A synthesis for 5,5-dideuterohexanone-2
by Graeme L Baker

A THESIS Submitted to the Graduate Faculty in partial fulfillment of the requirements for the degree of Master of Science in Chemistry at Montana State College
Montana State University

Abstract:
A method has been devised for the synthesis of 5,5-didenterohexanone-2. The synthesis is characterized by introduction of the deuterium through interchange with the active hydrogens of methylmalonic acid. The acid, containing the deuterium, is then decarboxylated and reduced to 2,2-dideutero-propanol-1 with lithium aluminum hydride. The 2,2-dideuteropropanol-1 is converted to 2,2-dideutero-l-chloropropane which is used for a standard acetoacetic ester synthesis of the desired ketone Several other routes for the synthesis were investigated, and the results of these trials are discussed.

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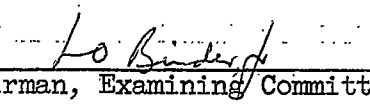

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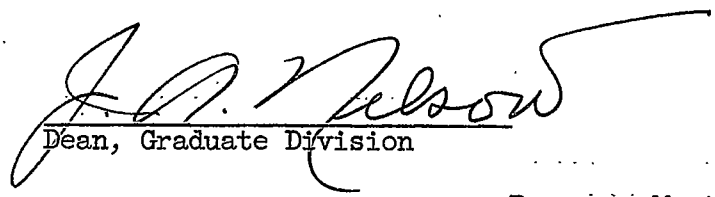

Dean, Graduate Division

Bozeman, Montana
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A method has been devised for the synthesis of 5,5-dideuterohexanone-2. The synthesis is characterized by introduction of the deuterium through interchange with the active hydrogens of methylmalonic acid. The acid, containing the deuterium, is then decarboxylated and reduced to 2,2-dideuteropropanol-1 with lithium aluminum hydride. The 2,2-dideuteropropanol-1 is converted to 2,2-dideutero-1-chloropropane which is used for a standard acetoacetic ester synthesis of the desired keton.

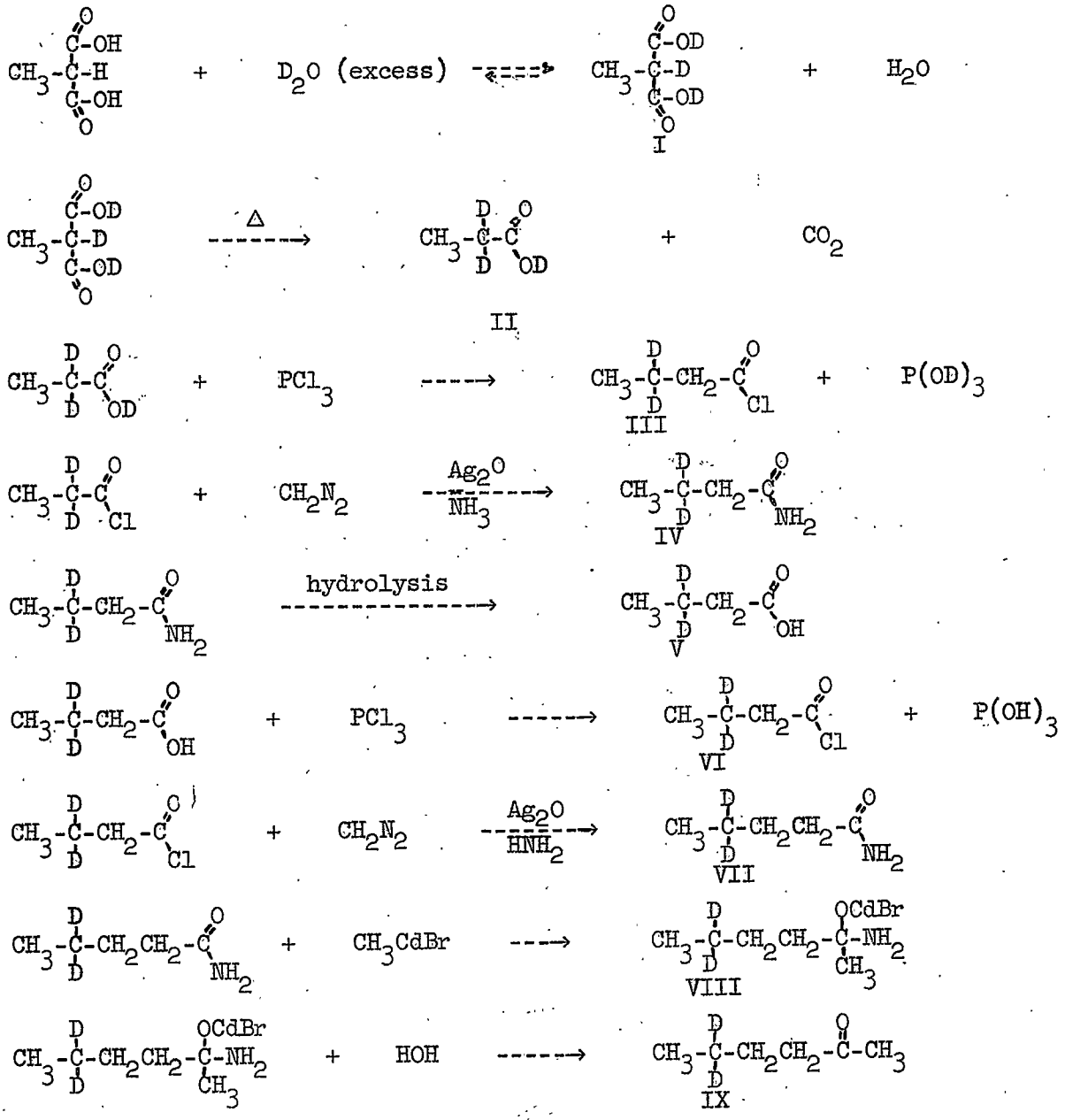
Several other routes for the synthesis were investigated, and the results of these trials are discussed.

Deuterated organic compounds have become increasingly useful in the investigation of the course and mechanism of organic reactions. One of the problems encountered in such work is the synthesis of the starting material, properly labeled by replacement of certain specific hydrogen atoms of the compound with deuterium. This paper deals with the development of one such synthesis. Included in the discussion are the results of various trials which, although unsuccessful in the desired results, are of interest because of the nature and scope of the reactions themselves.

Three general methods for the preparation of 5,5-dideuterohexanone-2 were investigated and a route to 5-deuterohexanone-2 was also explored.

The initial proposal (Reaction Sequence 1) utilized methyl malonic acid for the introduction of the deuterium by means of deuterium oxide. The deuterated product (I) was then decarboxylated to form propionic acid (II), and the acid converted to an acyl halide (III). Two successive Arndt-Eistert reactions were considered as a means of producing valeramide (VII) in which the deuterated methylene group would appear in the gamma position. An organocadmium reaction could then be utilized for the conversion of the valeramide to the desired ketone (IX).

The second method (Reaction Sequence 2) sought to by-pass difficulties encountered in carrying out the second of the Arndt-Eistert synthesis as proposed in Reaction Sequence 1. The deuterated butyramide (IV) was to be obtained exactly as in the previous method, whereupon it was to be converted to propyl bromide (XI). Two methods of bromide production were investigated. The first method involved a Hoffman hypobromite reaction to produce



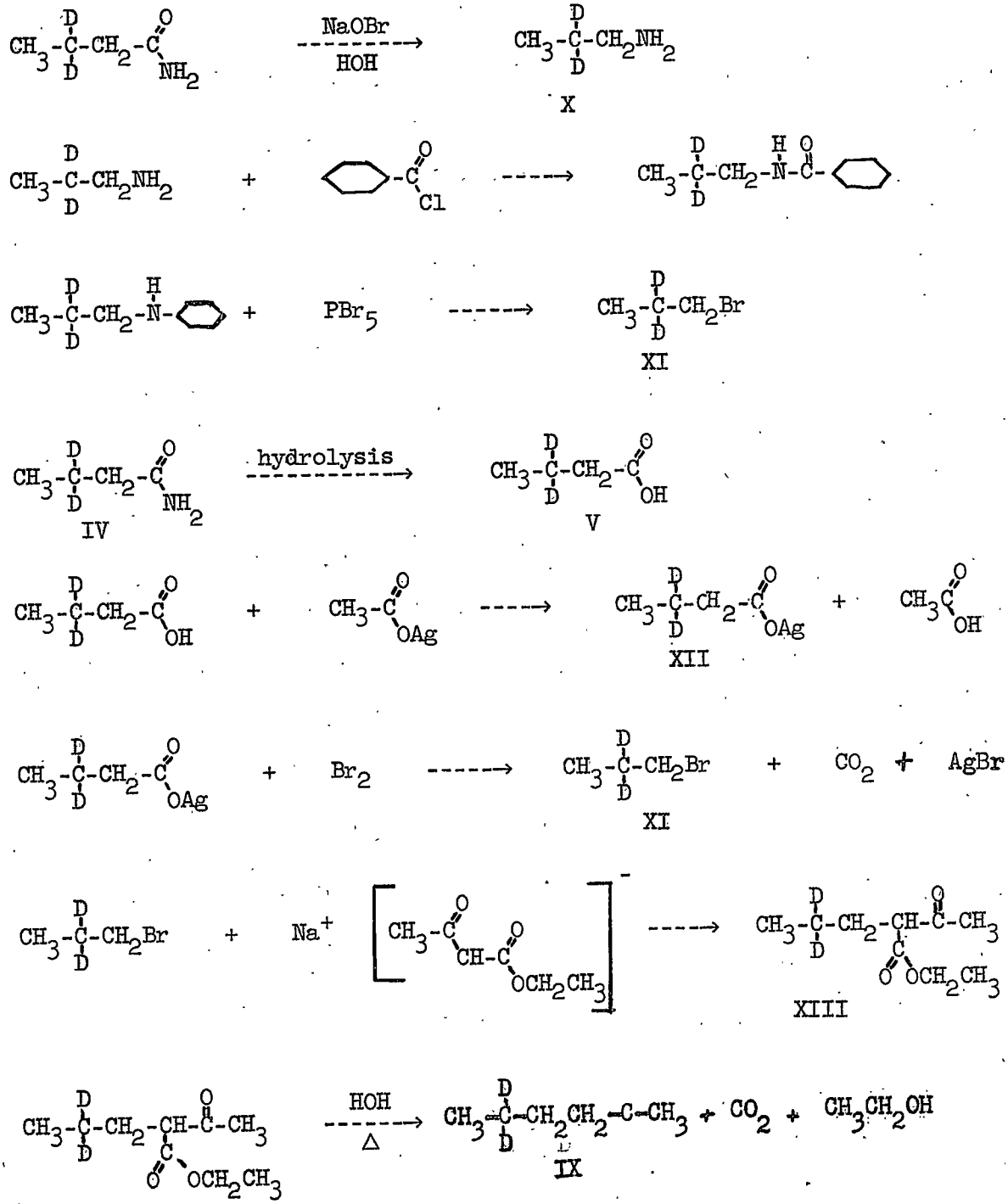
REACTION SEQUENCE I

propyl amine, followed by treatment with benzoyl chloride and phosphorus pentabromide to give propyl bromide. The second procedure required the production of the silver salt of butyric acid from which propyl bromide was obtained by treatment with bromine. The propyl bromide could then be used via an acetoacetic ester synthesis for the production of the 5,5-dideuterohexanone-2.

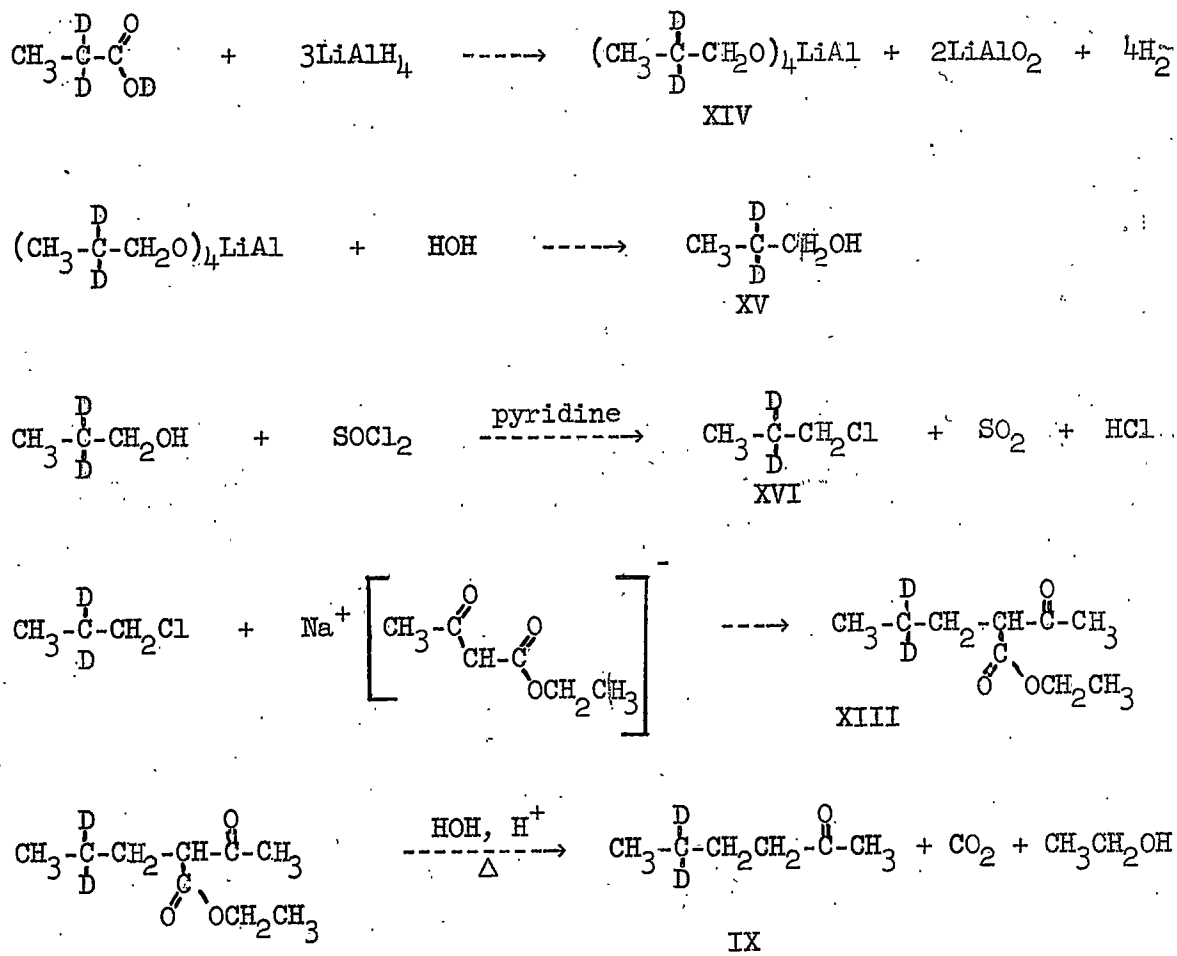
The third method (Reaction Sequence 3) which became apparent only after Reaction Sequences 1 and 2 had proven unsatisfactory for reasons discussed in subsequent portions of this thesis, is in the form of a proposal. Time did not permit the actual experimental investigation of this reaction sequence. However, the synthesis is considered to be entirely feasible since all of the individual reactions have been demonstrated by other investigators. The initial introduction of deuterium would again be achieved through interchange as illustrated in Reaction Sequence I. The methylmalonic acid thus obtaned could then be decarboxylated to yield 2,2-dideuteropropanoic acid which, when reduced with lithium aluminum hydride should give 2,2-dideuteropropanol-1. The 2,2-dideuteropropanol-1 could be converted to 2,2-dideutero-1-chloropropane which would be a suitable starting material for a standard acetoacetic ester synthesis of the desired ketone.

This last procedure would, in all probability, prove to be the most convenient and economical method of preparation for the desired ketone. However, valuable information was obtained from the previously outlined methods, and the significance of these trials will be discussed.

The fourth procedure, in reality, should not be grouped with the previous methods. Prior to the development of Reaction Sequence 3 the problems



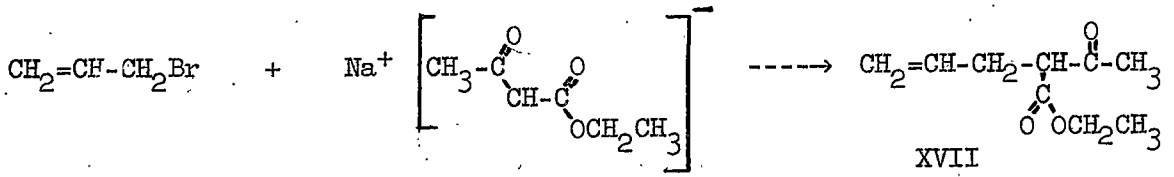
REACTION SEQUENCE 2



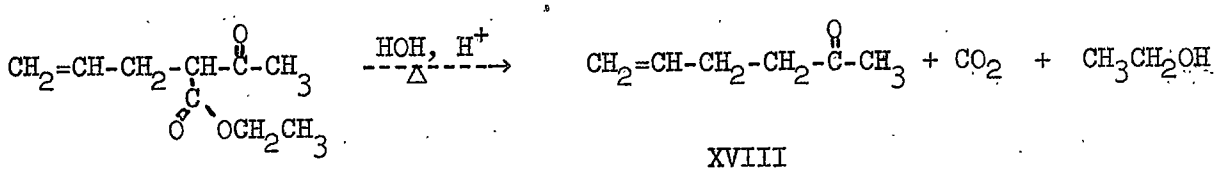
REACTION SEQUENCE 3

involved in the preparation of 5,5-dideuterohexanone-2 seemed almost insurmountable insofar as a practical synthesis was concerned. 5-deuterohexanone-2 (XXIII), although not as desirable as 5,5-dideuterohexanone-2, was considered suitable for the intended tracer experiments and a possible synthesis (Reaction Sequence 4) of this compound was proposed. Allyl bromide was to be converted to allylacetone (XVIII) through an acetoacetic ester condensation, followed by hydrolysis and decarboxylation. It was hoped that a hydrohalogenated ketal (XX) could be obtained by treating allylacetone with ethylorthoformate. A Grignard reagent (XXI) could then be obtained from the hydrohalogenated ketal and such Grignard reagent reacted with deuterium oxide to give a monodeuterated ketal (XXII). Hydrolysis of the deuterated ketal would then yield the 5-deuterohexanone-2.

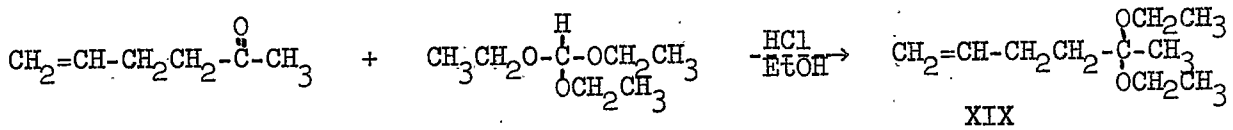
This procedure failed and the reasons for such failure as well as the advantages in the method of deuterium introduction will be discussed in the next section.



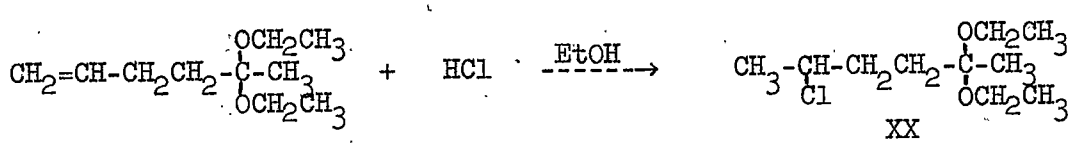
XVII



XVIII



XIX



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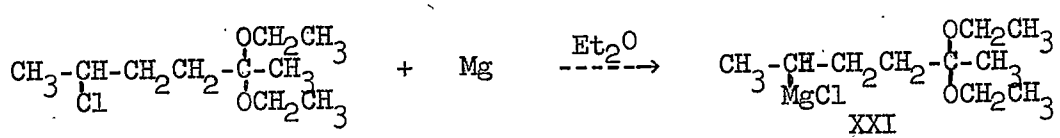
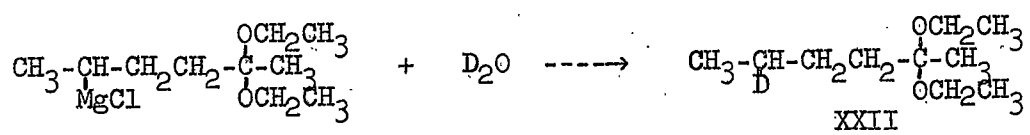


XXI



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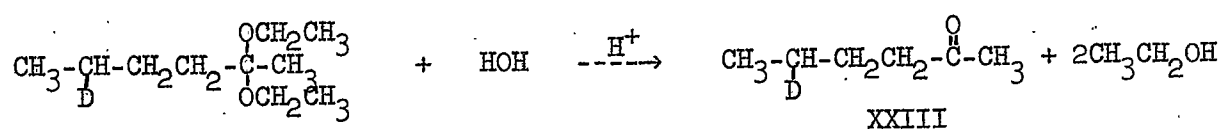


XXIII

REACTION SEQUENCE 4

THEORETICAL DISCUSSION

The initial consideration in the preparation of any deuterated compound is the introduction of deuterium into the desired position or at least into a position such that subsequent reactions will result in the desired deuterium placement. The problem reduces to the method of introduction of the deuterium and retention of the deuterium by the carbon to which it is initially bonded.

Two methods for the introduction of deuterium into the desired intermediates were proposed. One method, involving an interchange reaction between deuterium oxide and methylmalonic acid, was investigated for its applicability to Reaction Sequences 1, 2, and 3. The second method of introduction, although never attempted, should prove to be a convenient method for the economical introduction of deuterium. This method, involving the decomposition of a Grignard reagent with deuterium oxide has been illustrated in Reaction Sequence 4 and will be mentioned again with regard to this particular synthesis. The interchange procedure was adapted from papers by Holeman and Clusius (26), and Halford and Anderson (21)(22)(23) in which the method of introduction and extent of interchange are discussed. The deuterated methylmalonic acid (I) is decarboxylated to yield propionic acid which should have deuterium in both alpha positions.

The propionic acid produced by this method is reportedly about 95 per cent dideuterated. The yield was ca. 80 per cent of the theoretical when based on the methylmalonic acid. However, the deuterium oxide is the critical material and the yield is only about 19 per cent of theoretical on this basis. This low yield, as referred to deuterium oxide is due to the

necessarily large excess of deuterium oxide which is required to promote a shift in the interchange equilibrium so that the methylmalonic acid is about 95 per cent in the deuterated form.

Reaction Sequence 1 utilizes 2,2-dideuteropropanoic acid as outlined in the introduction. The series of reactions indicated appeared to be a plausible route if the diazomethane reaction (Arndt-Eistert Synthesis) could be utilized to introduce methylene groups between the deuterated carbon and the terminal functional group. A literature survey gave no indication that the Arndt-Eistert reaction had ever been successfully applied to an acyl halide with fewer than five carbons in the chain. It was decided, however, to attempt a pilot reaction using butyryl chloride; this reaction being necessary in the course of the proposed procedure. The attempt was carried out in accordance with established practices or slight modifications thereof for the Arndt-Eistert Synthesis (11), and failed in every case to yield a separable product of valeramide, the expected compound. Attempts were also made to modify the reaction to the extent of decomposing the diazoketone intermediate with water, rather than ammonia, thereby producing valeric acid (11). These trials were also failures. However, with every attempt to produce valeramide a characteristic amide odor was noted so that it was thought that the reaction may have proceeded as expected but for some unknown reason was not yielding to isolation of the product. This then led to a trial using similar conditions but employing propionyl chloride as the starting reagent. Slight modifications in procedure (reaction time and amount of solvent) produced a 46 per cent yield of butyramide. Repeated trials gave yields which were consistently in the 40 - 50 per cent range. It was assumed

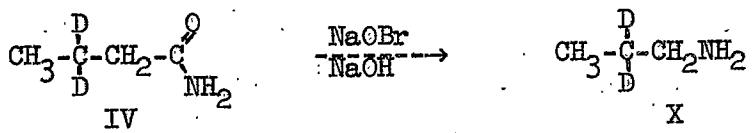
that the deuterated methylene group, if it had been unaltered by this reaction, would not appear in the beta position and reactions which followed could be performed without fear of rupturing the desired carbon-deuterium bond. The retention of deuterium by the alpha carbon during the Arndt-Eistert reaction is subject to some doubt as indicated by Lane, et.al. (28). They attribute the racemization of a secondary assymmetric carbon atom attached to the carbonyl group of diazomethyl ketone to a preliminary tautomerization of the diazomethyl ketone at the surface of the silver oxide catalyst. This evidence, although indicative of the lability of alpha deuterium, is certainly not proof of loss of the alpha deuterium as it exists in the optically inactive system under question in this investigation. That is, although the tautomerization of α,α-dideuteroethyldiazomethyl ketone is likely, it is equally probable that the deuterium involved in the tautomerization will, in the final analysis, be retained by the original carbon to which it was bonded. The very lack of evidence with regard to retention of the deuterium by the alpha carbon left the way open for at least a trial attempt of the Arndt-Eistert Synthesis to produce butyramide. The investigation was continued on the premise that β,β-dideuterobutyramide (IV) was the primary product obtained from the action of ammonia on α,α-dideuteroethyldiazomethyl ketone.

With this in mind, Reaction Sequence 1 was abandoned at this point in favor of an alternate procedure (Reaction Sequence 2) which would bypass the unsuccessful preparation of valeramide. The general plan was to convert the butyramide to n-propyl bromide and then proceed with an acetoacetic ester ketone synthesis. Two routes to convert to the bromide were investigated.

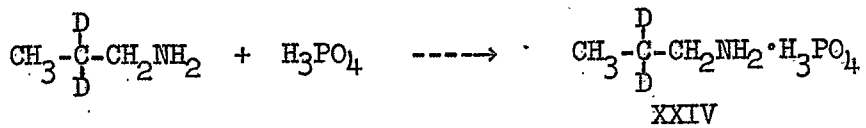
As indicated by the equations in Reaction Sequence 2, the first method involves a Hoffman hypobromite degradation (25) to produce propyl amine. The amine thus produced is treated in accordance with the Schotten-Baumen and von Braun Reactions, in a fashion similar to that used by Leonard and Nommensen (29) to produce n-propyl bromide. The second series of reactions to produce the bromide was adapted from a paper by Arnold and Morgan (7) in which they treated a carboxylic acid to produce a silver salt and then converted to the alkyl halide with bromine. This method necessitated the hydrolysis of butyramide to butyric acid. An investigation of the hydrolysis methods indicate that the acidic (HCl) and basic (NaOH) hydrolyses were about equivalent, and that both were superior to the nitrous acid procedure. Reaction Sequence 2 represents a plausible route to the production of 5,5-dideuterohexanone-2. The procedure has the extreme disadvantage inherent with the many steps involved. Twelve distinct operations, excluding purification procedures, are involved in obtaining the product by the better combination of reactions (Schotten-Baumen and von Braun) taken from Reaction Sequence 2. It is evident from this that the over-all yield is extremely low in spite of relatively good per cent yield values for most of the individual reactions.

The question of the exact position of the deuterium was subject to some doubt, however, and steps were taken to evolve a proof as to their presence at the beta position of the butyramide (IV). It was known (32) that the deuterium in 2-deuteropropene (XXV) could be identified as such. This fact provided the basis for a series of reactions intended to reduce the butyramide to propene for the purpose of deuterium identification. The reactions were chosen so that only β,β -dideuterobutyramide would result in the

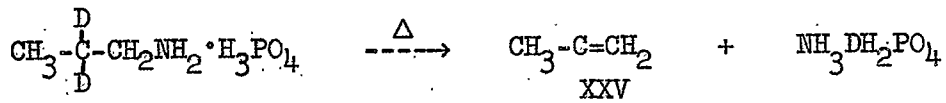
production of 2-deuteropropene. If it could be proven that the synthesis had developed correctly to the point at which the deuterium was properly situated in the beta position, it could be assumed that subsequent reactions would not result in migration or exchange with hydrogen. The propene was produced from butyramide through a Hoffman hypobromite degradation to propyl amine and conversion to the phosphate salt (XXIv), which will undergo pyrolysis to yield propene (24). The conversion route is indicated by the following equations.



IV X



XXIV



XXV

Exhaustive methylation was also attempted as a method obtaining the desired propene and was found inferior to the phosphoric acid method.

Reaction Sequence 2 for the preparation of 5,5-dideuterohexanone-2 was carried through twice with water, rather than deuterium oxide. Water was used to insure the validity of the synthesis. Once the method was considered dependable, the entire amount of available heavy water (25 g) was utilized to prepare butyramide which was then converted to 2-deuteropropene by the method outlined above. In actuality the product produced could only be assumed to be 2-deuteropropene and had been made for the express purpose of checking for the proper deuterium substitution. The propene was produced,

but the analytical aid necessary for proof of 2-deuteropropene structure proved unattainable. The entire method of preparation immediately collapsed due to the doubtful nature of deuterium placement along with the extremely low over-all yields.

Reaction Sequence 4 was the immediate outgrowth of these previous failures. The synthesis of 5,5-dideuterohexanone-2 was abandoned in favor of a proposed sequence of reactions for the preparation of 5-deuterohexanone-2 (XXIII). The procedure as outlined had one extremely advantageous feature in that the deuterium was introduced by means of one of the last reactions. Moreover, the decomposition of the Grignard reagent (XXI) with heavy water, followed by hydrolysis of the ketal was expected to yield 5-deuterohexanone-2 at ca. 95 per cent of theory (based on deuterium oxide). The per cent yield of all foregoing reactions thus became insignificant since the indicated starting materials and all subsequent reagents are inexpensive as compared to the cost of deuterium oxide.

All of the reactions were relatively untried but by adapting procedures taken from the limited literature (8)(9)(10)(10)(12)(27)(34)(36)(37) synthesis was carried through conveniently to the preparation of allylacetone (XVIII). Allylacetone was obtained in reproducible 20 per cent yields (based on acetoacetic ester). The conversion of allylacetone to the ketal (XIX) was doubtful due to the difficulty generally associated with the preparation of ketals. This particular case posed an additional problem in the highly reactive character of the unsaturated system with the resultant tendency toward polymerization under acid conditions. The ketal was obtained, however, and characterized by its boiling point and its ready hydrolysis back to a product

which could be identified as allylacetone. The series of reactions was terminated by the failure to obtain the expected hydrohalogenated ketal (XX) from the unsaturated ketal (XIX). With every attempt to add hydrogen chloride, both before and after ketal formation, the polymerization tendency previously noted took precedance over the normal addition. The use of hydroquinone as an inhibitor was tried, but failed to prevent the formation of a black, viscous material which increased in viscosity to the point of becoming a solid as hydrogen chloride treatment was continued. The material thus produced was soluble in ether from which a varnish-like residue resulted upon evaporation of the solvent.

Although time has not permitted the further study of this reaction, a detailed investigation could quite possibly result in a satisfactory hydrogen halide addition. Possibilities which would merit consideration are the use of another hydrogen halide or variations of conditions along with the use of other inhibitors.

Chronologically, Reaction Sequences 1, 2, and 4 had resulted in failure to produce a suitably deuterated ketone. Eventually the procedure illustrated as Reaction Sequence 3 was formulated. The sequence has gone completely untried but, because of the documentation available for the success of the individual reactions, presents a very promising method for the preparation of 5,5-dideuterohexanone-2.

The primary problem manifested by the basic proposal of Reaction Sequence 3 was the reduction of 2,2-dideuteropropanoic acid (II) to the corresponding alcohol (XV). The deuterium substituents exist in the labile alpha positions and as such are extremely susceptible to interchange with hydrogen.

Most method of reduction involve rather drastic conditions, or the use of aqueous solutions, both of which are to be avoided if the deuterium configuration is to be maintained.

The use of lithium aluminum hydride to reduce the deuterated propionic acid to the corresponding alcohol was suggested by its use in the reduction of acetone-d_6 to the related propanol. This work was carried out by Condon (14) and the evidence to indicate that no appreciable deuterium-hydrogen exchange occurred was obtained from mass spectra and infra-red data. Additional information indicating the adaptability of lithium aluminum hydride to the proposed method stems from information proffered by Condon (13) to the effect that a lithium aluminum hydride reduction of 2,2-dideuteropropanoic acid would not alter the alpha deutero configuration. The mildness of the method is further indicated by its use in the reduction of various sugar acids to glycitols wherein the optical configuration of the alpha carbon in the acid is identical to that of the glycitol (31). The use of lithium aluminum hydride as a reducing agent for acids was first considered by Nystrom and Brown (33) who utilized it for the reduction of several carboxylic acid with no apparent disruption in the alpha configuration. The use of lithium aluminum hydride thus lends itself admirably to this particular reduction since the acid is actually reduced in an ethereal solution devoid of water. The hydrolysis of lithium aluminum propoxide (XIV) should offer no problem since at this point the activating carbonyl structure is nonexistant.

There exists some possibility that the structure of the alcohol so produced would involve a deuteroxyl group rather than a hydroxyl structure.

This possibility is extremely slight since the formation of the intermediate structure involves a displacement of deuterium from the deuteroxyl group of the acid by a metal. The possibility of the deuteroxyl reforming arises from the small amount of deuterium which could conceivably be present and which might cause some interchange when the metallo-derivative is hydrolyzed. However, the consideration offers no practical problem since the next step involves the conversion of the alcohol to an alkyl halide by replacement of the hydroxy (or deuteroxy) structure with a halide.

Attempts to produce halides from alcohols containing adjacent deutero groups have shown some interchange of hydrogen and deuterium when acid conditions prevailed (13). The method suggested by Condon (13) which eliminated this trouble in the case of a propane 1,1,1,3,3,3-d_6-ol-2 could be readily applied to 2,2-dideuteropropanol-1. The method involves the preparation of halides from alcohols by the use of thionyl chloride in pyridine (25)(34)(35). This method, which maintains a basic condition throughout the process, was first proposed by Darzens (17), and its application by Whitmore (35) to produce amyl halides from alcohols without the production of isomers adds further support to its projected use in the production of 2,2-dideutero-1-chloropropane (XVI) from 2,2-dideuteropropanol-1. The final steps of the synthesis as illustrated in Reaction Sequence 3 utilize established procedures for the condensation of the deuterated propyl chloride with acetoacetic ester followed by hydrolysis and decarboxylation to produce the desired ketone. The deuterium exists in a stable configuration in 2,2-dideutero-1-chloropropane which makes migration or exchange of deuterium improbable in all subsequent reactions. The reactions are all standard procedures

which leads to the conclusion that this reaction sequence could be used for the production of 5,5-dideuterohexanone-2. The product should be reasonably free of any nondeuterated or undesirably deuterated structures.

EXPERIMENTAL

A. Preparation of ethyl ethoxalylpropionate (15).

69 g (3 g atoms) of sodium was powdered by warming with xylene in a three liter 3-necked flask. When the sodium had melted, the flask was stoppered and shaken vigorously until the sodium reverted to a solid. The cooled xylene was decanted and the powdered sodium washed twice with small portions of dry ether (previously dryed with sodium and distilled).

One liter of absolute ether (dryed with sodium) was added to the powdered sodium, and the flask fitted with a mercury sealed stirrer, reflux condenser, and dropping funnel (drying tubes wer necessary on all openings to the air).

138 g (175 ml, 3 moles) of absolute ethyl alcohol (dryed by distillation from sodium) was added from the funnel dropwise. This addition required 4 to 6 hours and was accompanied by constant stirring of the mixture. After addition of the alcohol and when no unchanged sodium remained, the flask was immersed in an ice-water bath and allowed to cool completely. 306 g (3 moles) of ethyl propionate was mixed with 438 g of ethyloxylate and the mixture was added slowly through the dropping funnel. This addition was made slowly so that the ether did not reflux.

After the ester mixture had been added, the stirrer was removed, and the flask fitted with a condenser for downward distillation. The ether and the alcohol formed in the reaction were removed by heating on a water bath. Heating was discontinued when a yellow scum had formed on the surface of the red, viscous layer. This layer usually solidified on cooling and after cooling it was treated with 600 ml of cold 33 per cent acetic acid solution.

This mixture was allowed to stand for several hours with occasional shaking to decompose the sodium derivative completely. The product was extracted with four 500 ml portions of ether and the combined ether extracts were washed successively with 1000 ml of water, two 500 ml portions of 10 per cent sodium bicarbonate solution, and finally with 1000 ml of water. The ether was then removed by distillation from a steam bath, and the residue fractionated to obtain the product. The fractionation was carried out with an oil bath and a heated column, collecting the fraction boiling 114 - 116°/10 mm.

The yield varied from 363 to 425 g or 60 to 70 per cent of theory.

B. Preparation of diethylmethylmalonate (16).

345 g (1.7 moles) of ethylethoxalyl propionate, b.p. 114 to 116°/10 mm was placed in a round bottom flask fitted with a reflux condenser and a thermometer suspended from the top of the condenser such that it was immersed in the material within the flask. The flask was then heated slowly until a vigorous evolution of carbon monoxide began (130 - 150°C). The temperature of the liquid was gradually increased as the gas evolution diminished, with eventual refluxing to insure complete elimination of carbon monoxide. The diethylmethylmalonate was then distilled and the product boiling at 189 - 193°C/600 mm was collected. The yield was 260 g or 95 per cent of theory.

C. Preparation of methyl malonic acid (20).

96 g of diethylmethyl malonate was poured in small portions, with shaking, into a round bottom flask containing a cooled solution of potassium hydroxide (76 g in 100 ml of water). The flask was fitted with a reflux condenser and the emulsion which was first formed soon set to a solid mass of ethyl porassium methylmalonate as the mixture cooled. The mixture was then

heated on a gently boiling water bath until hydrolysis set in with a vigorous evolution of heat. Heating was continued until the layer of oil had disappeared (or until the layer no longer decreased). The flask was then allowed to cool and the solid paste obtained was extracted with two portions of ether in order to remove any residual ester which may have escaped hydrolysis. The ether was decanted and the flask cooled in an ice bath. When cooled, the paste was made acid to congo paper by addition of ca. 6 N hydrochloric acid. The acid solution was extracted with five individual 125 ml portions of ether and the combined ether extracts dried over sodium sulfate. The ether was removed by distillation and methyl malonic acid was caused to crystallize from the residue by cooling and rubbing the sides of the container. The methylmalonic acid can be purified by recrystallizing from benzene. This purification requires large quantities of benzene and is not very efficient and it was found unnecessary for conversion of the methylmalonic acid to propionic acid.

An additional amount (ca. 9 g) of product was obtained by dissolving the mother liquor in ether and then adding an equal amount of benzene. Any oil which separated was separated from the mixture, dissolved in more ether, and equal amounts of benzene again added. The solution was allowed to evaporate to 5 to 10 ml whereupon crystallization occurred or was induced by rubbing the sides of the beaker. Hygroscopic impurities which appear at this point are removed by washing with several 10 ml portions of benzene. The crystals thus obtained were identified as methylmalonic acid by means of mixed melting point with the crystals obtained in the original fashion.

The average yield was 36 per cent.

The average yield by means of the described recovery procedure was 50 per cent.

D. Introduction of deuterium and decarboxylation to yield 2,2-dideutero-propanoic acid (26).

16 g of methyl malonic acid was dissolved in 12 g deuterium oxide and immediately sealed in a heavy pyrex test tube. The test tube was then suspended in a vapor bath of acetone which maintained a temperature of ca. 52°C (640 to 660 mm pressure). The reaction was allowed to proceed in this manner for eight hours at which time the sealed tube was removed and allowed to cool. The tube was then opened and tube fitted with a stopper and an access tube which was connected to a vacuum whereby the solvent could be evaporated. The solvent was completely removed and the tube again recharged with 12 g of deuterium oxide, resealed, and placed in the vapor thermostat for an additional eight to ten hours. The tube was again allowed to cool at the end of this period and the solvent removed in exactly the same manner as before. The deuterated methyl malonic acid was then subjected to decarboxylation by heating the material in a small flask fitted with a specially designed reflux condenser (Fig. A). An oil bath was used and heated to maintain a reasonable rate of carbon dioxide evolution. The heating was continued until carbon dioxide evolution ceased, and the material was then distilled from the same apparatus. The yield of 2,2-dideuteropropanoic acid was about 19 to 20 per cent theory when referred to the deuterium oxide utilized.

Figure A

E. Preparation of 2,2-dideuteropropanoyl chloride (α,α-dideuteropropionyl chloride) (26).

The decarboxylation of the deuterated methyl malonic acid was carried out in the flask to be used for the preparation of 2,2-dideuteropropanoyl chloride, (Fig. A) and it was unnecessary to purify the material. Trial runs indicated that the yield would be approximately 6 to 7 g and the subsequent reagent additions were made on this basis.

5.0 g (0.066 mole) of phosphorus trichloride was added dropwise to the propionic acid in the reaction flask (ca. 7.0 g; 0.09 mole), mixed, and allowed to stand one-half hour. The water bath was then heated at 40 - 50°C for one hour to insure completion of the reaction which was indicated by separation into two layers. An oil bath was not substituted for the water bath, and the reaction mixture heated in such a manner that the upper layer was completely distilled. The distillate thus obtained was redistilled to yield 2,2-dideuteropropanoyl chloride in approximately 70 per cent yield.

F. Preparation of N-Nitrosomethylurea (3).

a. A solution of 40 g (1 mole) of sodium hydroxide in 160 ml of water was added dropwise, and with hand stirring, to a solution of 59 g (1 mole) of acetamide in 88 g (0.55 mole) of bromine in a four liter beaker. Gentle

heating on a steam bath aided in dissolving the acetamide but care had to be exercised to prevent loss of bromine. The resulting yellow reaction mixture was heated on a steam bath until effervescence set in, after which the heating was continued for an additional two or three minutes. Crystallization of the product from the yellow to red colored solution usually started immediately, and was completed by cooling in an ice bath for one hour. When the solution was colorless at this point the product was slower in crystallizing, contained more sodium bromide, and gave lower yields, therefore, a slight excess of bromine was maintained. The weight of the white crystalline acetylmethylurea obtained by filtration and air drying varied from 59 to 52 g (84 - 90 per cent theory) and had a melting point of 169 - 170°C. After the initial preparations the material was used iwthout drying for the preparation of N-nitrosomethylurea.

b. A mixture of 49 g (0.42 mole) acetylmethylurea and 50 ml of conc. hydrochloric acid was heated on a steam bath until it was apparent that no more solid would dissolve. (Thre crude acetylmethylurea contains some sodium bromide which appears as a white crystalline material insoluble in conc. hydrochloric acid. The sodium bromide dissolved when the solution was diluted and had no effect upon the subsequent treatment with sodium nitrite). Heating was continued for three or four minutes longer (total time on the steam bath was eight to twelve minutes), after which the solution was diluted with an equal volume of water and cooled below 10°C in an ice bath. A cold saturated solution of 38 g (0.55 mole) of sodium nitrite in 55 ml of water was then added dropwise and with stirring. This addition resulted in considerable frothing and had to be conducted slo3ly and in a large beaker. The

mixture was allowed to remain in the ice bath for ten to fifteen minutes after all the sodium nitrite had been added. The N-nitrosomethylurea was then filtered with suction and washed with about 10 ml of ice water. Air drying gave 33 to 36 g (76 to 82 per cent theory) of N-nitrosomethylurea as pure yellow crystals melting at 123 - 124°C.

G. Preparation of diazomethane (2).

To 300 ml of dry ether (dried by distilling from sodium) was added 90 ml of 40 per cent potassium hydroxide and the mixture cooled to 5°C. To this, with continued cooling and shaking, was added 28.2 g of finely powdered nitrosomethylurea in small portions. The deep yellow ether layer was readily decanted. The ether layer contained about 8.4 g of diazomethane, together with some dissolved impurities and water. The water was removed by drying for three to four hours over solid potassium hydroxide pellets.

H. Preparation of β,β -dideuterobutyramide (11).

6 g of 2,2-dideuteropropanoyl chloride was added dropwise to the diazomethane-ether solution from G. After all signs of reaction had ceased, the solution was treated with 15 ml of 10 per cent silver nitrate solution and 28 ml of conc. ammonium hydroxide, after which the mixture was shaken periodically and allowed to stand for twelve to eighteen hours. After this time the mixture was filtered to remove the precipitated silver products and the filtrate decolorized by heating with Norite and repeating the filtration. The ether and water were then removed by evaporation in a vacuum and the crude β,β -dideuterobutyramide distilled to yield ca. 2.5 g of β,β -dideuterobutyramide, b.p. 210 -212°C/640 mm. The crude butyramide was generally used with distillation for conversion to 2,2-dideutero-1-bromopropane, or to 2-deuteropropene-1.

I. Preparation of 2,2-dideutero-1-aminopropane (25).

18.4 g of bromine was dissolved in a solution of 24.7 g of potassium hydroxide in 400 ml of water and the resulting solution was added to 10 g of β,β -dideuterobutyramide, heated rapidly to boiling, and distilled into 50 ml of water until approximately two-thirds of the material had been distilled. The propyl amine was not isolated but was utilized for further reactions as it appeared in this aqueous solution. In the previous work the propyl amine had been isolated and condensed with a dry-ice acetone condenser in order to establish its identity.

J. Preparation of N-(2,2-dideutero-1-propyl)benzamide) (29).

The distillate of 2,2-dideutero-1-aminopropane as obtained from 10 g of β,β -dideuterobutyramide (2,2-dideuterobutanamide) was treated immediately upon completion of the distillation with a solution of 5.8 g of potassium hydroxide dissolved in 12 ml of water. 16.8 g of benzoylchloride was then added dropwise and with stirring to the basic mixture. This resulted in precipitation of N-(2,2-dideutero-1-propyl)benzamide which was purified by vacuum distillation. The product was used without further characterization or purification to produce the desired 2,2-dideutero-1-bromopropane.

K. Preparation of 2,2-dideutero-1-bromo propane (29).

16.3 g (0.1 mole) of N-(2,2-dideutero-1-propyl) benzamide was mixed in equimolar amounts with phosphorus pentabromide by adding 27 g (0.1 mole) of phosphorus tribromide and 16 g (0.1 mole) of bromine to the amide while cooling in an ice bath and with constant stirring. The mixture was then heated and distilled directly from the 3-necked flask onto cracked ice. The distillate was distilled onto the ice to destroy any excess phosphorous

pentabromide and allowed to come to room temperature to allow the slow hydrolysis of any phosphorous oxybromide. The mixture was then warmed for several minutes to insure the complete hydrolysis of phosphorous oxybromide, and then washed with water, concentrated sulfuric acid, water, sodium bicarbonate, and finally twice with water. The bromide layer was then drawn off, dried over calcium chloride and distilled. The product weighed about 2.5 g and boiled at 67 - 68°C. The yield was about 20 per cent of theory.

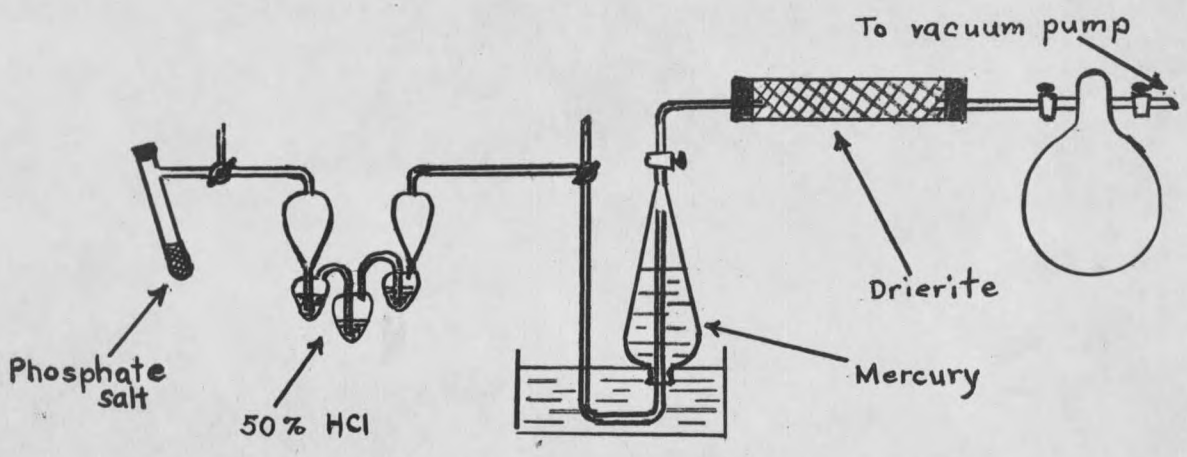
L. Preparation of the phosphate salt of 2,2-dideutero-1-aminopropane (24).

The 2,2-dideutero-1-aminopropane from (I) was steam distilled into a phosphoric acid solution of 8 g of syrupy phosphoric acid dissolved in 12 ml of water thereby producing the desired phosphate salt which was recovered by vacuum evaporation to dryness. Comple crystallization is induced by washing with a small amount of 95 per cent alcohol and filtering. The product was air dryed and the yield was approximately 20 per cent of theory.

M. Preparation of 2-deuteropropene-1 (24).

The phosphate salt from (L) was pyrolized by gradual heating in the indicated apparatus. The products evolved on pyrolysis were cooled and passed through a Geissler tube containing 50 per cent hydrochloric acid in order to insure the removal of all nitrogenous bases. The propene was collected and measured by means of the pressure changes indicated by the manometer.

Preliminary studies indicated the product to be propene as evidenced by a bromine addition derivative as well as the boiling point of the gas itself. The bromine addition product had a boiling point of 139 - 142°C which compares favorably with the 141.6°C boiling point of 1,2 dibromopropane. The boiling point of the gas was establishes as -46°C to -48°C with a low temperature distillation column.



N. Preparation of ethylallylacetoacetate (30)(37).

A 3-liter round bottom flas fitted with an efficient mechanical stirrer, reflux condenser and dropping funnel (all points protected from moisture) was arranged for heating on a steam bath.

In the flask was placed 1250 ml of absolute alcohol (dried with sodium ethoxide and distilled) and then there was added, gradually, 58 g (2.5 atos) of sodium ribbon (cut into small pieces). This addition required three to four hous. After all the sodium had dissolved 325 g (2.5 moles) of ethyl-acetoacetate was added. The stirrer was started and the solution heated to gentle boiling. To the boiling solution 332 g (2.74 moles) of allyl bromide was added over a period of about two hours. The refluxing and stirring were continued until a sample of the solution was neutral to moist litmus paper. The time required was ten to fourteen hours.

When the reaction was complete the mixture was cooled and the solution decanted from the sodium bromide. The salt was washed with 50 ml of absolute alcohol and the washings added to the main solution. The alcohol was separated from the substituted acetoacetic ester by distilling through a

short column from a steam bath. The crude residue was used without further purification for hydrolysis to allylacetone. Distillation at 12 mm gave a clear liquid boiling at 102.5°C.

O. Preparation of allylacetone (hexene-1-one-5) (27).

In a five liter round bottom flask fitted with an efficient mechanical stirrer was placed 2.5 liters of 5 per cent sodium hydroxide solution (3.13 moles). To this was added the crude acetoacetate substitution product obtained from 2.5 moles of ethylacetoacetate. The mixture was stirred at room temperature for four hours during which time the monosubstituted acetoacetic ester was completely saponified and passed into solution. The mixture was then allowed to stand until the unsaponified material separated completely as an oil layer. The aqueous layer was transferred to a flask fitted with a separatory funnel and a condenser set for downward distillation. Through the separatory funnel was added, slowly, 250 ml (1.1 moles) of 50 per cent sulfuric acid (sp. gr. 1.40) which was somewhat more than the required amount for neutralization of the alkali used in the saponification. When the volution of carbon dioxide ceased to be vigorous the reaction mixture was heated slowly to boiling and from one-third to one-half the total volume was distilled. The distillate was made alkaline (to remove all acids formed from the acid decomposition of the substituted ester) with solid sodium hydroxide and redistilled until 80 - 90 per cent had been collected.

In the distillate, the ketone layer was separated from the water (a saturated solution of calcium chloride was used to break the emulsion when necessary) and the latter was distilled until one-third has been collected. The ketone layer in this distillate was again separated and the water layer

again distilled. This procedure was repeated as long as any considerable amount of ketone was obtained in the distillate. The combined ketone fraction was washed four times with one-third its volume of a concentrated solution of calcium chloride (sp. gr. 1.3 or greater) to remove alcohol, and then dried over calcium chloride, filtered, and distilled. The fraction boiling at 128 - 129°C was collected.

P. Preparation of allylacetone ketal (12).

35 g (45 ml) (0.75 mole) of absolute alcohol (dried with sodium and distilled was placed in a 500 ml round bottom flask with 25 g (0.25 moles) of allylacetone. 45 g (0.3 mole) of ethylorthoformate was then added dropwise through a dropping funnel. When the addition of orthoformate was complete, dry hydrochloric acid (made by dropping conc. hydrochloric acid into concentrated sulfuric acid) was bubbled into the reaction mixture previously cooled in an ice-salt bath for about one minute (or until the mixture just began to darken) and the mixture allowed to come to room temperature and stand for about ten to twelve hours.

The resultant dark colored solution was neutralized with sodium ethoxide, filtered, and the alcohol removed by warming in a vacuum. After the alcohol had been removed the residue was distilled at reduced pressure and the fraction boiling between 45 - 65°C/10 mm was collected. The material was checked at atmospheric pressure and exhibited a boiling point of 155 - 165°C. The material was characterized as being primarily the desired ketal by its ready hydrolysis to allylacetone for which the physical properties were known.

DISCUSSION OF EXPERIMENTAL RESULTS

A review of the reactions outlined in Reaction Sequence 3 for the preparation of 5,5-dideuterohexanone-2 is of little consequence to a discussion of experimental results in that the reactions were not actually carried out. With this in mind this portion of this paper is devoted to a discussion of the results obtained from the various reactions attempted in the course of Reaction Sequences 1, 2, and 4.

Reaction Sequence 1, involving the Arndt-Eistert procedures is unsatisfactory on two counts; the failure to produce valeramide and the low over-all yeild. Although the production of 5,5-dideuterohexanone-2 is impractical by this procedure the reactions involved were individually successful and as such are of interest. The preparation of 2,2-dideuteropropanoic acid was accomplished without complication as already described. The problem of the lability of deuterium in the alpha position presents itself and is of immediate importance in the preparation of 2,2-dideuteropropanoyl chloride from 2,2-dideuteropropanoic acid. Phosphorus trichloride was used because of advantageous yields and ease of handling (19). An alternative procedure, which could prove to be a superior method, is the use of excess benzoyl chloride to produce the propanoyl chloride through interchange. This reaction was tried and resulted in yields of about 75 per cent. The possible advantage of this method over the phosphorus trichloride procedure lies in the possibly greater retention of deutero groups in the alpha position via the benzoyl chloride procedure. The use of phosphorus trichloride and the subsequent hydrogen chloride evolution is apparently somewhat likely to incite deutero exchange (13)(34). The question remains unanswered, however,

since no evidence was available to either prove or disprove the correct positioning of the deuterium when 2,2-dideuteropropanoyl chloride was produced via a synthesis involving the use of phosphorus trichloride.

The reaction in this procedure which proved to be of primary interest is the Arndt-Eistert Synthesis. The Arndt-Eistert procedure has been utilized for the preparation of a great many compounds by conversion of acids or acid derivatives into their next higher homolog (4)(5)(6)(11)(18)(38). Previous work has been done, primarily with relatively long carbon chain acyl halides, cyclic structures, or the aryl-acyl derivatives (11). The literature indicates that all successful applications of the Arndt-Eistert reaction involve a starting acid chloride of not less than five carbons (1)(4)(11). Nearly all of the practical applications of the method involve even larger molecules with cyclic or aromatic structural components. The single report of the synthesis being applied to smaller acid halides is in the work of Arndt, Eistert, and Amende, wherein acetyl chloride was the initial reactant (4). The reaction was successful only to the extent that a detectable trace of propionamide was produced. The present work investigated application of the reaction to butyryl chloride and propionyl chloride. The decomposition of the diazoketones were carried out with ammonium hydroxide and silver nitrate in an attempt to produce the amides. The attempt to prepare valeramide from butyryl chloride met with complete failure. Variations in conditions and solvent made no effective difference in obtaining the desired valeramide. However, it seemed that a characteristic amide odor could be detected when the supposed diazoketone mixture was decomposed with ammonium hydroxide. This indicated the possibility that the diazoketone preparation

had been successful followed by at least partial conversion to the desired amide. There was evidence of decomposition in every case and it is possible that some unknown factor was causing the decomposition of valeramide in every attempt to purify and isolate the product. The indication was, however, that the failure may lie primarily with recovery and purification rather than with the actual production of the desired amide. It was thought possibly that butyramide might be prepared in measurable yields even through the valeramide had not. Propionyl chloride was treated in exactly the same way that the butyryl chloride had been handled and resulted in consistent yields of 40 - 50 per cent of theory of the expected butyramide. As indicated, the procedure followed was almost identical with the general methods previously established, and for which other workers had reported no success when utilized with acyl halides containing fewer than five carbons in the chain. In retrospect, it seems that previous research may have encountered the very difficulties which we experienced in dealing with the preparation of valeramide. The general characteristics of the reaction indicate decreased yields with decreased molecular size. This fact, coupled with the negative results experienced with butyryl chloride, was probably instrumental in the failure to attempt the reaction with any of the lower acid chlorides. The work as carried out here gives no indication as to the true cause for the failure of buryryl chloride to produce significant yields of valeramide. The actual production of the diazoketone, and its subsequent decomposition to the amide may actually occur in both cases, as evidenced by the similarity in odor. The failure to obtain valeramide may be due to a catalyzed decomposition of the product when an attempt is made at isolation. Another possibility which

deserves consideration is the effect that is sometimes noted in comparing odd and even carbon chains. As previously indicated, propionyl chloride and valeryl chloride have both been used successfully as starting materials for the Arndt-Eistert reaction, whereas both acetyl chloride and butyryl chloride failed. The synthesis was successful then for three and five carbon systems, and has failed for two and four carbon systems. No evidence can be presented to substantiate the view that the odd or even characteristics were in reality the cause for the outcome of the reactions but the coincidence is such that any investigation into the Arndt-Eistert synthesis itself would conceivably consider the possibility.

The failute to obtain valeramide in suitable yields via the Arndt-Eistert synthesis necessitated the revised procedure for production of 5, 5-dideuterohexanone-2 as explained in Reaction Sequence 2. The reactions, as utilized, involved standard procedures and offered no unusual problems. The impractical feature of the entire synthesis lay not in the adaptability of the individual reactions but was, rather, a consequence of the very number of individual steps.

The knowledge that a mono-deuterated ketone would prove suitable for the intended tracer purposes opened the way for what appeared to be an excellent procedure. The preparation of 5-deuterohexanone-2 as indicated in Reaction Sequence 4, involved relatively few steps, and, of utmost importance, the introduction of deuterium was not made until virtually the last reaction was carried out.

The procedure for the preparation of allylacetone is readily adapted from standard procedures for the preparation of methyl-n-amyl ketone (27).

The use of allyl bromide and acetoacetic ester resulted in consistant 20 per cent yields of allylacetone. The allylacetone could be converted to the corresponding ethyl ketal by using ethyl orthoformate (12). This method required rather careful control of the dry hydrogen chloride addition. The hydrogen chloride which was necessary to the ketal formation was also an initiator for polymerization of the allyl acetone. The problem then resolved itself to control of the hydrogen chloride addition such that the ketal formation would occur without appreciable polymerization. The most satisfactory means of treatment was a visual control wherein dry hydrogen chloride was bubbled through the reaction mixture until the first trace of brown coloration appeared. This brown coloration proved to be the first indication of polymerization and if the hydrogen chloride addition was stopped at thistime, the extent of polymerization was small.

Reaction Sequence 4 failed because allyl acetone could not be converted to 2,2-diethoxy-5-chlorohexane. The structure of allylacetone is apparently particularly susceptable to polymerization and the hydrohalogenation of the unsaturated linkage could not be promoted without excessive polymerization. If this polymerization could be suppressed it should be possible to promote the expected hydrohalogenation. If 2,2-diethoxy-5-chlorohexane could be obtained, the Grignard preparation and deuterium oxide decomposition should proceed rather smoothly. It would appear that the problem must be approached by producing the ketal in the described manner before attempting the hydrohalogenation, since hydrogen chloride could be added to allylacetone with no greater degree of success than was observed with 5,5-diethoxyhexene-1.

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