide	very weak

Table V

Compounds which have no effect upon detonation

Ammonium plumbic chloride

Benzaldehyde lead

Diphenyl lead diacetate

Lead tetrastearate

Lead tetraacetate

Diphenyl lead dinitrate

Lead diphenylcarbazide

Stannic bromide

Zirconium tetrachloride

Zinc sodium ethyl

Auric chloride

Tungstic chloride

Ferric chloride

Ferric dimethylglyoxime

Ferric ethylxanthogenate

Triethyl aluminum

Aluminum chloride (anhyd.)

Triphenyl bismuth dichloride

Triphenyl bismuth dibromide

Platinum tetra chloride

Nickel dimethylglyoxime

Nickel diphenylcarbazide

Cupric dimethylglyoxime

Table V (continued)

Compounds which have no effect upon detonation

Cuprous diphenylcarbazide

Cobalt ethylxanthogenate

Cobalt succinimide

Mercury ethylxanthogenate

Pentaphenyl chromium bromide

Zinc ethylxanthogenate

Nitrogen sulfide (N_4S_4)

Phenylisocyanide

Ethylisocyanide

From a study of these tables, it is evident that a good anti-knock reagent should have certain characteristics. It should be an organometallic compound for organic valences appear to be absolutely essential. Organolead compounds are very much superior to the organic derivatives of any other metal studied. The problem then resolves itself into a matter of determining the best configuration that an organolead compound should have to be the most effective anti-knock reagent. A description of such a study is given in the following pages.

Tetraethyl lead is itself an excellent anti-knock compound and is readily available. In this work derivatives of tetraethyl lead have been studied almost exclusively because of the various advantages tetraethyl lead offers as a starting material. In the preparation of these derivatives, the first problem that appeared was to find a good method for the preparation of triethyl lead chloride and diethyl lead dichloride. This was the object of the first experiments performed in this field.

EXPERIMENTAL

Methods for the Preparation of Triethyl Lead Chloride and Diethyl Lead Dichloride

Historical

The stability of the alkyl lead chlorides as contrasted with the corresponding bromides and iodides make them very desirable reagents. Grüttner and Krause (17), for example, take great pains to emphasize the unstable nature of diethyl lead dibromide which may not be crystallized because of the extent of its decomposition into lead bromide. They also report (18) that the chloride reacts somewhat less rapidly than the other halides but no such difference was apparent in this work.

Triethyl lead halides have been prepared in several ways. Löwig and Klippel (20) treated tetraethyl lead with silver nitrate and formed triethyl lead nitrate which was then shaken with sodium hydroxide to form triethyl lead hydroxide. The triethyl lead hydroxide formed triethyl lead sulfate when neutralized with sulfuric acid. Triethyl lead chloride was the product of the reaction of barium chloride with triethyl lead sulfate. Cahours (21) and Buckton (22) have made triethyl lead chloride by warming what was undoubtedly impure

(17) Grüttner and Krause, Ber., 49:1415(1916).
(18) Grüttner and Krause, ibid., 49:1125(1916).
(19) Löwig, J. prakt. chem., 60:304(1853).
(20) Klippel, ibid., 81:287(1860).
(21) Cahours, Ann., 122:48(1862).
(22) Buckton, ibid., 109:218(1859).

tetraethyl lead with concentrated hydrochloric acid. More recently, Browne and Reid (23) have given excellent directions for the preparation of triethyl lead chloride in 86% yields from tetraethyl lead and concentrated hydrochloric acid with a trace of silica gel used as a catalyst. Pfeiffer and Truskier (24) led dry hydrogen chloride into an ether solution of tetraethyl lead and obtained triethyl lead chloride in very good yields.

Tafel (25) added bromine to a "well cooled" solution of tetraethyl lead in ethyl acetate and obtained impure triethyl lead bromide. When two moles of bromine were added to the cooled solution of tetraethyl lead, diethyl lead dibromide was formed. Grüttner and Krause (17) used this method but were much more careful to specify the temperature. They found that at -60° bromine and chlorine reacted with tetraethyl lead to form triethyl lead halide, while at -20° the dihalide was formed. They object to any method using hydrogen chloride or hydrochloric acid on the grounds that the yield is lowered when large quantities are used. It has been found, in the present study, that this objection is not valid for as much as 113 g. (0.35 mole) of triethyl lead chloride has been prepared in 96% yields. Grüttner and Krause (17) do not state the quantities necessary to cause a lowering of the yield.

(23) Browne and Reid, J. Am. Chem. Soc., 49:830(1927).
(24) Pfeiffer and Truskier, Ber., 37:1125(1904).
(25) Tafel, ibid., 44:323(1911).

The most generally used method for preparing the diethyl lead dihalides has been given, i.e., halogenation of tetraethyl lead at -20° (17). Grüttner and Krause (17) recommend that the triethyl lead halide be prepared first at -60° and then converted to the dihalide as the solution becomes warmer up to -20°. They explain that the objection to adding the halogen at the higher temperature is not serious, inasmuch as only when using large quantities is the reaction vigorous enough to be explosive. Goddard and Goddard (26) have prepared diethyl lead dichloride by the reaction of thallic chloride on tetra-ethyl lead and on triethyl lead chloride. They also found that when diethyl diphenyl lead was treated with thallic chloride, diethyl lead dichloride was a product of the reaction. Möller and Pfeiffer (27) caused diethyl diphenyl lead to react with dry hydrogen chloride and obtained diethyl lead dichloride. Similarly, diphenyl dicyclohexyl lead forms dicyclohexyl lead dichloride when treated with hydrogen chloride (28).

It is rather easy to convert an alkyl lead halide to a different halide by either one of two reactions. Krause and Pohland (29) used one of the methods to prepare triethyl lead fluoride from triethyl lead bromide. Triethyl lead hydroxide was prepared from triethyl lead bromide by the action of dilute potassium hydroxide. When this triethyl lead hydroxide was

(26) Goddard and Goddard, J. Chem. Soc., 121:482,256(1922).
(27) Möller and Pfeiffer, Ber., 49:2441(1916).
(28) Grüttner, ibid., 47:3257(1914).
(29) Krause and Pohland, ibid., 55:1282(1922).

added to a 33% solution of hydrofluoric acid in alcohol, triethyl lead fluoride was formed.

Löwig and others (19,20,21,22) have used another method for the conversion of the halides to other halides. Their method consists of causing a double decomposition reaction to take place between an alkyl lead halide and an appropriate halide of sodium or potassium. Both of these reactions are applicable to dihalides as well as to monohalides.

Since the preparation of triethyl lead chloride is rather laborious when the method of Grüttner and Krause (17) is used, experiments have been carried out to determine a good method of preparation involving the use of hydrogen chloride. It has been found that triethyl lead chloride can be prepared in 98.2% yields by passing an excess of dry hydrogen chloride into a solution of tetraethyl lead in dry absolute ether. Dry hydrogen chloride has been led into a suspension of triethyl lead chloride in dry ether for an hour. At the end of that time the triethyl lead chloride was recovered unchanged. When the material was washed with acid ammonium acetate solution (30) and the washings treated with a solution of potassium dichromate, there was no precipitate of lead chromate to indicate the formation of lead chloride. A sample of the recovered product dissolved completely in moist ether which shows that diethyl lead dichloride was not formed for it is quite insoluble in

(30) See p.35, Part A, ref.44, THIS THESIS.

moist ether. Triethyl lead chloride then, is not decomposed by prolonged treatment with hydrogen chloride into lead chloride or diethyl lead dichloride. This method seems to offer advantages over previously described procedures.

The method for the preparation of diethyl lead dichloride that has been worked out is an entirely new one. Hydrogen chloride is passed into a solution of tetraethyl lead in toluene at 90° with the formation of diethyl lead dichloride in nearly quantitative yields. Diethyl lead dichloride is formed in a benzene solution in 80-85% yields with the temperature at 50° but the product is not so pure and the hydrogen chloride is absorbed much more slowly than in the toluene solution. In the following experiments, it has been found that diethyl lead dichloride prepared in the toluene solution is free from triethyl lead chloride and lead chloride and so may be used directly. Grüttner and Krause (17) have led chlorine into a suspension of dimethyl lead dichloride for several hours at room temperature with the formation of no lead chloride. Dialkyl lead dichlorides appear to be very resistant to the further action of chlorine and hydrogen chloride.

It is interesting to note that when chlorine is added to a solution of tetraethyl lead in ether which is cooled with an ice-salt mixture, diethyl lead dichloride is formed in excellent yields and the reaction is quite smooth. Grüttner and Krause (17) do not recommend this procedure for as they say, the reaction may become explosive when large quantities are

used. They do not state any quantities but in this work, 16.5 g. (0.05 mole) of tetraethyl lead have been treated with chlorine under these conditions and there was a very smooth reaction.

Triethyl Lead Chloride: 48.5 g. (0.15 mole) of tetraethyl lead is dissolved in 400 cc. of dry absolute ether and saturated with dry hydrogen chloride. This requires about thirty minutes or more depending upon the rate of flow of the gas. The rate at which the gas is absorbed appears to reach a maximum and ethane is evolved at a rather constant rate. The best way to determine the end of the reaction is to wait until the ethane is only very slowly evolved and then filter the solution from the precipitated needles of triethyl lead chloride. The solution is again saturated with hydrogen chloride and if no more needles appear the reaction is completed. The yield of triethyl lead chloride is 48.6 g. (98.2%). The yields may vary between 92% and 98% depending upon how carefully the last traces of tetraethyl lead are halogenated. This material is very pretty and Pfeiffer and Truskier (24) have found by analysis that triethyl lead chloride prepared in this way is very pure.

There are two precautions that must be observed. All moisture must be kept from the flask and ether solution. Triethyl lead chloride is soluble in moist ether but quite insoluble in dry ether in the presence of moderate amounts of hydrogen chloride. Triethyl lead chloride is appreciably soluble in dry ether that has large amounts of hydrogen chloride

present. In proof of this statement, it has been found that boiling a solution to remove excess hydrogen chloride will often cause another crop of needles to appear, while saturating a suspension of triethyl lead chloride in ether with hydrogen chloride will cause the material to go into solution. This last case is quite unusual and is not often met with (31).

Diethyl Lead Dichloride: 107.5 g. (0.3 mole) of tetra-ethyl lead is dissolved in 500 cc. of toluene in an open Erlenmeyer flask and the solution is heated to 90°. Dry hydrogen chloride is led into the solution at a moderate rate and since the triethyl lead chloride which first forms is soluble in toluene, no precipitate forms until one-half of the hydrogen chloride has been absorbed. The end of the reaction may be determined approximately by adding hydrogen chloride at the same rate for double the time necessary to cause the first precipitate of diethyl lead dichloride to form. At this time the precipitate is filtered from the solution and hydrogen chloride again added to precipitate any unreacted triethyl lead chloride. If no precipitate forms the reaction is ended. The product is pure diethyl lead dichloride containing no lead chloride. The yield of 107 g. (97.5%) has been checked repeatedly. The temperature of the solution should be maintained at 90° by the ap-

(31) Care should be taken against long exposure to this compound. The observation of Krause and Pohland (29), that compounds of this type produce severe headaches, has been verified.

plication of heat although a variation of 10° does little harm (32).

Any triethyl lead chloride left unreacted with hydrogen chloride is very soluble in toluene and so would not contaminate the precipitate of diethyl lead dichloride. A sample of material prepared by the above procedure, was washed with a solution of ammonium acetate and the washings treated with a solution of potassium dichromate to precipitate any dissolved lead chloride as the chromate. There was no precipitate which shows that the material was free from lead chloride. Similar treatment of samples of triphenyl lead chloride and diphenyl lead dichloride showed that they were also free from lead chloride. Triphenyl lead chloride and diphenyl lead dichloride do not give a precipitate with potassium dichromate under these conditions.

Tetraethyl Lead with Chlorine: In the one experiment performed, 16.5 g. (0.05 mole) of tetraethyl lead was dissolved in 150 cc. of dry absolute ether and cooled with an ice-salt bath to -10°. Chlorine was bubbled slowly through this solution while it was being stirred rapidly. This reaction was smooth and when the chlorine colored the solution, the reaction was considered complete and the diethyl lead dichloride was filtered out. The yield of pure material was 16.6 g or 98.6%.

(32) This material is in the reactive form and need not be treated further before use. See Grüttner and Krause, Ber., 49:1546(1916).

Summary

Methods are given for the preparation of triethyl lead chloride and diethyl lead dichloride in nearly quantitative yields.

Mixed Alkyl Lead Compounds

Historical

Gilman, Sweeney, and Kirby (33) prepared the four tri-phenyl butyl leads to be tested as anti-knock compounds but unfortunately were not able to obtain a satisfactory rating because of the difficulties of testing compounds which are solid at ordinary temperature. The results obtained by Gilman and Balassa (34) from the four diphenyl dibutyl leads indicate that the effectiveness of the molecule as a knock suppressor increases slightly with a branching of the groups. But in neither case was a lead compound containing a tertiary carbon atom attached directly to lead tested for its anti-knock properties. The first of such compounds was prepared in this laboratory by Dr. Balassa (34).

The four triethyl butyl leads have been prepared including the very interesting triethyl tert-butyl lead and have been tested for their anti-knock effectiveness. The results are surprising and seem to indicate that the nature of the radical attached to lead has very little influence upon the anti-knock effectiveness of a compound. When tested by Midgley's bouncing pin method (7) against tetraethyl lead for comparison, all these compounds were found to be equally effective: namely, 85% as effective as tetraethyl lead upon a mole basis.

(33) Gilman, Sweeney and Kirby, Iowa State Coll. J. Sci., 3:1 (1928).
(34) Gilman and Balassa, ibid., 3:105(1929).

Three of these compounds, triethyl n-butyl lead, triethyl iso-butyl lead and triethyl sec-butyl lead, have been prepared before (35). Triethyl tert.-butyl lead, however, is a new compound and is of especial interest because of the tertiary carbon joined directly to lead. In making this compound the recommendations of Gilman, Sweeney, and Kirby (33) were found to be invaluable. In one experiment triethyl lead chloride was added to a solution of tert.-butylmagnesium chloride. The solution became a deep red and metallic lead precipitated as indicated by the appearance of the reaction mixture. When the reaction mixture was worked up, tetraethyl lead was the chief product. When the solution of RMgX compound was added in insufficient quantities to triethyl lead chloride, the reaction was smooth and triethyl tert.-butyl lead was formed.

The presence of tetraethyl lead can be explained by postulating the formation of diethyl lead as an intermediate compound which decomposes into tetraethyl lead and metallic lead. This idea of diethyl lead is not a new one. Tafel (25) in the electrolytic reduction of acetone using lead electrodes observed this deep red color and found di-iso-propyl lead dibromide when bromine was added to the colored solution. When the red solution was warmed he obtained tetra iso-propyl lead and metallic lead. From these facts and others he concluded that this red solution contained di-iso-propyl lead although he was unable

(35) Grüttner and Krause, Ber., 50:202,574(1917); ibid., 49:1125 (1916).

to isolate the compound because of its great instability.
Renger (36) observed similar properties from solutions of di-
ethyl ketone and methyl ethyl ketone when they were reduced
electrolytically with lead electrodes. Möller and Pfeiffer
(27) postulate that R_2Pb compounds are formed intermediately
during the preparation of R_4Pb compounds from lead chloride
and a Grignard reagent. It seems very probable then that di-
ethyl lead is formed when triethyl lead chloride is added to
tert-butylmagnesium chloride which decomposes to form tetra-
ethyl lead and metallic lead. Triethyl lead would result in
the same products if it were present, but it is of a pale green
color.

Experimental

In the preparation of these compounds the constants re-
corded agree with those given in the literature (35) unless
stated otherwise. When the boiling points are determined at
pressures different than those given in the literature, they
are recorded here. The general procedure is given for the prep-
aration of triethyl n-butyl lead and unless otherwise stated
all the compounds are prepared in this way.

Triethyl n-Butyl Lead: 11 g. (0.033 mole) of triethyl
lead chloride was suspended in 50 cc. of dry ether and an ex-

(36) Renger, Ber., 44:337(1911).

cess (37) of n-butylmagnesium bromide was added to it. The solution was stirred and allowed to reflux from the heat of the reaction. When this had died down, the solution was refluxed and stirred for thirty minutes more. After hydrolysis with iced dilute hydrochloric acid, the ether layer was dried with calcium chloride and distilled under reduced pressure in an atmosphere of nitrogen to prevent decomposition. The material boiling at 108°/13 mm. was 10 g. (85.5%). The thermometer and the manometer used had been checked against tetraethyl lead of known purity.

Triethyl iso-Butyl Lead: 11 g. (0.033 mole) of triethyl lead chloride when treated with an excess of iso-butylmagnesium bromide formed 10 g. (85.5%) of triethyl iso-butyl lead boiling at 102°/10 mm.

Triethyl sec-Butyl Lead: In a duplicate experiment using sec-butylmagnesium bromide, 9.5 g. (81%) of triethyl sec-butyl lead was obtained which boiled at 105-6°/14 mm.

Triethyl tert-Butyl Lead: 20 g. (0.06 mole) of triethyl lead chloride was added to an excess of tert-butylmagnesium chloride (38) whereupon the solution became deep red and a black precipitate of lead was formed. The mixture was hydrolyzed with iced, dilute hydrochloric acid and the ether layer

(37) Gilman and Schulze, J. Am. Chem. Soc., 47:2002(1925); Bull. soc. chim., (4)41:1479(1927) and Gilman and Heck, Ber., 62:1379(1929), have described a qualitative color test for RMgX compounds which will be used throughout this work to determine the presence of these compounds.
(38) Gilman and Zoellner, J. Am. Chem. Soc., 50:425(1928).

dried and fractionated. Seven grams (28%) of an oil boiling at 75-6°/9 mm. was obtained. This oil was analyzed for lead by the method recommended by Calingaert (39) and was shown to be tetraethyl lead. Calingaert's method is to brominate a carbon tetrachloride solution of the lead compound and dissolve the lead bromide formed in ammonium acetate solution. The lead is then precipitated from this solution with potassium dichromate and weighed as lead chromate.

Analysis: Calc. for $C_8H_{20}Pb$; Pb, 64.08%. Found: Pb, 63.72 and 63.86%.

As a further test of this material, 4.059 g. was dissolved in dry ether and treated with an excess of hydrogen chloride. The gas evolved was led through a condenser and collected over water which absorbed the excess hydrogen chloride and any ether vapor that passed through the condenser. Three hundred and ninteen cubic centimeters of unabsorbed gas was collected which when corrected to standard conditions left 277 cc. The theoretical volume of ethane evolved from this much tetraethyl lead, on the basis of one ethyl group being removed, is 282 cc. The gas in the reaction flask was displaced completely, by a measured volume of water, into the gas receiver and a sample of 12 cc. taken for analysis. By exploding this sample in a mixture with oxygen and measuring the contraction and absorbing the carbon dioxide formed, the gas was shown to be ethane.

(39) Private communication.

When 0.06 mole of <u>tert-butylmagnesium</u> chloride (based upon a 60% yield from <u>tert-butyl</u> chloride (38)) was slowly added to an ether solution of 24.2 g. (0.075 mole) of triethyl lead chloride, there was a smooth reaction and no red color or black precipitate was observed. The solution was stirred and refluxed for thirty minutes after the initial heat of reaction had abated, and was then hydrolyzed with iced ammonium chloride. The ether layer was dried with calcium chloride and distilled under reduced pressure. Fifteen grams (70%) of triethyl <u>tert</u>-butyl lead boiling at $76^{\circ}/5$ mm. ($90-91^{\circ}/10$ mm.) was obtained. Tetraethyl lead boils at $68^{\circ}/5$ mm. This compound is the only new one of this series and the first compound containing a tertiary carbon attached directly to lead to be tested for its anti-knock effectiveness. Calingaert's method was used to analyze this material for lead.

Analysis: Calc. for $C_{10}H_{24}Pb$; Pb, 58.97%. Found: Pb, 58.54 and 58.45%.

Conclusions

The four triethyl butyl leads have been prepared and their anti-knock effectiveness determined. This is the same for all four of the compounds: namely, 85% as effective as tetraethyl lead upon a mole basis. Triethyl <u>tert-butyl</u> lead is the first compound containing a tertiary carbon attached directly to lead to be tested.

There is evidence of the formation of diethyl lead when triethyl lead chloride is added <u>to</u> <u>tert-butylmagnesium</u> chloride.

Alkyl-aryl Lead Compounds

Historical

Charch, Boord and Mack (10) report that tetraphenyl lead is 59% as effective an anti-knock compound as tetraethyl lead upon a mole basis. In the same paper, diphenyl diethyl lead is given a rating 93.7% as great as tetraethyl lead upon a mole basis. These facts are very interesting and indicate that the anti-knock effectiveness is influenced more by the weight of the groups than by the symmetry of the molecule. It appears that the ratings of the series of ethyl phenyl lead would be of interest.

All of these compounds have been prepared prior to this study although the constants of diethyl diphenyl lead are rather imperfectly described. The tetraphenyl lead used was prepared according to the directions of Gilman and Robinson (40) who also give improved directions for the preparation of triphenyl lead chloride and diphenyl lead dichloride (41). Triethyl phenyl lead was prepared by the method of Grüttner and Grüttner (42) and the directions of Krause and Schmitz (43) were used for the preparation of triphenyl ethyl lead. Möller and Pfeiffer (27) give good directions for the preparation of diphenyl diethyl lead but do not report a boiling point for

(40) Gilman and Robinson, J. Am. Chem. Soc., 49:2315(1927).
(41) Gilman and Robinson, ibid., 51:Oct.(1929). Accepted for pub.
(42) Grüttner and Grüttner, Ber., 51:1293(1918).
(43) Krause and Schmitz, ibid., 52:2150(1919).

the compound while Goddard and Goddard (26) use their method
and give as a boiling point 186°/16 mm. The method of Möller
and Pfeiffer was used and it was found possible to check ap-
proximately the boiling point reported by Goddard and Goddard.
The compound that has been prepared boils at 176°/8 mm.

Experimental

These compounds were all prepared by adding the appropri-
ate organolead halide to a solution of the Grignard reagent.
It is doubtful whether the reverse of this procedure would have
made any appreciable difference in the preparation for the
groups here attached to lead are quite stable and not easily
affected by mild reagents. The constants given were found to
check with those recorded in the literature. When the material
was distilled at a different pressure than that recorded the
boiling point at that pressure will be given also.

Triethyl Phenyl Lead: 22.6 g. (0.07 mole) of triethyl
lead chloride was added to 0.1 mole of stock phenylmagnesium
bromide solution. This was an excess of Grignard reagent as
shown by a color test. The mixture was hydrolyzed with iced,
dilute, hydrochloric acid and the ether layer separated, dried
and evaporated. The residual oil was vacuum distilled and
12 g. (55%) boiling 136°/13 mm. (126°/6 mm.) was collected.

Diphenyl Diethyl Lead: 21.5 g. (0.05 mole) of diphenyl
lead dichloride was added to 50 cc. (0.1 mole) of stock ethyl-
magnesium bromide solution. The mixture was stirred and re-

fluxed for thirty minutes and at the end of that time there was a positive color test for RMgX compound. The mixture was poured on iced ammonium chloride to hydrolyze and the ether layer separated, washed, dried and evaporated. The residual oil was vacuum distilled and 11 g. (54%) of a liquid boiling at 176°/8 mm. was collected.

Triphenyl Ethyl Lead: 23.6 g. (0.05 mole) of triphenyl lead bromide was added to 0.1 mole of ethylmagnesium bromide solution. There was a positive color test for Grignard reagent and the mixture was hydrolyzed with iced hydrochloric acid and the ether layer was separated, washed, dried and evaporated. The oily residue crystallized from alcohol to furnish 15 g. (66%) of triphenyl ethyl lead melting at 43°.

Relative Anti-knock Effectiveness of the Compounds

The compounds were dissolved in gasoline using quantities corresponding to approximately 2.0 g. of lead per gallon. The solution was then analyzed for lead and matched against a solution of tetraethyl lead in gasoline by Midgley's bouncing pin method (7). Following are the results:

Compound	Moles of tetraethyl lead equivalent to one mole of compound
Tetraethyl lead	1.00
Triethyl phenyl lead	0.75
Diethyl diphenyl lead	0.70
Ethyl triphenyl lead	0.45
Tetraphenyl lead (44)	0.59

Conclusion

From these results it is apparent that the symmetry of the molecule is an important factor in the effectiveness of an anti-knock compound. Otherwise one might expect diethyl diphenyl lead and tetraphenyl lead to have a rating much lower than is given here. It is interesting to point out that it has not been possible to check the accepted value (10) for the effectiveness of diethyl diphenyl lead although all precaution has been taken to insure the purity of this compound (45).

(44) This value is taken from the publication of Charch, Boord and Mack (10). A very pure sample is being tested but the results are not available at this time.

(45) This material did not give off any ethane when treated with hydrogen chloride as tetraethyl lead should if it were present.

Series of Ethyl Methyl Lead Compounds and Triphenyl Lead Halides

Historical

In view of the results obtained in the series of triethyl butyl leads it is apparent that the branching of the group attached to lead has little influence upon the anti-knock effectiveness of a molecule. The results from the phenyl-ethyl-lead compounds indicate that the weight of a group and the symmetry of a molecule are both important in determining the proper configuration of a good anti-knock compound. From these facts, it appears that a compound of lead containing a light group in a symmetrical configuration would be a very effective anti-knock compound. In this study, a series of ethyl-methyl-lead compounds has been prepared in an attempt to satisfy these requirements.

None of these compounds are new, but the results of testing their effectiveness as anti-knock reagents have not been published before. The constants that have been reported for the compounds have been checked in this work although no attempt has been made to prepare them in the optimum yields. The purpose has been to prepare an especially pure sample from which the results of tests could be depended upon.

Tetramethyl Lead: A solution of methylmagnesium iodide was prepared from 284 g. (2 moles) of methyl iodide and 48.6 g. (2 atoms) of magnesium and one liter of ether. To this solution, 225 g. (0.81 mole) of lead chloride was added in small

portions. The mixture was refluxed and stirred for four hours and hydrolyzed with iced hydrochloric acid. The ether layer was separated and the ether distilled from a water bath. The residual oil was distilled under ordinary pressure and a fraction boiling over a long range was collected. Upon redistillation, 25 g. or 23.6% of tetramethyl lead was obtained boiling at 110°. The intermediate fractions were dissolved in dry ether and the solution saturated with hydrogen chloride to form 12 g. of trimethyl lead chloride. The combination of these two compounds results in a 35% yield of tetramethyl lead.

Trimethyl Ethyl Lead: The general procedure given by Grüttner and Krause (13) was used in this preparation. The trimethyl lead chloride used was prepared from tetramethyl lead by the action of hydrogen chloride. A solution of ethylmagnesium bromide was prepared from 10.9 g. (0.1 mole) of ethyl bromide in 100 cc. of dry ether and 2.4 g. (0.1 atom) of magnesium. This solution was added to 9.5 g. (0.03 mole) of trimethyl lead chloride and the solution stirred and refluxed for thirty minutes. At the end of that time there was a positive color test for Grignard reagent and the mixture was hydrolyzed with iced hydrochloric acid. The ether layer was separated and the ether distilled from a water bath. The oil that remained was distilled at ordinary pressure and 7.5 g. (89%) of material was collected boiling at 128-130°.

Diethyl Dimethyl Lead: This compound has been prepared

by Grüttner and Krause (46) who report its boiling point as 51°/13 mm. To a solution of methylmagnesium iodide prepared from 48.4 g. (0.2 mole) of methyl iodide in 200 cc. of ether and 4.8 g. (0.2 atom) of magnesium, 25 g. (0.075 mole) of diethyl lead dichloride was added. There was an excess of Grignard reagent after this mixture had been stirred and refluxed for one hour. The material was hydrolyzed with dilute, iced hydrochloric acid and the ether layer separated and the ether distilled on a water bath. The oil that remained gave a fraction boiling at 59°/18 mm. There was 17 g. or 77% of this liquid.

Methyl Triethyl Lead: Grüttner and Krause (18) give excellent directions for the preparation of this compound and give its boiling point as 69°/13 mm. An excess of a stock solution of methylmagnesium iodide was added to 22 g. (0.067 mole) of triethyl lead chloride. The reaction mixture was stirred and refluxed for thirty minutes and hydrolyzed with iced ammonium chloride. The ether layer gave 20 g. (92%) of a fraction boiling at 69°/13 mm.

Triphenyl Lead Halides: Samples of triphenyl lead chloride, triphenyl lead bromide and triphenyl lead iodide were prepared of a very high degree of purity to be tested as antiknock reagents. The bromide and iodide were prepared from the chloride by the methods given by Gilman and Robinson (41). The materials were very carefully crystallized from alcohol

(46) Grüttner and Krause, Ber., 49:1546(1916).

and melted correctly for pure compounds. The chloride melted at 207°, the bromide melted at 165°, and the iodide melted at 139°.

The triphenyl lead halides have been tested and have been found to be about 20% as effective as tetraethyl lead upon a mole basis. The values are 25%, 20%, and 15% for the iodide, bromide and chloride respectively. The ethyl methyl series of lead compounds are being tested but the results are not available at this time. It is expected that the values will be rather high and may exceed that for tetraethyl lead.

Miscellany

In this work there were a number of compounds prepared and their anti-knock effectiveness determined, which do not properly form any complete series. The experiments on these compounds have been grouped together in this section. In some of the work, the attempts to prepare compounds of interest as anti-knock reagents failed. These experiments will also be described and various recommendations made.

Triethyl Allyl Lead: This compound was prepared prior to this work by Grüttner and Krause (47). In this work the constants that they report for their compound have been checked readily enough and a slight improvement in the method of preparation has been made. A stock solution of allylmagnesium bromide was prepared after the directions of Gilman and McGlumphy (48) from 15 g. (0.6 atom) of magnesium turnings and 36 g. (0.3 mole) of allyl bromide in 300 cc. of ether. To this solution, 50 g. (0.15 mole) of solid triethyl lead chloride was added and the mixture stirred and refluxed for thirty minutes. At the end of that time there was an excess of Grignard reagent. Water was added to hydrolyze the material and the ether layer was separated and washed well with alkali. Upon distillation of the ether layer, 20 g. (39%) of triethyl allyl lead was obtained boiling at 86°/10 mm. (93°/13 mm.).

(47) Grüttner and Krause, Ann., 415:338(1918).
(48) Gilman and McGlumphy, Bull. soc. chim., 43:1322(1928).

<u>Triethyl Benzyl Lead</u>: The directions of Grüttner and Grüttner (42) were followed in this preparation and their constants were checked. A solution of benzylmagnesium chloride was prepared from 2.4 g. (0.1 atom) of magnesium and 12.7 g. (0.1 mole) of benzyl chloride in 100 cc. of dry ether. This solution was added to 20 g. (0.06 mole) of triethyl lead chloride and the resulting mixture was refluxed for two hours. There was an excess of RMgX compound at the end of that time. The material was hydrolyzed by pouring on iced ammonium chloride and the ether layer was separated and the ether distilled off. The residual oil was distilled under 10 mm. in an atmosphere of nitrogen and boiled at 147-152°/10 mm. This fraction was cooled for some time in an ice-salt bath and the crystals of dibenzyl that formed were filtered out. When redistilled, the oil boiled at 147-148°/10 mm. and did not form any crystals when cooled. The yield of pure material was 16.5 g. (80%).

<u>Diethyl Diallyl Lead</u>: A solution of allylmagnesium bromide was prepared from 56g. (0.3 mole) of allyl bromide in 300 cc. of dry ether and 12 g. (0.5 mole) of magnesium turnings according to the recommendations of Gilman and McGlumphy (48). To this solution, which contained an excess of allylmagnesium bromide, 25 g. (0.075 mole) of diethyl lead dichloride was added and the mixture stirred and refluxed for one hour. The solution was hydrolyzed with iced ammonium chloride and the ether layer separated and the ether distilled. The oil that remained was distilled in an atmosphere of nitrogen under

reduced pressure, and 7 g. (28%) of an oil was obtained boiling at 84°/16 mm. (74°/7 mm.) which decomposed quite rapidly. The best analysis that could be obtained was too high which can be explained by the fact that there was considerable of this decomposition. It is probable that this compound could be prepared in better yields by adding the solution of RMgX compound to the diethyl lead dichloride suspended in dry ether.

Analysis: Calc. for $C_{10}H_{20}Pb$; Pb, 59.65%. Found: Pb, 60.72 and 60.75%.

Diethyl di tert-Butyl Lead: A solution of tert-butyl-magnesium chloride was prepared from 42 g. (0.5 mole) of tert-butyl chloride in 500 cc. of ether and 12 g. (0.5 atom) of magnesium (38). This solution was added to 25 g. (0.75 mole) of diethyl lead dichloride suspended in ether. This was an insufficient quantity of Grignard reagent for the diethyl lead dichloride. The mixture was stirred and refluxed for one hour and at the end of that time was poured on iced ammonium chloride to hydrolyze. The ether layer was separated and the ether distilled from a water bath. The residue was distilled under reduced pressure in an atmosphere of nitrogen. A fraction of 11g. (46%) was collected boiling at 88°/13 mm. (80°/10 mm.) which analyzed for diethyl di tert-butyl lead.

Analysis: Calc. for $C_{12}H_{28}Pb$; Pb, 54.61%. Found: Pb, 54.31 and 54.93%.

Triethyl tert-Amyl Lead: A series of three runs were made in an effort to prepare this compound but they all result-

ed in the formation of tetraethyl lead from a deep red solution of what was probably diethyl lead. The first run was made by adding the triethyl lead chloride to a solution of _tert-amyl-magnesium_ chloride. The second experiment was performed in just the reverse order: the solution of _tert-amylmagnesium_ chloride was added to an excess to the triethyl lead chloride, and, in the third, the triethyl lead chloride was in excess at all times and the solution of RMgX was added to it.

1. A solution of _tert-amylmagnesium_ chloride was prepared from 12.2 g. (0.5 atom) of magnesium and 53 g. (0.5 mole) of _tert-amyl_ chloride in 300 cc. of dry ether. To this solution, 22 g. (0.07 mole) of triethyl lead chloride was added slowly in the solid state. The solution became deep red and when heated there was a deposition of black metallic lead. The mixture was hydrolyzed with iced ammonium chloride and the ether layer, which was a deep red color, was evaporated and the residual oil vacuum distilled in an atmosphere of nitrogen. Fifteen grams (66%) of an oil boiling at 136-7°/14 mm. was collected which analyzed for tetraethyl lead. The analysis for lead was made by the method of Calingaert. Besides the regular lead analysis, these oils were analyzed by treatment with hydrogen chloride. The results of this treatment (49) showed that they were all samples of tetraethyl lead for an equivalent quantity of gas was evolved which was shown to be ethane by

(49) 'See p.113, THIS THESIS.

exploding an aliquot part with oxygen.

Analysis: Calc. for $C_8H_{20}Pb$; Pb, 64.08%. Found: Pb, 61.67 and 61.83%; Calc. for $C_{11}H_{26}Pb$; Pb, 56.71%.

2. A solution of tert-amylmagnesium chloride prepared exactly as the one described in the previous experiment, was added to an ether suspension of 46 g. (0.144 mole) of triethyl lead chloride. The RMgX compound was in excess at the end of the addition and the solution became first orange and finally deep red in color. When the mixture was warmed gently, there was a deposition of metallic lead and the red color was discharged. The mixture was hydrolyzed with iced ammonium chloride and the ether layer steam distilled. The oil collected from this procedure was vacuum distilled and at 190° (oil bath) there was considerable decomposition. On examination the vacuum line was found faulty which probably explains the high boiling point of tetraethyl lead in the previous experiment. After inserting a new line for the vacuum, the remaining oil distilled at 80°/7 mm. and 76°/5 mm. Seventeen grams (37%) of this oil was collected which analyzed correctly for tetraethyl lead.

Analysis: Calc. for $C_8H_{20}Pb$; Pb, 64.08%. Found: Pb, 63.72 and 63.68%.

3. In this run, the Grignard reagent was added to a suspension of 50 g. (0.158 mole) of triethyl lead chloride and the addition was stopped before an excess had been added. The yield of tetraethyl lead was 32 g. (64.5%), boiling point 68°/5 mm.

Analysis: Calc. for $C_8H_{20}Pb$; Pb, 64.08%. Found: Pb, 63.76 and 63.82%.

Triethyl β-Styryl Lead: All attempts to prepare this compound, resulted in failure. The product formed by the coupling reaction which takes place during the formation of the Grignard reagent, diphenyl butadiene, causes a lot of trouble during distillation for it seems to occlude the oil and decrease its volatility. The lead compound is only very slowly volatile in steam and separation by such treatment is not feasible. When heated to about 200° in an oil bath under 5 mm., the compound decomposes with considerable violence.

There is evidence of the formation of tetraethyl lead although no fraction could be obtained which would analyze within 12% of the theoretical value for tetraethyl lead. In each of the three experiments, about 35% of an oil was obtained which boiled at about 72°/5 mm. This is probably a mixture of β-bromostyrene and lead tetraethyl. The material gives a test for halogen by the fusion method although it is not strong. There was no evidence of the formation of either diethyl lead or triethyl lead for both would decompose with the deposition of metallic lead and no such deposit was observed. The analyses of the oils, which boiled at 72°/5 mm., were from 43-48% while the theoretical value for triethyl β-styryl lead is 52.14% and for tetraethyl lead is 64.08%. Even with the distillation of this compound there is a great deal of decomposition and it is possible that this oil is a mixture of decom-

position products. Redistillation of this oil gives a large constant boiling fraction which is the main portion of the crude product. In all the experiments, the Grignard reagent was added to the triethyl lead chloride in excess of the theoretical quantities.

A solution of β-styrylmagnesium bromide was prepared from 7.2 g. (0.2 atom) of magnesium and 55 g. (0.3 mole) of β-bromostyrene. The RX compound was added slowly to the magnesium to minimize the coupling reaction. This solution was then added to a suspension of 22 g. (0.07 mole) of triethyl lead chloride in ether until an excess had been added. The mixture was refluxed for thirty minutes and hydrolyzed with iced ammonium chloride. The ether layer was collected and evaporated and the oil vacuum distilled. An oil, which was assumed to be styrene, boiling at 60°/35 mm., was collected and then a fraction boiling at 72°/4 mm. was obtained. There was 10 g. of this compound which when redistilled gave 8 g. (35%) of a constant boiling portion boiling at 74°/4 mm. This material contains lead and gives a slight test for halogen. The lead analysis was 47.75 and 47.60% lead after the method of Calingaert (39) while the calculated value for $C_{14}H_{23}Pb$ is 52.14% lead.

Triethyl p-Anisyl Lead: In the two experiments performed, this compound was undoubtedly prepared but could not be purified because of the decomposition which prevented distillation even under a pressure as low as 5 mm.

A solution of p-anisylmagnesium bromide was prepared from 7.2 g. (0.3 atom) of magnesium and 56.4 g. (0.3 mole) of p-bromoanisole in 250 cc. of dry ether. This solution was added to a suspension of triethyl lead chloride in dry ether. There was 50 g. (0.175 mole) of triethyl lead chloride used and the solution was added until there was just an excess of the RMgX compound. This required about 0.2 mole of the Grignard reagent. There was a smooth reaction and after stirring and refluxing for thirty minutes, there was still a positive color test for Grignard reagent. The mixture was hydrolyzed with iced dilute hydrochloric acid and the ether layer evaporated and the residual oil vacuum distilled. At an oil bath temperature of about 200° there was sudden and rather complete decomposition with the deposition of metallic lead. It is probable that with a lower pressure this oil could be distilled for the lowest pressure used was 5 mm. and at that pressure the oil was just about to distill when decomposition took place.

Triethyl β-Phenylethyl Lead: A solution of β-phenylethyl-magnesium bromide was made up from 93 g. (0.5 mole) of phenyl-ethyl bromide in 350 cc. of dry absolute ether and 12.3 g. (0.5 atom) of magnesium. This solution was added to 48 g. (0.146 mole) of triethyl lead chloride suspended in dry ether. After about 0.2 mole of β-phenylethylmagnesium bromide had been added, there was a positive color test which persisted after thirty minutes refluxing. The mixture was hydrolyzed with iced hydrochloric acid and the ether layer washed repeatedly

with dilute sodium hydroxide solution to remove any excess triethyl lead chloride as the hydroxide. The ether was distilled off and the oil distilled under reduced pressure. Under 7 mm. at a temperature (oil bath) of 200° the compound decomposed with the formation of metallic lead. No liquid fraction could be obtained that analyzed correctly for triethyl β-phenylethyl lead. A fraction was obtained which boiled at 147°/7 mm. with decomposition. This was analyzed for lead by the method of Calingaert (39) and the values were 49.80 and 50.00%. The theoretical lead content of triethyl β-phenylethyl lead is 51.38%. It is very probable that at a lower pressure this material could be distilled with very little decomposition.

Tetra tert.-Butyl Lead: The following is the information gained from two experiments performed in an attempt to prepare tetra tert-butyl lead. A solution of tert-butylmagnesium chloride was prepared according to the directions of Gilman and Zoellner (38) from 24.3 g. (1 atom) of magnesium and 92 g. (1 mole) of tert-butyl chloride in 750 cc. of dry ether. The yield was estimated at 35% as a minimum and this solution was then treated with 50 g. (0.18 mole) of solid lead chloride. There was only a moderate reaction but the characteristic red color formed and there was a precipitate of metallic lead. At the end of the addition of lead chloride there was a positive color test for the Grignard reagent (37). The solution was refluxed for six hours and poured on iced ammonium chloride to hydrolyze. The ether layer was separated and evaporated to

a small volume and dried very carefully with calcium chloride.
There was no test for lead (50) in this ether solution and dry
hydrogen chloride did not form any precipitate or any material
which remains after complete evaporation of the ether. During
the evaporation of the ether, there was no precipitate which
indicates that the decomposition of any intermediate lead com-
pound took place before hydrolysis or during hydrolysis.

Tetra Allyl Lead: In each of the three experiments per-
formed, a solution of allylmagnesium bromide was made up accord-
ing to the directions of Gilman and McGlumphy (48) from 72 g.
(3 atoms) of magnesium turnings and 150 g. (1.25 mole) of allyl
bromide in 800 cc. of dry ether. The yield of RMgX compound
was estimated as 87%, but not titrated, for the magnesium used
was of ordinary size rather than the 30 mesh recommended by
them. Lead chloride was slowly added to this solution until
139 g. (0.05 mole) had been added. During the addition the
solution became red and later light green in color while a
precipitate of metallic lead formed. This was observed after
each portion of lead chloride was added. At the end of the
addition there was a positive color test for the Grignard re-
agent (37). The ethereal solution was refluxed for three hours
and hydrolyzed by pouring on iced ammonium chloride. The
ether layer was separated and evaporated to a volume of 50 cc.
This evaporation caused no precipitation but the solution gave

no test for lead (50). It is highly probable that diallyl lead is first formed from lead chloride which decomposes into lead and diallyl rather than into tetra allyl lead. Möller and Pfeiffer postulate the formation of this intermediate dialkyl lead compound in the preparation of all tetra alkyl leads (27).

Tetra sec.-Butyl Lead: In two experiments a solution of sec.-butylmagnesium bromide was prepared from 12.4 g. (0.5 atom) of magnesium and 69 g. (0.5 mole) of sec.-butyl bromide in 400 cc. of dry ether. To this solution, 50 g. (0.185 mole) of lead chloride as a solid was added in small quantities. There was a smooth reaction and the solution became red and deposited metallic lead, turned green and finally yellow. The solution was refluxed for ten hours and poured on iced hydrochloric acid to hydrolyze. The ether layer was separated, washed with water and steam distilled. A yellow-green oil distilled over very slowly which solidified when allowed to stand under the water over night and when crystallized from alcohol formed pretty, thick needles which melted at 60° with decomposition. This product decomposed quite rapidly in air and more slowly in a solvent. A sample was dried for three hours over sulfuric acid under 5 mm. pressure and was then analyzed for lead by the method of Gilman and Robinson (51). The material had decom-

(50) The solution was tested for lead by adding a 30% solution of bromine in carbon tetrachloride and extracting with a mixture of 20 cc. of aqua ammonia (sp.gr. 0.9) and 50 cc. of 50% acetic acid. This gives a solution of lead acetate from which the lead may be precipitated with a solution of potassium dichromate. This test is quantitative.
(51) Gilman and Robinson, J. Am. Chem. Soc., 50:1714(1928).

posed appreciably for it gave a milky solution when dissolved in carbon tetrachloride and the analysis gave a low value for lead. The yield was 10 g. (25%).

Analysis: Calc. for $C_{16}H_{36}Pb$; Pb, 47.58%. Found: Pb, 46.28 and 46.15%.

The linkage of a secondary carbon atom to lead is very much weaker than that of a primary carbon atom (35). This sort of compound is unstable in air and decomposes with the formation of a flocculent precipitate. The action of halogens is much more vigorous for at -75° halogens will remove two secondary groups while only one primary group is removed under those conditions. Tetra iso-butyl lead melts at -23° while tetra iso-propyl lead melts at -53°. Isomers of these compounds show no tendency to crystallize at much lower temperature. Compounds containing a secondary carbon atom attached to lead may not be heated even in a vacuum because of the thermal decomposition. They are purified by steam distillation. Because of the properties of analagous compounds, it is not surprising that tetra sec.-butyl lead should have the properties that it has.

Dimethyl Diphenyl Lead: The general procedure recommended by Möller and Pfeiffer (27) was used in the preparation of this compound. An excess of a stock solution of methylmagnesium iodide was added to 15 g. (0.035 mole) of diphenyl lead dichloride and the mixture stirred and refluxed for one hour. The solution was hydrolyzed with iced ammonium chloride and the

ether layer fractionated. A fraction was collected boiling at
168°/6 mm. which weighed 11.3 g. (82%).

Phenylmagnesium Bromide with Triethyl Lead Chloride: It
is conceivable that in the preparation of an organolead com-
pound by the reaction of a Grignard reagent upon an organolead
halide, free radicals may be formed intermediately. This ex-
periment was carried out in an effort to find evidence in sup-
port of this theory. A stock solution of phenylmagnesium bromide
was prepared from 157 g. (1.0 mole) of bromobenzene in 500 cc.
of ether and 24.3 g. (1.0 atom) of magnesium and the volume kept
at 500 cc. An aliquot of this solution (100 cc.) was hydrol-
yzed and steam distilled for the diphenyl present. In this way
it was found that 0.6 g. of diphenyl formed. A sample of 66 g.
(0.2 mole) of triethyl lead chloride was added to 125 cc.
(0.25 mole) of this solution of Grignard reagent. The solution
was stirred and refluxed for one hour and at the end of that
time there was no RMgX compound present as evidenced by a
negative color test. An additional 25 cc. (0.05 mole) of the
stock solution was added and the procedure repeated. This time
there was a positive color test and the mixture was poured on
iced ammonium chloride to hydrolyze and the ether layer separ-
ated and steam distilled. There was no solid diphenyl formed
but the first oil that distilled was separated from the water
and vacuum distilled. There was a fraction of 2.5 g. (4%)
boiling at 68°/5 mm. which gave the correct volume of gas when
analyzed for tetraethyl lead and whose boiling point agrees
with that for pure tetraethyl lead. The temperature rose slow-

ly after this fraction had been collected and by fractionation of this material collected over a wide range, 1.7 g. of diphenyl was obtained. The residue from the steam distillation was vacuum distilled and the oil frozen with an ice-salt mixture. By this method, an additional 0.4 g. of diphenyl was obtained. Theoretically from this volume of stock solution, 0.9 g. of diphenyl should have been obtained while actually 1.2 g. in excess of this quantity was found. If it is true that the diphenyl is formed by the coupling of two free radicals in the preparation of triethyl phenyl lead, and that the tetraethyl lead is formed by the decomposition of triethyl lead, then for every mole of tetraethyl lead formed there should be one mole of diphenyl formed. From 2.5 g. (0.00775 mole) of tetraethyl lead a corresponding quantity of diphenyl might be expected. This is the case for the 1.2 g. of diphenyl is 0.0078 mole. The yield of triethyl phenyl lead was 54.5 g. (73%) boiling at 126°/5 mm.

Triphenyl Lead Chloride with Phenylmagnesium Bromide: A similar experiment was performed using triphenyl lead chloride instead of triethyl lead chloride. To a suspension of 47.3 g. (0.1 mole) of triphenyl lead chloride in ether, 125 cc. of the previously described solution of phenylmagnesium bromide was added and the mixture stirred and refluxed for one hour. At the end of that time there was a positive test for RMgX compound and the mixture was hydrolyzed with iced ammonium chloride and the ether layer was separated and steam distilled.

This treatment separated 0.75 g. of diphenyl from 50 g. of tetraphenyl lead. There was no green color or any solubility evidence of the formation of triphenyl lead. The yield of tetraphenyl lead was nearly quantitative and the quantity of diphenyl formed was the same as the blank.

Aeration of Tetraethyl Lead: In every sample of alkyl lead compound that is allowed to stand for some time, a turbidity appears which has not been explained. It is possible that this turbidity is due to the formation of lead diethoxide due to the oxidation of the air. Accordingly, this experiment was carried out. A small amount, 6.6 g. (0.02 mole), of tetraethyl lead was placed in a test tube and dry air was drawn through it for six hours. At the end of that time there was no turbidity that might be lead diethoxide.

A number of these compounds were tested for their anti-knock effectiveness by Midgley's bouncing pin method. The results are given in a tabular form below.

Compound	Moles of tetraethyl lead necessary to produce the same effect as one mole of compound.
Triethyl allyl lead	1.00
Diethyl diallyl lead	0.70
Diethyl di tert.-butyl	0.65
Triethyl benzyl lead	0.65

The results are too few to be of value in drawing conclusions but it appears that a loosely bound group, such as the allyl or benzyl group, is not the answer to the anti-knock problem.

Some General Considerations of Manipulations and Tests

In this work on organolead compounds, a miscellany of re-actions has been developed which may be of value to those work-ing with this class of compounds. They are reported here in a group in order to be more readily available to the reader al-though they are also given throughout this paper at the various points where they have been used.

One of the most important things to be considered in work-ing with organolead compounds is their toxicity. They are all very toxic especially the liquids which may volatilize and so permeate a whole laboratory. The salts of triethyl lead hydrox-ide and the base itself are very disagreeable to work with for the dust from the dry samples causes sneezing and nasal secre-tion. Where these compounds come in contact with the more sensitive skin such as the face, they cause mild inflammation. As Krause and Pohland (29) have pointed out, long exposure to this class of compounds causes severe headaches. Calingaert (52) has discussed the toxicity of organolead compounds in his very complete paper and has made several valuable recommenda-tions. He suggests that the entire laboratory should be washed frequently with bromine water in order to decompose the dust that accumulates from this work. There is also an advantage in wearing rubber gloves when handling these materials, and a good hood with a good draft is absolutely essential. When a

(52) Calingaert, Chem. Reviews, 2:43(1925).

vacuum pump is used for low pressure distillations, it should be reserved for this work exclusively.

Besides the poisonous nature of these compounds, there is the danger of explosions when the liquids are being distilled. In this work it has been found that an explosion results when liquid is heated above 200-225° (oil bath temperature). In this laboratory, the glassware has been cleaned in a hot bath of concentrated sulfuric and nitric acids. It has been found that a small quantity of organolead compound present when a piece of glassware is placed in a very hot bath will often cause a violent explosion which throws acid about the room. In this connection it is well to point out that such a method of cleaning glassware must result in the formation of lead sulfate which adheres quite tenaciously to the glass. This may be removed by rinsing the apparatus with a solution of ammonium acetate which will be described later.

A stock solution of ammonium acetate was found very useful in these experiments. The one that was used was prepared by mixing 20 cc. of concentrated ammonium hydroxide (sp.gr. 0.9) and 50 cc. of 50% acetic acid. This solution will dissolve most forms of inorganic divalent lead compounds such as lead halides, lead sulfate, etc. In this way it is possible to test for the presence of inorganic divalent lead in any compound with considerable accuracy.

It is necessary to have two qualitative tests for lead. Both of the tests used in this work are simply rough adapta-

tions of the two quantitative methods used to determine lead.
For oils and liquids, the material is dissolved in chloroform
or carbon tetrachloride and treated with a 30% solution of
bromine in chloroform or carbon tetrachloride until the red
color of bromine persists. The white precipitate of lead
bromide that forms is extracted from the organic liquid with
this stock ammonium acetate solution. The lead is precipitated
from this solution of lead acetate as the chromate by means of
a 5% solution of potassium dichromate. For solids, which are
much more stable and not readily decomposed with this solution
of bromine, a different method is used, which consists of
heating the material in a test tube with a mixture of about
3 cc. of concentrated sulfuric acid and 5 drops of concentrat-
ed nitric acid to burn out all the organic matter and precipi-
tate the lead as lead sulfate. Since concentrated sulfuric
acid is a rather good solvent for lead sulfate, the test is
made more delicate by diluting the acid mixture with water.

A Beilstein test for halogen is useless when applied to
an organolead compound for there is a colored flame formed by
the lead which obscures the green of the halogen test if it is
present. The test that has been used for halogens is the regu-
lar sodium fusion and subsequent treatment with silver nitrate.

It is not good policy to ignite these lead compounds upon
a piece of platinum foil to determine if they are organic or
not for such a procedure will ruin the platinum. The lead or
lead oxide formed during the ignition appears to dissolve the

platinum and leave great holes.

The method of Calingaert that is referred to repeatedly
in this paper has been used to analyze liquids for lead. This
method is essentially the same as the qualitative test used to
test liquids for lead. Of course it is necessary to add the
refinements that good quantitative analytical procedure de-
mands but the chemistry is the same. The method for analyzing
solids for lead has been published by Gilman and Robinson (51).

Tetraethyl lead has been found in so many of these ex-
periments that in order to be sure of the compound a method
has been developed to be used in connection with the customary
lead analysis. This method depends upon the fact that when
tetraethyl lead is treated with dry hydrogen chloride in dry
ether solution, one ethyl group is removed and volatilizes as
ethane. A weighed sample is dissolved in dry ether in a small
flask and the solution saturated with hydrogen chloride. The
ethane that is formed is collected over water in an eudiometer.
Of course all the gas that is collected is not ethane but the
volume is the same as though it were. All the gas may be
swept from the apparatus by filling it with a measured volume
of water and an aliquot of that gas taken for analysis. By ex-
ploding a sample with oxygen and measuring the contraction and
the carbon dioxide formed, the quantity of ethane present may
be calculated. The water added is equivalent to the original
gas in the apparatus and when subtracted from the final total
volume gives the volume of ethane.

SUMMARY

A number of organolead compounds have been prepared and their anti-knock effectiveness determined. There is evidence of the formation of diethyl lead when triethyl lead chloride is added to tert.-butylmagnesium chloride or to tert.-amylmagnesium chloride. It appears that free radicals are formed intermediately during the preparation of triethyl phenyl lead.