I. THE ATTEMPTED SYNTHESIS OF CYCLOBUTANE FROM TETRAMETHYLENE DIBROMIDE

II. ATTEMPTED NEW SYNTHESES OF 1,3 CYCLOBUTANE DICARBOXYLIC ACID

III. THE SYNTHESIS OF ORTHO AND META ARSANILIC ACID

Thesis by
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Presented in partial fulfillment of the requirements for the degree of Master of Science

California Institute of Technology
Pasadena, California
June, 1945

ACKNOWLEDGEMENT

It is a pleasure to acknowledge the aid of Dr. Edwin R. Buchman, who is responsible for suggesting the subjects of research in the cyclobutane field, and without whose knowledge and guidance this work could not have been carried out.

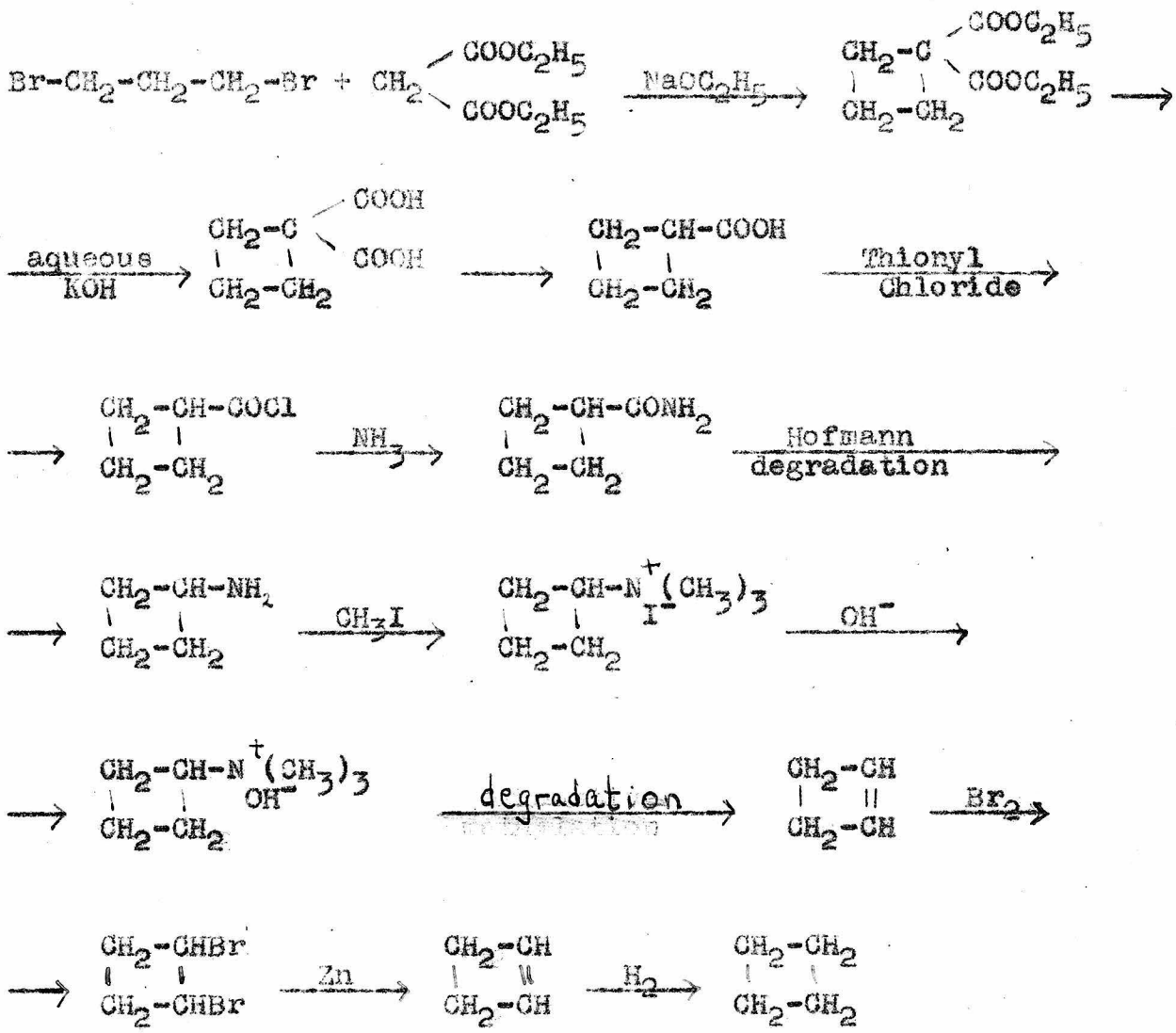
I also wish to thank Dr. David Pressman for his able direction of the research in the field of the arsanilic acids.

I. THE ATTEMPTED SYNTHESIS OF CYCLOBUTANE FROM TETRAMETHYLENE DIBROMIDE

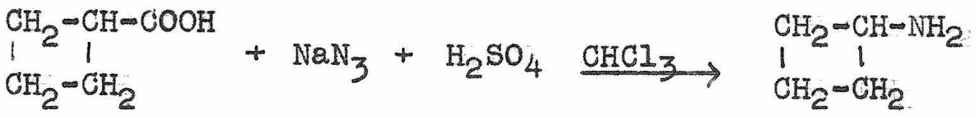
In connection with studies of derivatives of cyclobutane (1,2,3) which for some time have been underway in these laboratories, a method for the large scale preparation of cyclobutane itself, the parent compound of four carbon ring chemistry, was desired. As the simplest member of this group of compounds, it is the obvious starting material for syntheses in this series. In addition, the compound is of theoretical interest (4); for example, the heats of combustion of cyclopropane (5), cyclopentane (6), and cyclohexane (7) are known, whereas that of cyclobutane is unknown. Its general relation to the other members of the series of saturated cyclic hydrocarbons is of great interest in these laboratories, where it was desired to undertake electron diffraction studies of cyclobutane.

Cyclobutane was first synthesized by Willstätter and his co-workers (8,9,10) in 1907, through a tedious series of experiments starting from trimethylene dibromide and malonic ester. A reaction first carried out by Perkin, with sodium ethylate as catalyst (11), effected a ring closure and yielded 1,1-cyclobutanedicarboxylic ester, which upon hydrolysis and decarboxylation (12) gave the monocarboxylic acid (13,14). The synthesis proceeded through the acid chloride (15) and then through the amide (9). A Hofmann degradation was then carried out to yield cyclobutane amine. A quaternary ammonium base was prepared from the amine, a base which,

when degraded, yielded cyclobutene. This compound was purified by brominating the double bond, distilling the dibromo cyclobutane and regenerating the cyclobutene by zinc reduction. Hydrogenation of this compound resulted in the desired end product, cyclobutane. A schematic presentation of this synthesis follows:



It was not until Heisig (16), in 1941, prepared cyclobutane amine directly from the monocarboxylic acid, that the synthesis was substantially improved. By treatment of the acid with sodium azide and sulfuric acid in chloroform, he obtained the amine salt in good yield.



Despite this improvement, the synthesis still involves many steps and the yield is rather low. Consequently, it was decided to investigate simpler methods of preparing the compound. One of the simplest and most obvious of these methods was apparently to start with a 1,4-tetramethylene dihalide and bring about an intramolecular Wurtz-type reaction to yield cyclobutane in a single step. If successful, this promised to be quick and direct, with the added advantage of involving easily obtainable starting materials.

Some work had previously been done in an attempt to reduce 1,4-tetramethylene dihalides with metallic reducing agents in various solvents, none of which yielded cyclobutane. Hamonet (17) attempted the reduction of the dibromide with zinc in an alcoholic medium, a reaction which resulted in straight chain butane. Gauthier (18) used magnesium as the reducing agent and obtained a mixture of organic magnesium derivatives which, upon addition of carbon dioxide, yielded both adipic and sebacic acids. (cf. V. Braun and Sobecki(19)) Colman and Perkin (20) claimed a closure of the four ring in this manner by treating 1,4-dibromopentane with finely

divided sodium in toluene, but the identity of the end product with methyl cyclobutane is questionable.

The preparation of 1,4-tetramethylene dihalides has been reported. W. Schmidt and F. Manchen (21) prepared 2-butyne-1,4-diol from formaldehyde and acetylene, reduced it, and then chlorinated it with thionyl chloride to yield 1,4-dichlorobutane. S. Fried and R.D. Kleene (22) prepared the dibromide in 70% yield by passing dry HBr into tetrahydrofurane, and later (23) prepared the dichloride by using dry hydrogen chloride in the presence of zinc chloride, and the diiodide by using dry hydrogen iodide. A. Luttringhaus and D. Schade (24) reported the preparation of the dibromide in 21% yield from silver adipate by treatment with bromine. J. von Braun (25) prepared the dibromide by splitting benzoylpyrrolidine with phosphorus pentabromide. Heisig (26) prepared the diiodide by treating tetrahydrofurane with phosphorus and iodine and refluxing.

It was decided to use the dibromide in the investigations described in this paper, since it is more easily prepared and probably more stable than the diiodide, although it would not be as reactive. 1,4-Tetramethylene dibromide was ultimately prepared from furoic(or pyromucic) acid, which was decarboxylated (27) to yield furane. This was catalytically hydrogenated (28) with Raney Nickel catalyst (29) to tetrahydrofurane, which was, in turn, treated with dry hydrogen bromide to yield the desired product (22).

Some work has been reported on ring closure effected by reduction of α,ω- polymethylene dibromides to yield the

corresponding saturated cyclic hydrocarbon. Cyclopropane has been prepared from trimethylene dibromide by heating it with sodium (30); by adding it to sodium under boiling xylol (31); by warming it to 50-60°C with zinc dust in 75% ethanol (32); by heating with zinc wool in isoamyl alcohol (33); by treatment with magnesium in ether (34); by treatment with sodamide in liquid ammonia (35); and by the action of zinc dust in 50% acetic acid solution at water bath temperature (36). 1,5-Dibromopentane has been converted to cyclopentane (37) by the action of zinc dust in ethanol, and 1,6-dibromohexane has yielded cyclohexane (38) when treated with sodium in xylol.

In 1936, Hass and coworkers (39) synthesized cyclopropane by reducing trimethylene dibromide with zinc dust in a medium of molten acetamide at 170-180°C in the presence of sodium carbonate and sodium iodide. In preparing cyclopropane from trimethylene dibromide by reduction with magnesium, they discovered that iodide ion has a catalytic effect. The catalytic effect of iodine and organic iodides on the formation of Grignard reagents was well known, and led them to the conclusion that the ring closure took place through the formation of a Grignard reagent as intermediate. They also found that removal of the iodide, even after reaction had begun, would cause the reaction to cease, but that if 1-chloro-3-iodopropane or 1,3-diiodopropane were used as the starting material, the reaction would proceed without iodide ion. When zinc was used as reducing agent in place of magnesium, the iodide ion was rapidly used up, presumably due to the formation of zinc iodide, which is largely unionized. Consequently, it

was necessary to apply some method for regenerating the iodide ion from zinc iodide. Two methods could be applied: a) adding to the reaction mixture, sodium carbonate, which reacts with zinc iodide to yield zinc basic carbonate, sodium iodide, and carbon dioxide or b) the use of a compound such as acetamide which forms an ionized complex ion with zinc iodide as follows:

$$ZnI_2 + 4\ CH_3CONH_2 \longrightarrow Zn(CH_3CONH_2)_4^{++} + 2\ I^-$$

It was brought to light that the presence of both sodium carbonate and acetamide in the reaction mixture would cut down the amount of zinc dust which must be used and also the amount of sodium iodide.

Recently, Murray (40) applied this method to the preparation of spiropentane from pentaerythrityl tetrabromide. Donohue, Humphrey, and Schomaker (41), of this laboratory, have recently proved the structure of spiropentane by electron diffraction methods. The success of Murray and Hass suggested the possibility of establishing the reduction of polymethylene dihalides, and perhaps of unsaturated dihalides, in this manner, as a general ring closure method for the formation of cyclic compounds, especially in the somewhat difficultly formed four ring.

The purest zinc dust available commercially was further purified before use, since we were advised by Murray in a private communication that the formation of spiropentane from pentaerythrityl tetrabromide depended directly upon the purity of zinc dust used.

In the first attempted reduction, following carefully the method used by Hass and by Murray, no cyclobutane was

formed, but a fair yield of straight chain butane was isolated, with no unsaturated hydrocarbons being formed, as indicated by treatment with bromine. This suggested that protons were being picked up by the molecule to yield a saturated straight chain compound, rather than a ring closing bond being formed.

It was then decided to substitute a solvent which, while sufficiently like acetamide, would not be as apt to yield free protons to the reaction mixture as would the strongly polar amide group, in the hope that ring closure would then be enforced. The substitutes subsequently decided upon were N-acetyl piperidine and N-benzoyl piperidine, both of which contain the $>N-\overset{O}{\overset{\|}{C}}-$ grouping in common with acetamide, but which replace the polar amide hydrogen atoms by a rather non-polar saturated ring system.

The use of an N-acetyl piperidine medium for reduction again yielded a large amount of butane, and no cyclobutane, but this time a quantity of unsaturated hydrocarbon, probably mixed butenes, was found to be present. A similar result was obtained when N-benzoyl piperidine was substituted as the solvent.

The presence of saturated compounds at this point suggested that the free radicals, presumably formed as an intermediate during the reaction, were active enough at this elevated temperature to draw protons from even such slightly polar compounds as N-benzoyl and N-acetyl piperidine. It was consequently decided to attempt to preclude these possibilities by running the reaction at reduced temperatures.

Previous runs having been made at 170-180°C, the reaction was now tried at 60°C in N-benzoylpiperidine, and resulted in a reduced yield of butane, with no unsaturated compounds isolated.

Since no unsaturated compounds were formed when acetamide was employed, while some unsaturation occurred here, it was thought possible that protons were being taken from the hydrocarbon dihalide. If this were the case, the protons present could not be eliminated by change of solvent. Consequently, reduction of the dihalide by zinc dust was attempted in the presence of sodium iodide and sodium carbonate at 170°C, but without use of solvent, and resulted in a mixture of butane and butenes, indicating that the hydrocarbon dihalide itself was the source of protons.

The only other alternative which presented itself was the use of less reactive reducing agents, but we were not prepared to undertake so extensive a problem at this time. Substitution of such agents as sodium amalgam or sodamide for the zinc dust under varying conditions might prove a worthwhile investigation, but such an undertaking promised to be a complete new task, having no connection with the Grignard type reaction which was postulated by Hass and his co-workers, as the mechanism which applies here. Consequently, it was decided to abandon the project. A summary of results is given in Table I.

TABLE I

Summary of Results

Exp. No.	Solvent	Temperature	Approximate Percentage of Material in product		
			Butane	Mixed Butenes	Higher Boiling Material
1	CH_3CONH_2	180-190°C	85%	0%	15%
2	N-Acetyl-Piperidine	180-190°C	80%	5%	15%
3	N-Benzoyl-Piperidine	165-175°C	80%	5%	15%
4	N-Benzoyl-Piperidine	55-100°C	90%	0%	10%
5	no solvent	165-175°C	40%	40%	10%

APPARATUS

The apparatus used for the reduction reaction was an all-glass one, consisting of a standard taper, one liter, three-necked, round bottom flask fitted with a stirrer, a dropping funnel and a condenser. From the top of the condenser, a tube was led into an ampule, which was cooled in a Dewar flask using a dry ice - butyl ether bath. A second dry ice trap was used to liquefy any gaseous products escaping from the ampule. Distillations were conducted from the ampule directly, using a four foot reflux column equipped for total reflux and variable take-off, and cooled by alcohol at minus sixty degrees centigrade. The alcohol was circulated by a centrifugal pump, and at one point in the system, passed through a coil which was immersed in a bath of ethanol and dry ice.*

* I am indebted to Dr. Herbert Sargent for his aid in setting up the equipment necessary for this work

EXPERIMENTAL

Furane (27)

148 gms. of quinoline and 130.5 gms. of pyromucic acid were placed with one gram of precipitated copper metal in a 1-liter, 3-necked flask, fitted with thermometer and 8 inch Hempel column leading to a 2-liter flask containing 250 gms. of sodium hydroxide in 750 ml. of water (25% solution). This flask had a thermometer and outlet to an 8 inch calcium chloride tower immersed in a four liter beaker of water for heating. The tower led to a 30 cm. vertical spiral condenser cooled with ice water, which ran into an Erlenmeyer flask, cooled by an ice - HCl - water mixture. This in turn was connected to a dry ice trap. The reaction vessel was heated in an oil bath at 220°C, the sodium hydroxide flask was kept at 65-70°C. Decarboxylation proceeded smoothly with 58.4 gms. of furane collecting in the Erlenmeyer flask. (80% of theory). The product was redistilled, the portion from 30.4-31.0°C. being collected. Very little impurity was present.

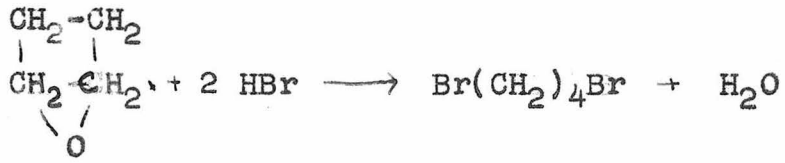
Tetrahydrofurane (28)

100 gms. of furane and 100 gms. of n-butyl alcohol were placed with 10 gms. of Raney Nickel (29) catalyst in a Burgess-Parr reduction apparatus at room temperature and a pressure of three atmospheres of hydrogen. Hydrogen was absorbed rapidly. Toward the end of the reaction, 5 gms. of catalyst were added and the temperature was increased to

55°C. Total hydrogen absorbed was approximately the theoretical value. The catalyst was removed by filtration and the filtrate was fractionated, the 60-80°C fraction treated with excess sodium to remove the alcohol and redistilled. 65 gms. (60%) of tetra hydro furane boiling at 66-67°C were collected.

Tetramethylene Dibromide (22)

Hydrogen bromide was generated by the action of bromine on cold technical tetralin, and purified by passing first through two towers of tetralin, and then through two drying tubes containing $CaCl_2$ and P_2O_5 successively. 160 gms. of dry HBr gas were then passed into 72 gms. of tetrahydrofurane, according to the reaction:



$$CH_2(CH_2)_2CH_2O + 2\ HBr \longrightarrow Br(CH_2)_4Br + H_2O$$

The temperature gradually rose to 105°C, and the reaction mixture colored slightly. When HBr ceased to be absorbed, the mixture was cooled, washed thrice with 100 ml. portions of 20% sodium bicarbonate solution, and thrice with 100 ml. portions of cold water. The product was taken up in 100 ml. of ether and dried over annydrous sodium sulfate. The solvent was removed, and the residue distilled at reduced pressure. 124.5 gms. (57.6%) of tetramethylene dibromide were collected at 101-105°C at 41 mm. pressure.

N-Acetyl-Piperidine

340 gms. of anhydrous piperidine were mixed with 316 gms. of pyridine. With cooling and stirring, 337 gms. of acetyl chloride were added dropwise over a period of three hours. The temperature was allowed to rise gradually to 50°C. Stirring was continued for one hour after addition was complete, and the mixture was then allowed to stand over night at room temperature.

The heavy sludge was extracted with isopropyl ether until the solution came through clear. The filtrate separated into two phases, and isopropyl ether phase, and an oily phase. The oily layer was extracted with 100 ml. of benzene and this was combined with the ether layer. The solvents were removed, and the residue distilled in vacuo. 241.5 gms. of N-acetyl piperidine boiling at 144-145°C at 78 mm. pressure were collected.

N-Benzoyl-Piperidine

To 255 gms. of piperidine and a solution of 120 gms. of NaOH in 500 ml. of water were added dropwise with cooling and stirring, 450 gms. of benzoyl chloride over a period of three hours. The mixture was stirred for one half hour after addition was complete. The two layers were separated and the oily layer was taken up in 250 ml. of isopropyl ether. A small sample of the solution was cooled in dry ice, and the crystals formed were used to seed the major portion which was cooled at 4°C over night. Crystals were filtered, washed with isopropyl ether and dried in air. These were twice

distilled *in vacuo*, and 324 gms. of white crystals melting at 48.5-49.5 C were collected.

Reduction of Tetramethylene Dibromide

a) In the apparatus described above, using a Truebore stirrer with a Hershberg arrangement, 190 gms. of acetamide (Merck reagent, dried *in vacuo*), 90 gms. of zinc dust (General Chemical, 93%, which had been further purified by rapid treatment with 5% HCl solution, three 100 ml. water washes, two 50 ml. alcohol washes, two 50 ml. ether washes, and drying in a vacuum oven at 70°C for one hour), 10 gms. of NaI and 30 gms. of Na_2CO_3 (anhydrous) were placed. The flask was heated in an oil bath at 185°C. 49.7 gms. of tetramethylene dibromide was added dropwise. Addition was made at 18 ml. per hour. If any faster addition was made, the reaction product carried liquid acetamide through the condenser, and deposited it in the exit tube. The addition took about two and one half hours. The reaction mixture was heated for 30 minutes after addition was complete. The crude yield was about 15 gms. This was distilled and about 10 gms. of material was collected at 0-3°C. About 2 ml. of higher boiling material was left as residue. The distillate was treated with bromine, and the excess of bromine destroyed with $Na_2S_2O_5$ solution. No bromo compounds separated, indicating no unsaturation.

b) The same quantities were used as before, except that 225 gms. of N-acetyl piperidine replaced the acetamide. 50 gms. of tetramethylene dibromide was added over three hours. The

product distilled at 0-2°C. On bromine treatment, a small amount of unsaturated material was found to be present. A residue of about 2 ml. was left undistilled. This boiled at 67-68°C, and was probably a higher hydrocarbon.

Distillation of the reaction mixture gave only a fraction boiling at 215-220°C, presumably N-acetyl piperidine.

c) In the reaction flask were placed 150 gms. of N-benzoyl piperidine, 25 gms. of Na_2CO_3, 70 gms. of zinc dust and 8 gms. of NaI. 30 gms. of tetramethylene dibromide were added at 165-175°C over two hours. 7 ml. of material was collected. This was distilled at 0-2.5°C, about 4 ml. of product being collected, which yielded 0.1 ml. of bromo compound, indicating again slight unsaturation.

d) Using the same quantities as in (c), the addition was made at 55-65°C over two hours. After four and one half hours of stirring no product had collected. The temperature was slowly increased to 100°C. At 80°C, the product began to distill over. After three hours, 2 ml. had been collected, which distilled at 0.5-1.5°C, and contained no unsaturated material.

e) 70 gms. of zinc dust, 8 gms. of NaI and 25 gms. of Na_2CO_3 were treated with 30 gms. of tetramethylene dibromide as before. About 5 ml. of product was collected, which yielded about 4 ml. of material after distilling at 0-2.5°C. This yielded, upon bromine treatment, about 2.5 ml. of a bromine addition compound, indicating about 50% of unsaturated material present.

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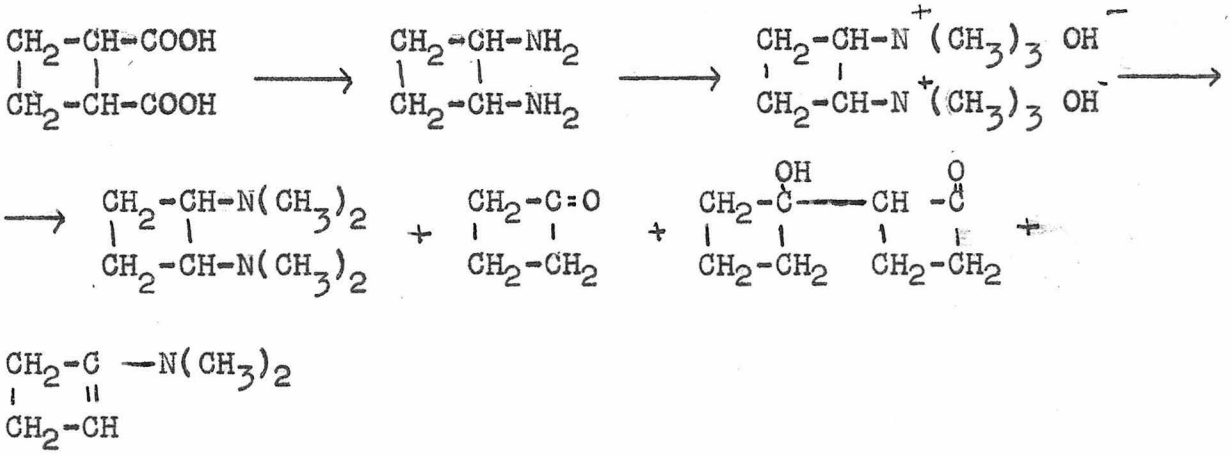
II. ATTEMPTED NEW SYNTHESES OF 1,3-CYCLOBUTANEDICARBOXYLIC ACID

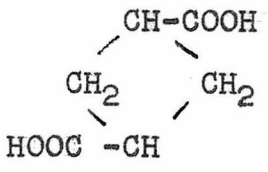
The synthesis of 1,3-cyclobutanedicarboxylic acid is of interest in these laboratories in connection with the projected synthesis of cyclobutadiene. Buchman, Schlatter, and Reims (1) attempted to prepare cyclobutadiene from trans-1,2-cyclobutane diamine, which had been obtained from the corresponding 1,2-acid (2). The diamine was converted to trans-1,2-cyclobutane-bis-(trimethyl ammonium)-hydroxide (1), which was pyrolyzed. Instead of the desired cyclobutadiene, however, the products of the pyrolysis were cyclobutanone, trans-1,2-tetramethyl-diamino-cyclobutane, 1-dimethylamino-cyclobutene-1, and some condensation products of cyclobutanone, as follows:



It is obvious that a similar series of reactions starting from trans 1,3-cyclobutanedicarboxylic acid and ending in the pyrolysis of trans-1,3-cyclobutane-bis-(trimethyl-ammonium)-hydroxide might lead to the desired goal.

Trans-1,3-cyclobutanedicarboxylic acid was first prepared by Markownikoff (3) in 1881 by the action of sodium ethylate on ethyl α-chloropropionate:

$$CH_3CHClCOOC_2H_5 \xrightarrow{NaOC_2H_5} CH_3\underset{OC_2H_5}{CH}\text{-}COOC_2H_5 +$$



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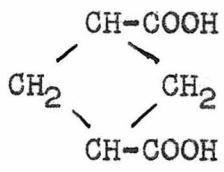


II

This was the first four-ring compound to be synthesized. Markownikoff also was able to convert his compound to an isomer (4), which he did not identify. The synthesis was later studied by Haworth and Perkin (5) who established that the original Markownikoff compound was the trans isomer (I), and who isolated the cis-isomer (II) from the same reaction and showed that it was identical with the isomer prepared by Markownikoff from the trans-isomer. The preparation of (II) by related reactions from formaldehyde and malonic ester (or their equivalents) was reported by Perkin, Simonsen and Bottomley (6,7,8). This latter synthesis received some attention recently in this laboratory, where Buchman, Reims, and Schlatter (9) showed that the product from malonic ester and formaldehyde was not the cis-isomer (II) as stated by Perkin but instead was α-methyleneglutaric acid. They showed that, while cis-1,3-cyclobutanedicarboxylic acid (II) resembles α-methyleneglutaric acid physically, the former has saturated properties consistent with its formula, while the latter reacts instantaneously with alkaline permanganate,

adds hydrobromic acid, and yields a pyrazoline derivative with diazomethane.

In unpublished work, Buchman, Reims, and Schlatter (28) reinvestigated the Markownikoff preparation of the trans-acid (I). In spite of much study, involving several modifications of the original method, the yields obtained were not entirely satisfactory. The preparation of large amounts of trans-1,3 acid (I) which would be required for an extended study of diquaternary salt formation and degradation thus presents a laborious and tedious undertaking (28).*

The present work has been undertaken in order to improve the Markownikoff synthesis and/or to develop a new and more practical method of preparing the trans-1,3 compound. The Markownikoff synthesis might be improved through a better understanding of the mechanism. The combined yield of cis- and trans-cyclobutanedicarboxylic ester in the original synthesis is approximately 10%. The major reaction product is α-ethoxy-ethyl propionate. In addition, other reaction products have been isolated (28), in small quantities, but the nature of these is not yet elucidated. The reaction is not limited to the action of sodium ethoxide with α-chloro-ethyl propionate. A bromine atom may be substituted for the chlorine without affecting the reaction products. The ethyl ester may be replaced with either the methyl (3) or the butyl ester (28), with only the effect in the latter case, of making the hydrolysis of the resulting ester more difficult. The reaction will also take place with compounds of the type $RCH_2CHClCOOR$. For example, bromobutyric ester may be con-

*Buchman, Reims, and Schlatter, in unpublished work, have carried the synthesis as far as the 1,3-diamine. The work has been held up due to present conditions.

densed to yield a higher homologue of cyclobutane-dicarboxylic ester (3).

The mechanism of the reaction is obscure. It is known that the reaction of methyl acrylate with sodium methoxide does not yield significant amounts of four-ring compound but instead yields α-methylene-glutaric ester (9). The Markownikoff reaction itself yields none of the latter open-chain isomer (28). If β-chloropropionic ester is treated with sodium ethylate, cyclobutane-dicarboxylic ester is not detectable, but the end-product is again (28), α-methylene-glutaric ester. None of these reactions yields a detectable quantity of 1,2-cyclobutane-dicarboxylic acid (9, 28) either cis or trans. Consequently, acrylic ester or any intermediate form which would stabilize itself in part to $CH_2=CH-COOR$ appears to be excluded as the intermediate. Thus, the polymer, $CH_2=C(-COOR)-CH_2-CH_2COOR$, α-methylene-glutaric ester, could probably not be an intermediate.

It is important to extend the knowledge of the limitations of the reaction. Experiments which might directly benefit this research are investigations of the action of sodium ethoxide upon compounds of the type: CH_3CHX-Y or $CH_3CX\langle^{Y}_{Y}$, where x represents a halogen atom and Y is a grouping such as COOR, CN, or NO_2.

In this work, the reaction of sodium ethoxide with α-chlor, α-methyl-malonic ester was carried out. The product was not 1,1,3,3,- cyclobutane-tetracarboxylic (19) ester as might be expected from analogy to the Markownikoff reaction, but was instead trans-dimethyl-succinic acid. The starting material was prepared by condensation of ethyl propionate

and ethyl oxalate in the presence of sodium ethoxide (10) to give $CH_3-CH(CO-COOC_2H_5)-COOC_2H_5$ which upon heating loses carbon monoxide (11) to yield α-methyl-malonic ester. Chlorination with sulfuryl chloride results in the required starting material, α-chlor, α-methyl-malonic ester, which has not previously been described.

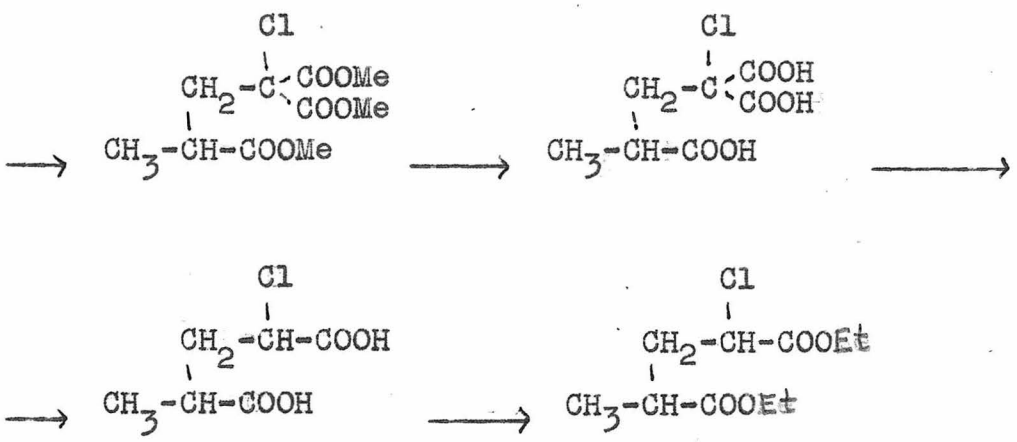
The structure of the condensation product, trans-dimethyl-succinic ester, was proved by saponification, conversion to the cis-anhydride, and then to the cis-acid. A sample of trans-acid was obtained from Professor H. J. Lucas and at each step, a satisfactory mixed melting point was obtained.

In the Markownikoff reaction, either a $-\overset{|}{C}-\overset{|}{C}-COOC_2H_5$ fragment reacts with another to yield the cyclobutane ring directly or two such fragments react to yield an intermediate of the type $-\overset{|}{C}(C_2H_5OOC-)-\overset{|}{C}-COOC_2H_5$.* An attempt was made in this series of experiments to synthesize α-chlor, α'-methyl-glutaric ester, $C_2H_5OOC-CH(CH_2CHClCOOC_2H_5)-CH_3$ by the following series of reactions:

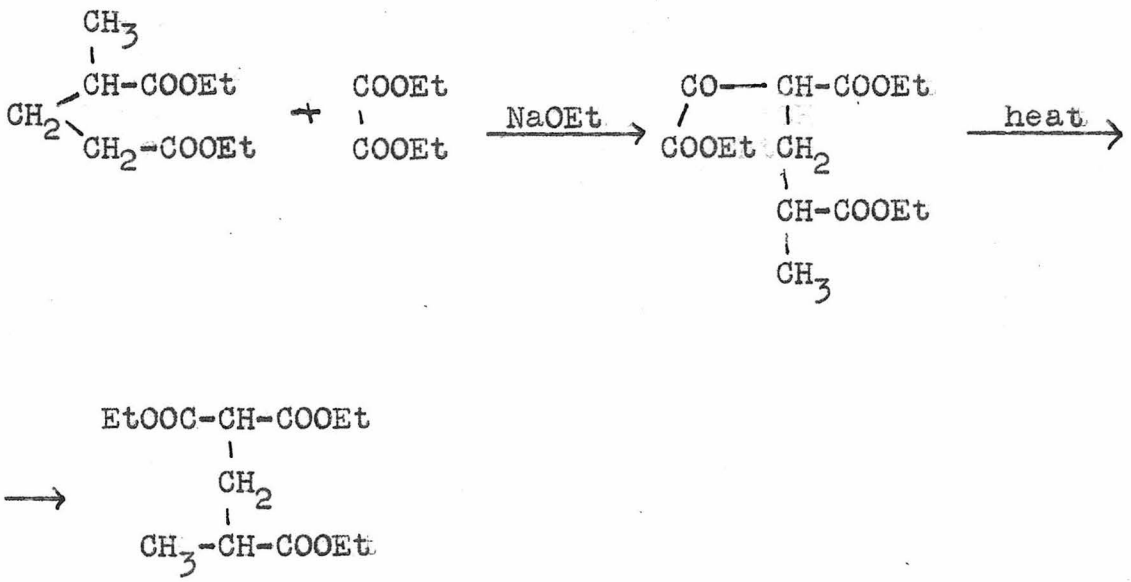
$$CH_2=C(CH_3)-COOMe + Na-CH(COOMe)_2 \xrightarrow{NaOMe} CH_3-CH(CH_2-CH(COOMe)_2)-COOMe \longrightarrow$$

---

*Dr. S. Winstein (U.C.L.A.) in a private communication, postulates $CH_3-C(CH_2-CH_2-COOEt)(Cl)-COOEt$ as a possible intermediate formed by the addition of a $CH_3CHClCOOEt$ fragment to $CH_2=CHCOOEt$ under the influence of sodium ethylate. Experiments to test this hypothesis have not yet been carried out.



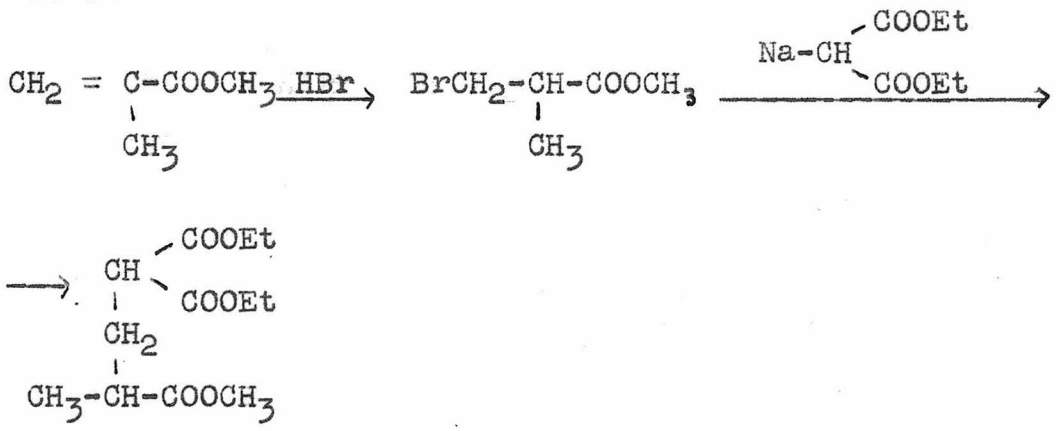
The literature contains examples of the formation of glutaric ester derivatives which are pertinent to the present problem. Cox, Kroeker, and McElvain (12), using sodium ethylate as the condensing agent, brought about the following reaction:



Gidvani, Kon and Wright (13) prepared α-carbethoxy-α'-methyl-glutaric ester by the reduction of ethyl- α-carbethoxy- γ-methyl-glutaconate with an aluminum amalgam.

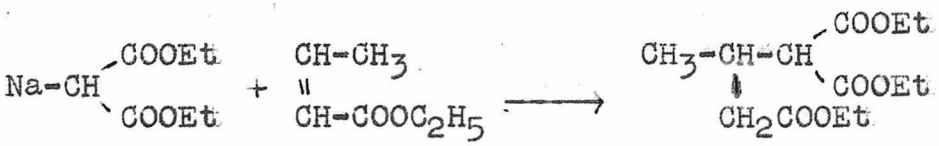
Vocke (14) carried out a series of reactions, starting from methacrylic ester, proceeding through α-methyl, β-bromo-propionic ester, which upon condensation with sodio-

malonic ester yielded α-methyl, α'-carbethoxyglutaric ester.

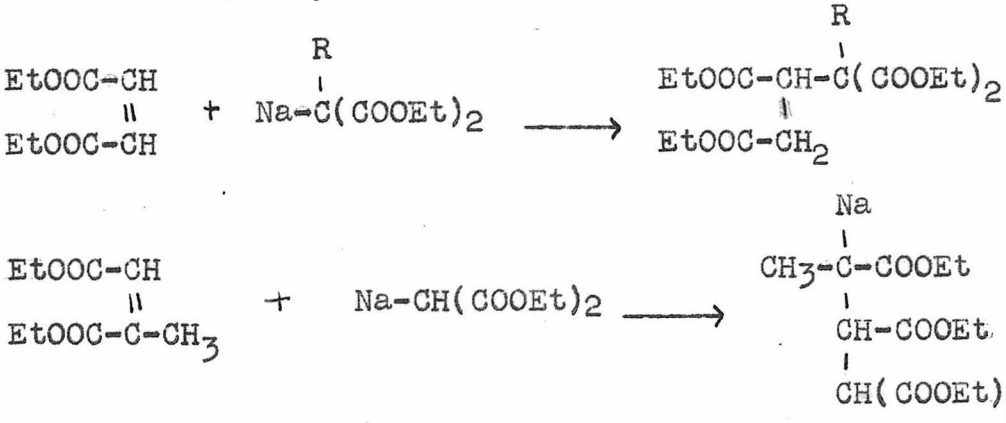


Ingold (15) carried out a condensation between α-methyl, α-hydroxypropionic ester and sodio-cyano-acetic ester to yield the corresponding cyano derivative, α-cyano, α'-methylglutaric ester.

Michael (16) reacted crotonic ester with sodio-malonic ester in the following manner:



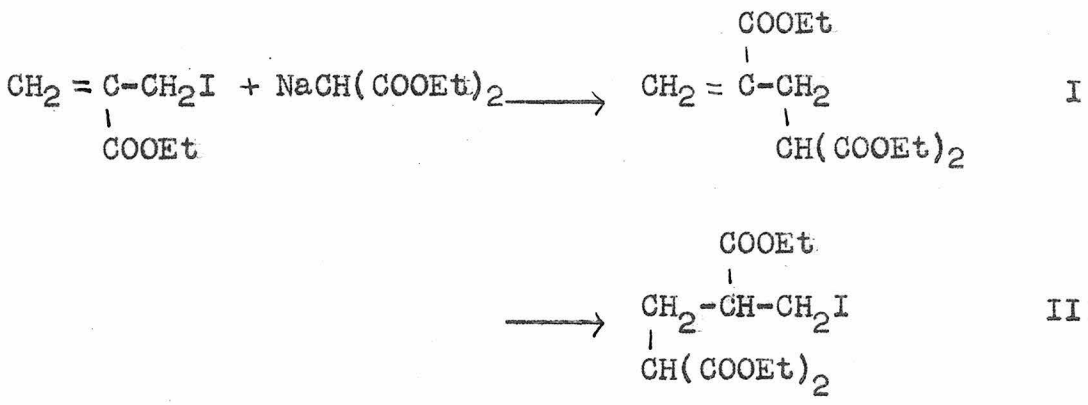
Auwers, Kobner, and Meyenburg (17) carried out the following types of reaction both with sodio-malonic ester, and with α-alkyl derivatives of it:



The attempt to condense methyl methacrylate with sodio - dimethyl-malonate in the presence of sodium-methylate resulted in a high boiling ester which did not analyze correctly, and could not be chlorinated. Further investigations were not carried out because of the pressure of other work.

Since our primary interest lay in finding a practical method of preparation for 1,3-cyclobutane-dicarboxylic acid it was decided to seek other possible methods of preparation of the desired compound.

Welch (18) described the preparation of α-iodomethyl-acrylic acid from ethyl di-(hydroxymethyl) malonate and — hydriodic acid. Analogously to the work described above (12, 13, 14, 15, 16), this compound should react with sodio malonic ester in one or both of the following ways:

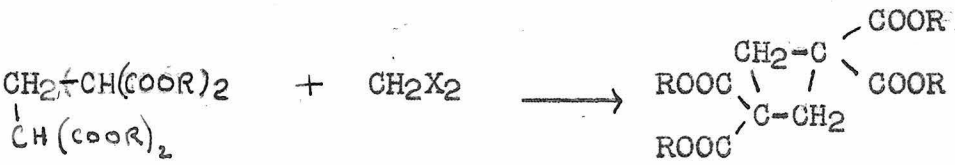


If reaction I takes place, addition of a hydrogen halide to this compound, should, since β-unsaturated acids act contrary to Markownikoff's rule for the addition of a hydrogen halide to a double bond, give the same product as that which would result if reaction II occurs.

In any case, condensation of either of these compounds with sodium ethylate may result in the closure of the four

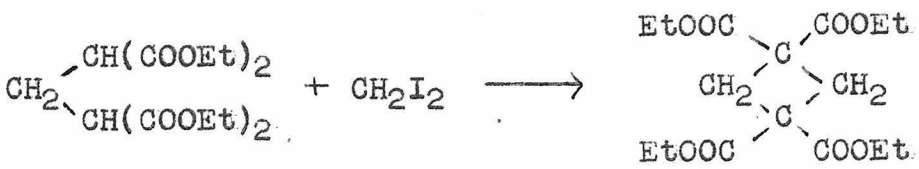
ring. The starting material, α-iodomethacrylic acid, has been prepared at this writing, but the condensation was not attempted. Difficulty was encountered in esterifying the compound and this work had to be abandoned for the duration of the war.

In connection with this line of attack, other possible syntheses of 1,3-cyclobutane derivatives have been considered and are projected for such a time as this work can be undertaken once more. The condensation of α, α'-dicarbethoxyglutaric ester with methylene dihalide in the presence of sodium ethoxide

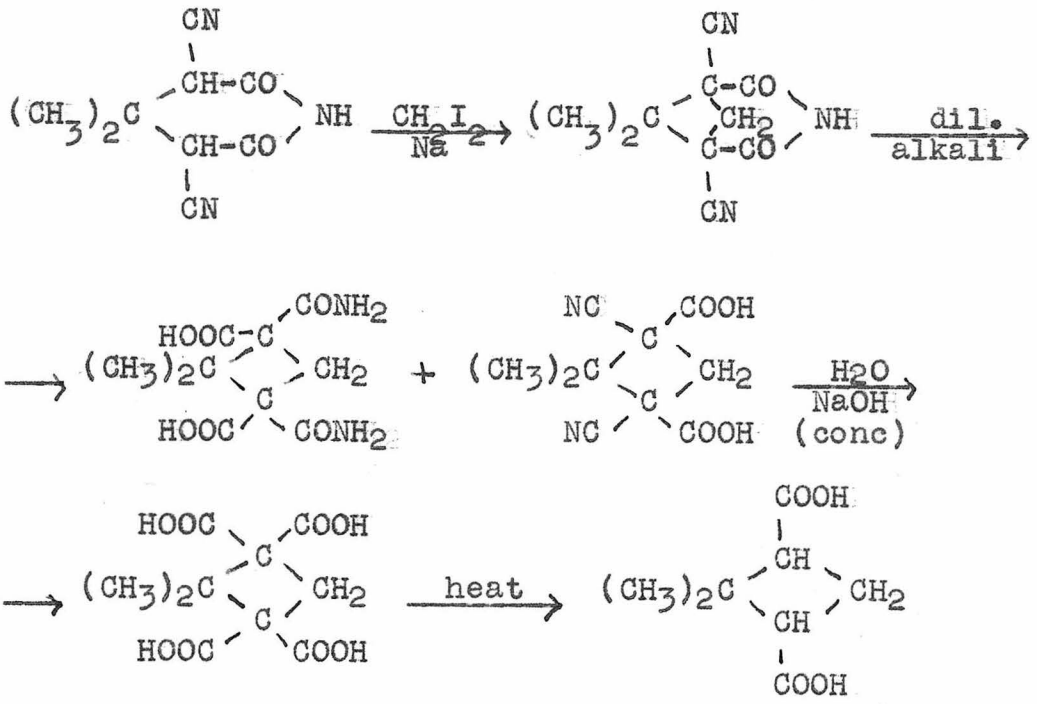


has received some preliminary investigation at the hands of Buchman and Schlatter (28). The results were not promising, but further work on the reaction is deemed worthwhile, since many examples of condensations with methylene halides have been reported in the literature. The preparation of 1,1,3,3-tetracarbethoxycyclobutane has been reported (19).

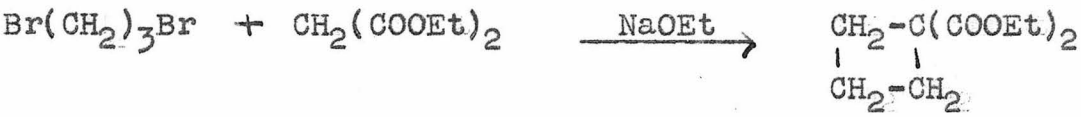
Guha and coworkers have been responsible for much work in condensing methylene halides with various esters and the following reactions have been carried out (20, 21):



Kerr (22) condensed Guareschi's imide (23) with methylene iodide to yield ultimately norpinic acid in the following manner:

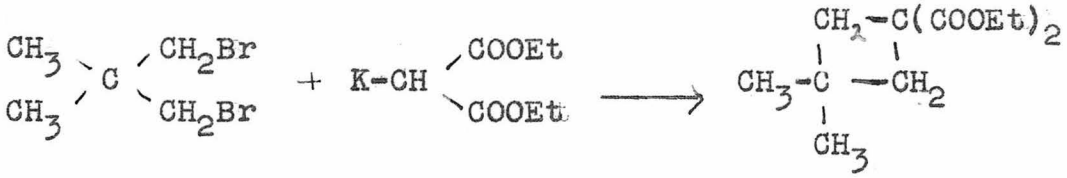


In 1887, Perkin (24) prepared 1,1-cyclobutanedicarboxylic ester by the condensation of ethyl malonate with trimethylene dibromide in the presence of sodium ethylate:

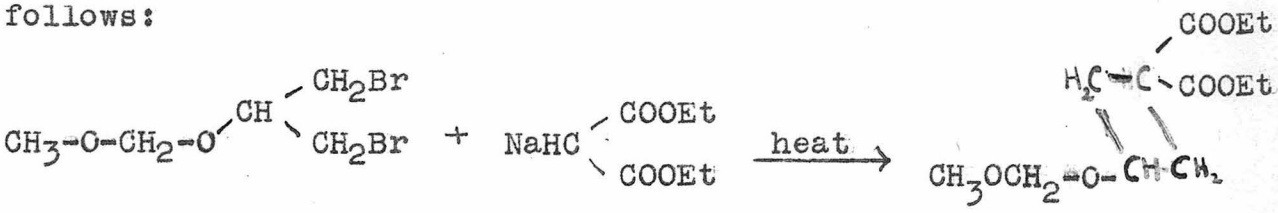


Improvements of this synthesis were made by Heisig and Stodola (25), Wibaut (26) and Fischer (27).

Similarly Owen, Ramage, and Simonsen (29) prepared 3,3-dimethyl-1,1-cyclobutanedicarboxylic ester by heating a mixture of potassio-malonic ester with 1,3-dibromo-2,2-dimethylpentane at 130-140°C for thirty-six hours:

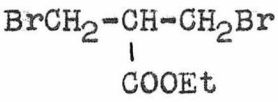


L. Blanchard (30) carried out a reaction of the same type as follows:



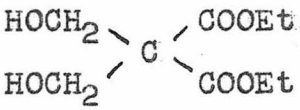
Analogously, it should be possible to carry out the condensation of 2-carbethoxy-1,3-dibromopropane with sodiomalonic ester to give 1,1,3-tricarbethoxycyclobutane, which could easily be hydrolyzed and decarboxylated to yield the desired 1,3-dicarboxycyclobutane.

In order to investigate this possibility, it was necessary to prepare the starting material, 2-carbethoxy-1,3-dibromopropane.

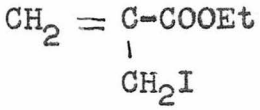


The possible methods which presented themselves were:

a) starting from dimethylolmalonic ester (31),

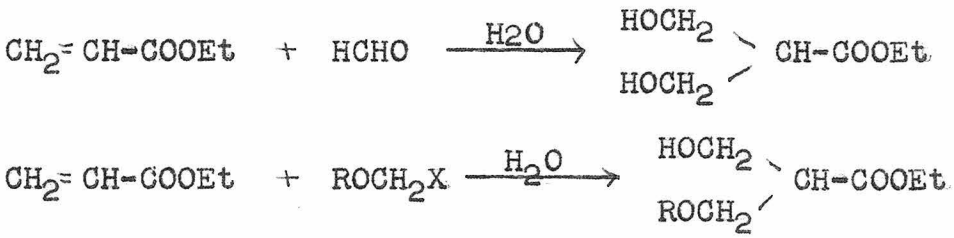


or starting from α-(iodomethyl) acrylic ester (18),

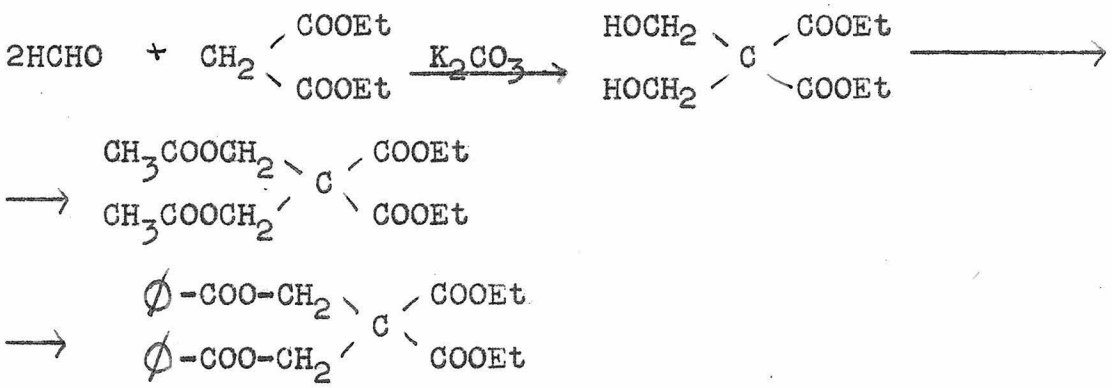


b) starting from dimethylolacetone or its equivalent,

c) starting from acrylic ester and adding formaldehyde or its equivalent,



a) I. H. Gault and A. Roesch (31) prepared dimethylolmalonic ester by the condensation of formaldehyde with malonic ester in the presence of potassium carbonate. The compound has also been prepared by Welch (18). Gault and Roesch (loc. cit.) prepared the diacetyl and dibenzoyl derivatives of dimethylolmalonic ester.

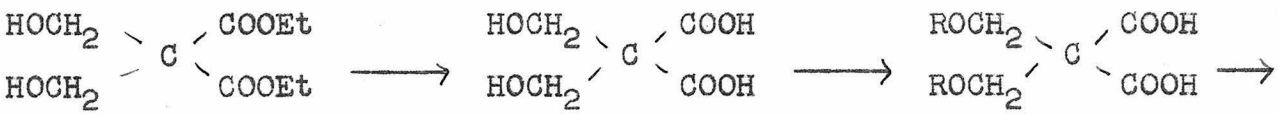


The dibenzoate was a crystalline, stable compound and the diacetate was easily distillable, whereas the glycol derivative itself was extremely heat labile, yielding methylenemalonic ester upon heating. They were unable to carry out the hydrolysis of this ester with hydrochloric acid, but were successful, when it was carried out in 10% potassium hydroxide, in isolat-

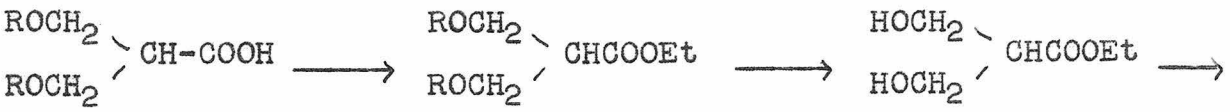
ing dimethylol-malonic acid. They attempted to decarboxylate this compound, but were unsuccessful, and succeeded only in isolating a compound which was almost completely insoluble in water and practically all inorganic solvents. They were unable to identify this material. An attempt was made to prepare monomethylol-malonic ester by addition of one mole of formaldehyde to one mole of malonic ester, and also by decomposition of the dimethylol compound, but both methods resulted in the formation of methylene-malonic ester. The latter compound was the usual end product when the dimethylol-malonic ester was subjected to even mildly strenuous conditions.

Starting from dimethylol-malonic ester, several routes presented themselves.

1) The material could be saponified, converted to an ether, and decarboxylated as follows:



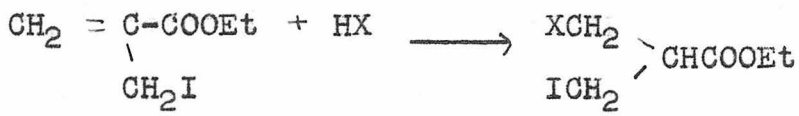
The latter material might then be esterified, reconverted to the diol, and bromination of the alcohol groupings attempted.



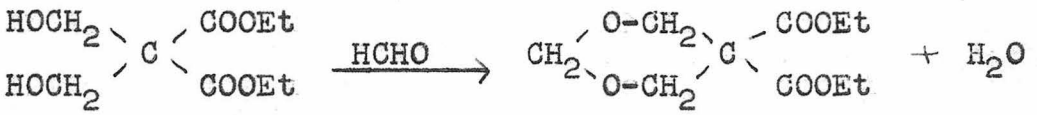
2) The diacetyl derivative of dimethylol-malonic acid could be prepared and an attempt made to convert it directly

to di-(bromomethyl) malonic ester with saturated, aqueous HBr by the method of Wilson and Lucas (32):

3) The starting material might be converted to ∝-(iodomethyl) malonic acid, by the method of Welch (18), esterified, and this reacted with hydro halogen acid.

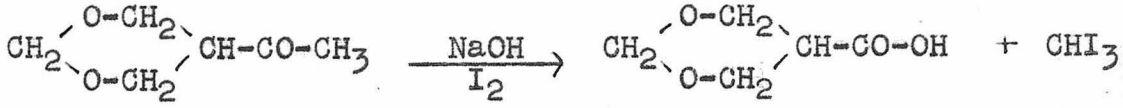


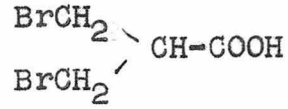
4) The dimethylolmalonic ester could be stabilized by the addition of a molecule of formaldehyde to close the 1,3-dioxane ring.



Saponification, decarboxylation, and reesterification would then prepare the molecule for efforts to brominate the alcohol linkages.

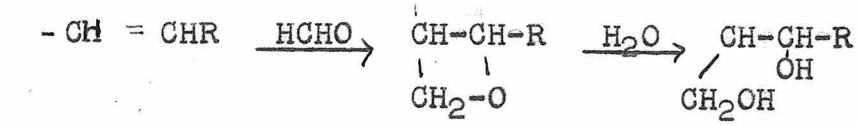
b) Dimethylolacetone may be prepared by the action of formaldehyde on acetone below 60°C in alkali at pH 10 (36). After protection of the methylol groupings, attempts may be made to convert the CH_3-CO- group to HOOC-, perhaps by the iodoform reaction; for instance:



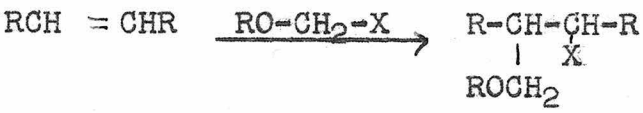
Attempts may then be made to convert this compound to the desired one, 

c) H. J. Prins (33) described the addition of formaldehyde

to such double bonds as are found in styrene, pinene, limonene, etc. He postulated the formation of a cyclic ether to which a molecule of water adds to yield the corresponding glycol:



F. Straus (34) reported an additive reaction of compounds of the formula $RO-CH_2-X$ with an olefin linkage in the following manner:



Further examples of this type of addition are given by F. J. Walker in his monograph on formaldehyde (35).

Occasion was offered to examine only reaction (a). In this investigation, the work of Gault and Roesch was repeated. Several attempts were made, following their directions carefully, but it was found impossible to crystallize the oil obtained from formaldehyde and malonic ester even after five months in the cold room. However, it was found possible to show the presence of the dimethylol-malonic ester in the oil by the preparation of a diacetyl derivative which distilled at the same temperature as that described by the original authors, and a dibenzoyl derivative which melted correctly and analyzed well.

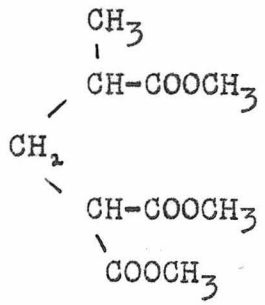
The diacetyl derivative was treated with saturated aqueous HBr (32) solution. Ethyl bromide separated, and, from the aqueous layer, an oil was isolated which reduced potassi-

um permanganate, decolorized bromine water and proved to be halogen free by sodium fusion test and was not further investigated.

Hydrolysis of the crude dimethylol-malonic ester could not be effected by potassium hydroxide. The instability of this compound which decomposed upon the slightest provocation to methylene-malonic ester, made further work in this direction rather unpromising. The problem was abandoned temporarily at this point due to the pressure of war work.

EXPERIMENTAL

Attempted Preparation of α-methyl, α'-carbmethoxyglutaric dimethyl ester.



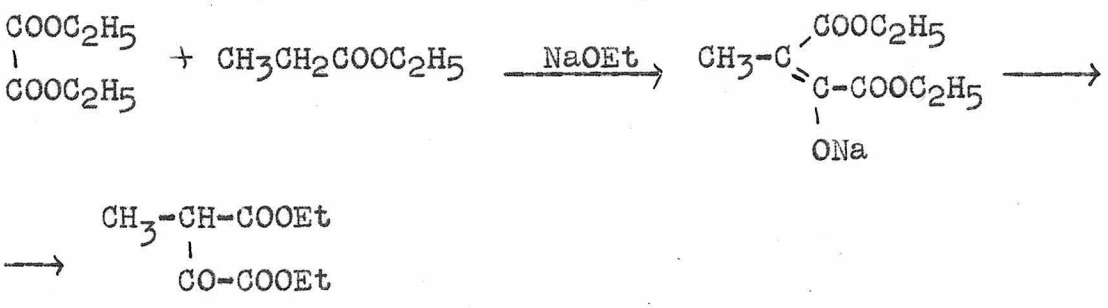
23 gms. of sodium were dissolved in 550 gms. of absolute methyl alcohol, with cooling. With stirring, was added 132 gms. of dimethyl malonate. The sodium salt of dimethylmalonate crystallized out in a fine slurry. 100 gms. of methylmethacrylate were then added with stirring. The crystals dissolved as the mixture warmed to 45°C. After stirring for 16 hours, the solution darkened to a light orange. It was then refluxed on a water bath for two hours, and drowned into one liter of ice water. The oily phase was taken up in ether, and the water layer extracted with ether. The ether extracts were combined and dried over Na_2SO_4, the ether evaporated and distilled *in vacuo*. 65 gms. of extremely viscous product were recovered at 209-212°C/29mm. It was refractionated and a fraction recovered at 139-139.5°C/0.2mm. It was analyzed poorly and attempts to hydrolize it with 4% alcoholic KOH failed. When chlorination attempts with sulfuryl chloride also were unsuccessful, it was assumed that the product was not the desired one and work on it was abandoned.

Analysis:

	C	H
Calc.	51.72%	6.90%
Found	53.56%	7.22%

Preparation of Ethyl Ethoxalyl-Propionate (10)

69 gms. of sodium were powdered under xylene in a 3 liter 3-necked flask. The mixture was cooled and the xylene was decanted, the sodium being further washed with dry ether, by decantation. 1 liter of dry ether was then added. The flask was fitted with a stirrer, reflux condenser and dropping funnel, the latter two being fitted with $CaCl_2$ drying tubes. 175 cc. of absolute ethanol were added dropwise and the mixture was stirred over night to dissolve the sodium. The flask was immersed in an ice bath and a mixture of 306 gms. of ethyl propionate and 438 gms. of ethyl oxalate were added dropwise. The mixture was stirred for two hours after the addition was complete. The solvent was removed on a water bath, and 600 cc. of 33% aqueous acetic acid solution were added. The sludge was broken up and extracted with five 500 cc. portions of ether. The combined ether extracts were washed with one liter of water, two 500 cc. portions of 10% $NaHCO_3$ and again with one liter of water, then dried over Na_2SO_4. The ether was removed on a water bath and the residue distilled. 319 gms. of product, were recovered, boiling at 117-122°C/12mm. (uncorr.) with little forerun and little residue.



α-Methyl-Malonic Ester (11)

319 gms. of ethyl ethoxalyl-propionate was heated gradually until an evolution of gas began. The temperature was slowly raised to maintain a smooth evolution of gas, with refluxing finally attained at about 200°C, and continued until gas evolution ceased. The residue was distilled. 247 gms. of α-methyl-diethyl-malonate boiling at 194-196°C (uncorr.) were isolated.

α-Chlor, α-Methyl-Diethyl Malonate

247 gms. of α-methyl, diethyl-malonate were placed in a 1 liter rb. flask with 200 cc. of thiophen-free dry benzene. At room temperature, 191.7 gms. of sulfuryl chloride were added with stirring. The temperature was increased to 50°C to initiate the reaction and it was then stirred over night. The benzene was removed on a water bath, and the residue distilled. 294 gms. (99%) of material were collected at 111.5-112.5°C/20mm. (uncorr.) Sodium fusion test for halogen was positive. The material boiled at 213°C at atmospheric pressure without decomposition.

Analysis:	C	H
Calc.	45.82%	6.68%
Found	46.32%	6.16%

Condensation of α-Chlor, α-Methyl-Malonic Ester

250 gms. of α-chlor, α-methyl, diethyl-malonate in a 1 liter rb. flask, fitted with reflux condenser, stirrer and rubber addition tube were heated to 100°C. The bath was re-

moved and 94 gms. of NaOEt was added over 1 hour with stirring at such a rate as to maintain the temperature. Much heat was evolved. The bath was replaced and stirring continued at 120°C for one hour more. The mixture was cooled and drowned in a solution of 40 cc. H_2SO_4 in 400 cc. H_2O. The oil was separated and the aqueous layer extracted with 3 portions of ether, 100 cc. each. These were combined with the oil and the whole was washed with saturated Na_2CO_3 solution until neutral. The washings were re-extracted with two 100 cc. portions of ether. All ether extracts were combined and dried over Na_2SO_4. The ether was removed on a steam bath and the residue distilled <u>in vacuo</u>, through a Vigreau column wound with asbestos cord. A fraction was separated at 118-182°C/10mm. This was refractionated and resulted mainly in two fractions: 1) 160-175°C/9mm. - 40 gms.; 2) 175-187°C/9mm. - 45 gms. These were hydrolized separately with 18% alcoholic NaOH, refluxing for six hours. Water was added and the alcohol distilled off, this procedure being continued until the alcohol was completely replaced by water. The solution was acidified and evaporated to dryness. The residue was taken up in ether and dried over Na_2SO_4. The ether was evaporated. Each fraction was treated in this manner. Each portion was recrystallized from dioxan, and resulted in identical crystalline compounds melting at 194.0-196.0°C. (uncorr.) A mixed melting point of the two fractions gave no depression. They were combined and recrystallized from alcohol. A mixed m.p. with a sample of 1,3-cyclobutanedicarboxylic acid resulted in a 40° m.p. depression. An

analysis gave: C - 49.28%; H - 6.83% corresponding to $C_6H_{10}O_4$. A mixed m.p. with trans - α, α'-dimethyl-succinic acid gave no m.p. depression. The material was heated above its m.p. for 1 hour, and readily gave up water. The product melted at 75-76°C and gave no m.p. depression with cis-dimethyl-succinic anhydride. The material melting at 75-76°C was boiled with a small quantity of water, cooled, and saturated with HCl gas. A crystalline compound separated melting at 120-121°C. It gave no m.p. depression with cis-dimethyl-succinic acid.

Dimethylol-Ethyl-Malonate (31)

80 gms. of diethyl-malonate were added in 10 cc. portions to a solution of 100 cc. of 37% HCHO in water and 1 gm. of K_2CO_3 in 3 cc. H_2O, over a period of 1 hour. After each addition, heat was evolved and the mixture was cooled to room temperature before the next addition was made. The mixture was stirred one hour after the addition was complete. 200 cc. of saturated $(NH_4)_2SO_4$ solution was added and the oily layer taken up in 100 cc. of ether. The resulting aqueous phase was saturated with $(NH_4)_2SO_4$ and extracted with 50 cc. of ether. The ether phases were combined and the solvent evaporated on the steam bath. A stream of dry air was run through the residue for 20 hours, and the residue was then placed in the ice box. No crystallization had occurred after five months at 4°C.

Diacetate of Dimethylol-Ethyl-Malonate (31)

66 gms. of crude dimethylol malonic ester were treated with 60 gms. of acetyl chloride while cooling in an ice bath, the addition being made slowly over 30 minutes. The solution was allowed to stand for two hours at room temperature, and was then drowned into an excess of $NaHCO_3$ solution and ice. This was extracted with ether, the extract washed with $NaHCO_3$ solution, then with water. It was dried over $MgSO_4$. The ether was removed under reduced pressure. 44 gms. of material boiling at 173-175°C/11mm. (uncorr.) were recovered.

Dibenzoate (31)

The dibenzoyl derivative was prepared similarly to the preparation of the diacetyl derivative, using benzoylchloride. It melted at 96-97°C (uncorr.) and gave in analysis: C - 64.42%; H - 5.78%. Calculated for the compound is C - 64.49%; H - 5.61%.

Attempted Preparation of Dibromomethyl-Ethyl-Malonate

44 gms. of diacetate of dimethylol-malonic ester were dissolved in 100 cc. of saturated aqueous HBr solution and allowed to stand at room temperature for 20 days. A current of air was run through the mixture at reduced pressure to remove the ethyl bromide which had separated. The solution was neutralized until still strongly acid but no longer miscible with ether. It was continuously extracted with ether for 24 hours. The ether was removed on a steam bath.

The residue was an oil which reduced alkaline $KMnO_4$. It distilled at 194-196°C to give a clear colorless product which was negative in sodium fusion test for halogen. It was not further investigated.

α-Iodomethyl-Acrylic Acid (18)

16 gms. of crude dimethylol-malonic ester and 66 gms. of hydriodic acid solution (d = 1.70) were refluxed for 45 minutes and then allowed to stand over night. The mixture was refluxed again for 40 minutes using hot water in the condenser to allow ethyl iodide to escape, but recondensing the hydriodic acid. On cooling, white crystals precipitated. These were filtered and recrystallized from hot water. 3 gms. of cream-colored plates melting at 98-100°C (uncorr.) were isolated. The silver salt was precipitated with $AgNO_3$, washed and refluxed with ethyl iodide in absolute ethanol for 5 hours. The precipitate was filtered off and the alcohol evaporated. The residue was distilled, and came over at 40-50°C/20mm. The distillate was dark red. An ether solution of the distillate was shaken with alkaline KI solution, thus extracting the iodine. The ether layer was dried, after washing, over $MgSO_4$. After removing the ether, the product distilled water white, but after standing for 24 hours, it had turned red, obviously liberating iodine again. No further work could be done on this because of the pressure of war work.

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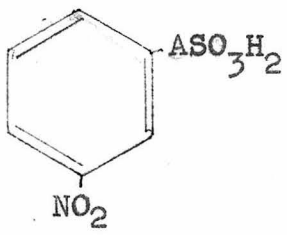
III. THE SYNTHESIS OF ORTHO AND META ARSANILIC ACID

With the purpose of paralleling the work done by L. Pauling, D. Campbell, D. Pressman, and others, (1) on precipitation reactions between antibodies and substances containing two or more para-arsanilic groups, research was undertaken to prepare ortho (IV) and meta (II) arsanilic acids.



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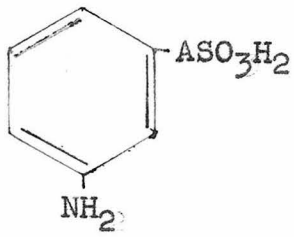

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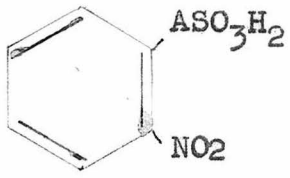
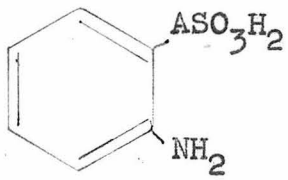


III



IV

Bertheim and Benda (2), by heating arsenic acid with paranitraniline, prepared, in very poor yield, 5-nitro-2-aminophenylarsonic acid which was deaminated to yield the desired m-nitrophenylarsonic acid. (I). This latter compound has also been prepared by Schmidt (3) by treatment

of diazotised meta-nitraniline with an alkaline solution of sodium arsenite, and by Michaelis and Loesner (4) by nitration of phenyl arsonic acid.

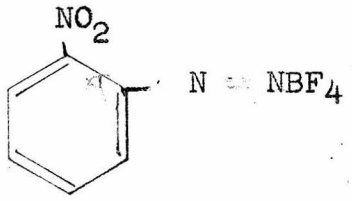
In this present work, a somewhat exhaustive study of the nitration of phenyl arsonic acid was made. The latter compound was prepared by the method of Bullard and Dickey (5) by treating diazotized aniline with sirupy arsenic acid. (80-85%). The nitration of this compound was found to be extremely sensitive to the amount of water present in the reaction mixture. Use of fuming nitric acid in concentrated sulfuric acid resulted in good yield if refluxing were carefully controlled. If the mixture was refluxed too vigorously, some water was lost through the condenser, and charring of the substance occurred. On the other hand, the presence of a comparatively large quantity of water, as represented by the substitution of concentrated HNO_3 for fuming HNO_3, resulted in no reaction whatsoever.

Reduction of m-nitrophenyl arsonic acid (I) to the corresponding m-arsanilic acid (II) has been reported by Boehringer and Soehne (6), who used catalytic hydrogenation with palladium catalyst on a barium sulfate carrier to bring about the reaction. Several attempts to repeat this process were unsuccessful, probably due to poisoning of the catalyst by free arsenic salts present either as an impurity or from reduction of the arsonic acid group. The latter possibility is included because of the lack of reaction even with carefully purified nitro body, or with material which had been

prepared under conditions in which no free arsenic salts were present.

The reduction of m-nitrophenylarsonic (I) acid was carried out by Jacobs and Heidelberger (7) through the use of ferrous hydroxide. This work was repeated, and was successful, but resulted in extremely poor yields. In the present work, extremely rapid reduction in almost quantitative yield was readily accomplished by the catalytic hydrogenation process, using Raney Nickel as catalyst.

O-nitrophenylarsonic acid (III) has been prepared by Jacobs and Heidelberger (7) by treatment of diazotised o-nitraniline with alkaline sodium arsenite. However, in the present work, the preparation of (III) was found to be much simpler if the preparation of it be carried out through the diazonium borofluoride (V) as intermediate (8).



V

(V) is a stable crystalline compound which can be washed thoroughly and recrystallized to purify it. The purification of the intermediate decreases the amount of decomposition in the subsequent reaction with sodium arsenite.

Investigations of the reduction of (III) to yield o-

arsanilic acid (IV) gave much the same results as reduction of the corresponding meta derivative (I). Catalytic reduction with palladium catalyst could not be accomplished, and ferrous hydroxide reduction resulted in poor yield, but catalytic reduction with Raney Nickel catalyst was easily and rapidly carried out in good yield.

EXPERIMENTAL

Phenyl-Arsonic Acid (5)

500 gms. of anhydrous sodium carbonate were dissolved in one liter of boiling water. When dissolved, 250 gms. of arsenious oxide and 11 gms. of crystallized copper sulfate were added. When all was dissolved, the mixture was allowed to cool slowly with stirring.

Concurrently, to a mixture of 186 gms. of technical aniline, 400 ml. of concentrated hydrochloric acid, one liter of water and crushed ice to a volume of 3 liters, was added slowly, a solution of 145 gms. of sodium nitrite in 500 ml. of water. This was stirred to an end point on KI-starch paper.

The solution of the diazonium salt was then added with stirring over a period of one hour to the suspension of sodium arsenite, which had been cooled to $0^{\circ}C$ in an ice bath. The temperature was held down below $5^{\circ}C$ during one hour after addition was complete. The mixture was then allowed to come to room temperature, filtered and evaporated to a volume of 1.5 liters, whereupon crystallization occurred. Precipitation was completed by the addition of 450 ml. of concentrated hydrochloric acid to a pH of 2.0. The voluminous precipitate was washed and reprecipitated from one liter of boiling water by the addition of 15 ml. of concentrated HCl. This was then recrystallized from 500 ml. of boiling water to which was added 2 gms. of decolorizing charcoal. The material was filtered and dried <u>in vacuo</u> over calcium chloride. 194 gms.

(45% of theory) were recovered, melting sharply at 156-7°C (uncorr.)

Nitration of Phenylarsonic Acid (4)

57 gms. of phenylarsonic acid were dissolved in 87.5 gms. of concentrated sulfuric acid. The mixture was warmed to 80°C, and partially dissolved. By heating to 135°C, the material was completely dissolved. The solution was transferred to an all-glass apparatus fitted for refluxing. 38.2 gms. of yellow fuming nitric acid were added. Solution became orange-brown in color. It was heated to boiling and refluxed for four hours, then cooled and allowed to stand for forty-eight hours. The solution was heated again to boiling and refluxed for three hours, then drowned into 100 gms. of ice, and left in an ice box over night. The white crystals which separated were filtered and recrystallized from 250 ml. of boiling water, with 2 gms. of decolorizing charcoal. After a second recrystallization from 150 ml. of water, 40.0 gms. (57.9%) of gleaming cream-colored crystals were recovered. Nitrogen positive by sodium fusion test.

Bart Reaction (3)

A catalyst was prepared by dissolving 106 gms. Na_2CO_3, 50 gms. As_2O_3 and 2.2 gms. $CuSO_4$ in 200 ml. boiling water, and subsequently cooling to 0°C with stirring.

Concurrently, a mixture of 32 gms. of meta-nitraniline in 115 ml. of water, 47 gms. concentrated HCl, and ice to a volume of 600 ml., was diazotised at 5-10°C with 16.9 gms.

$NaNO_2$ in 50 ml. of water. The diazonium solution was added with stirring to the cold catalyst in one hour, holding the temperature below 10°C. Much foaming occurred, and was controlled by the addition of small quantities of benzene at intervals. The mixture was stirred at 20°C for one hour after foaming had subsided and left in an ice box over night. The tarry precipitate which separated was filtered and the filtrate concentrated to a volume of 300 ml. Concentrated HCl was added to slight alkaline reaction to litmus. The tarry precipitate was again filtered and the product was precipitated by the addition of HCl to a pH of 1.9. The mixture was cooled at 0°C over night, the precipitate filtered and recrystallized from 250 ml. of boiling water, with use of decolorizing charcoal. 11.5 gms. of the desired material (20.3% of theory) were isolated. Nitrogen positive.

m-Arsanilic Acid (7)

40 gms. of m-nitrophenylarsonic acid was dissolved in 150 ml. of 6% sodium hydroxide solution, and cooled to room temperature. 250 gms. of ferrous sulfate heptahydrate was dissolved in 750 ml. of water and 200 ml. of 25% sodium hydroxide solution was added to strong alkaline reaction. To this was added the m-nitrophenylarsonic acid solution. The green sludge of ferrous hydroxide immediately became the reddish brown of ferric hydroxide. The mixture was stirred vigorously for five minutes, then centrifuged. The supernate was evaporated to 300 ml., acidified to slight reaction to Congo Red paper, and cooled over night at 0°C. Red needle-

like crystals were isolated and recrystallized from 300 ml. of boiling water, using 0.5 gms. of decolorizing charcoal. 13.1 gms. of yellow needles were collected (38%) which softened at 208°C and melted at 212-215°C with decomposition and gas evolution.

Reduction with Raney Nickel

Five gms. of m-nitrophenylarsonic acid were dissolved in 100 ml. of warm water, and just neutralized with sodium hydroxide solution. 10 gms. of Raney Nickel was added and the mixture hydrogenated at 50°C in a Burgess-Pahr apparatus at three atmospheres pressure of hydrogen. A quantitative volume of hydrogen was absorbed. The nickel was filtered and the solution acidified to pH 2.5 with HCl. This was cooled over night at 0°C, and the precipitate was filtered. Recrystallized from 200 ml. boiling water. 4.0 gms. (91%) of colorless crystals were recovered melting at 212-215°C with decomposition and gas evolution.

o -Nitro Phenyl Arsonic Acid (8)

184 gms. of boric acid was dissolved in 450 gms. of 48-52% hydrofluoric acid in a copper beaker. To 110 ml. of this solution of fluoboric acid were added 34 gms. of o-nitraniline. This was cooled to 0°C, and a cold solution of 17 gms. of sodium nitrite in 34 ml. of water was added with stirring. The mixture was stirred for twenty minutes, the precipitate filtered and washed successively with 25 ml. of HBF_4, two 30 ml. portions of 95% ethanol, and three 25 ml. portions of ether, then dried in air.

Concurrently 52 gms. of $NaAsO_2$ and 6 gms. of cuprous chloride were dissolved in 600 ml. of water. The dry diazonium borofluoride was added over one hour with stirring. 100 ml. of 2.5 M sodium hydroxide solution was added during the reaction to keep the pH at 8.5-9.5. The mixture was allowed to stand at 20°C overnight, then warmed at 65°C for thirty minutes. Hydrochloric acid was added to litmus acidity, and the solution was concentrated with charcoal to 200 ml. This was filtered and made acid to Congo Red with HCl. The precipitate was filtered and recrystallized from boiling water. 38 gms. of light yellow product was recovered which softened at 230-235°C and decomposed at 255-260°C.

o-Arsanilic Acid

The sodium salt of o-nitrophenylarsonic acid was catalytically hydrogenated with Raney nickel in 85% yield exactly as in the reduction of the meta compound. Reduction by ferrous hydroxide (7) was also accomplished as above in 45% yield.

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