

THE PREPARATION AND PROPERTIES OF SOME 2,2,2-TRIALKYL ETHANOLS

by  
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of the University of Maryland in partial fulfillment  
of the requirements for the degree of  
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## INTRODUCTION

It has been pointed out by Frankel (1) that among the chemical structures which have been found to be important in the production of hypnotic action there are alkyl radicals, the carbonyl group, amides, and aliphatic halogen substituted compounds. In addition it has been stated by Dyson (2) that the introduction of one hydroxyl group into an aliphatic hydrocarbon increases the narcotic action. Reasoning from these facts we might conclude that the monohydric alcohols would all possess hypnotic power and that the introduction of alkyl groups or halogen atoms in place of hydrogens in these alcohols would enhance their hypnotic activity.

In support of this conclusion it has been shown by Grant (3) and by Schneegans and von Mering (4) that secondary alcohols have a stronger narcotic action than their straight chain analogues. Moreover, tertiary alcohols were found to be still more active than the secondary members (5).

In view of the fact that 2,2,2-tribromoethanol (a hydrocarbon in which three halogens and an hydroxyl group have been substituted for hydrogens) is a powerful hypnotic frequently used in clinical medicine, it was thought possible that some of its analogues which contain alkyl groups in place of the bromines might also possess strong narcotic action. It was decided to prepare some of these alcohols and compare their action to that of 2,2,2-tribromoethanol. For this purpose 2,2-dimethyl-propanol-1; 2,2-dimethyl-butanol-1; 2-ethyl-2-methyl-butanol-1 and 2,2-diethyl-butanol-1 were made.

It was found that although all of these alcohols do possess decided

hypnotic activity they are not as active as the halogenated ethanol. In accordance with previous findings, the presence of the ethyl group enhanced activity more than did the substitution of hydrogen by methyl radicals.

## REVIEW OF THE LITERATURE

2,2-dimethyl-propanol-1: Tissier (6) was the first to report the preparation of this compound. He was able to obtain it in low yields by three different methods, (a) by the reduction of a mixture of trimethylacetic acid and trimethylacetyl chloride using three per cent sodium amalgam, (b) by chlorination of tetramethylmethane and saponification of the chloride obtained and (c) by the dry distillation of calcium trimethylacetate with calcium formate followed by reduction of the trimethylacetaldehyde formed.

Bouveault (7) utilized the Grignard reaction by forming trimethylcarbinyl magnesium chloride and allowing it to react with methyl formate at  $-10$  to  $-15^{\circ}$  C., but only small quantities of the desired product were obtained.

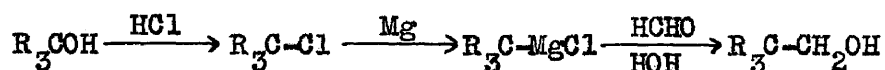
Courtot (8) also reports the preparation of 2,2-dimethyl-propanol-1 through the Grignard reaction by the treatment of trimethylcarbinyl magnesium bromide with paraformaldehyde. He gave no details of his procedure and did not mention his yields. Samec (9) followed the same method and reported two per cent yields.

In 1910, Richard (10) had occasion to prepare this alcohol in considerable quantities and was able to develop a procedure which was an improvement over previous ones in regard to yields obtained. He adopted the Bouveault-Blanc process (11) for reducing the fatty acids to their corresponding alcohols by treating the ethyl ester of trimethylacetic acid with four times its weight of absolute alcohol and an equal weight of sodium in large pieces. Although he experienced considerable difficulty in fractionating the product, he was able to obtain a 54 per cent

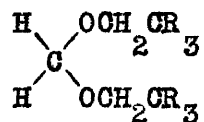
yield of the desired alcohol from the ester and to recover the greater portion of the unreacted ester as trimethylacetic acid.

Franke (12) reduced 2,2-dimethyl-3-bromopropanol with sodium amalgam and absolute methyl alcohol to obtain a 12.5 per cent yield of 2,2-dimethyl-propanol.

Conant, Webb and Mendum (13) modified Courtot's procedure in such a manner that they were able to pass from the tertiary alcohol to the primary alcohol in 40-50 per cent yields as:



They found that a considerable excess of formaldehyde passed into the reaction mixture changed as much as two-thirds of the product over to the acetal:



from which the alcohol might be recovered by boiling in alcoholic hydrochloric acid.

Acetate of 2,2-dimethyl-propanol-1: Tissier (6) reported the preparation of this ester by two different methods, (a) by heating glacial acetic acid with the alcohol in a sealed tube for several days and (b) by treating the alcohol with acetyl chloride. He found the latter method to be much faster and the yields were very much better.

Phenylurethane of 2,2-dimethyl-propanol-1: Richard (10) made this compound by mixing equimolar quantities of the alcohol and phenyl isocyanate



in petroleum ether solution and let the solution stand for a day. He purified the product by recrystallization from ligroin.

Gordon (14) claims to have prepared the urethane by heating equimolar quantities of the alcohol and phenyl isocyanate to boiling then allowed the solution to stand until solidification was complete. The product was purified by dissolving it in hot ligroin and filtering, then recrystallizing the residue on evaporation from methyl alcohol.

$\alpha$ -naphthylurethane of 2,2-dimethyl-propanol-1: Gordon (14) reported the synthesis of this compound by mixing equimolar quantities of  $\alpha$ -naphthyl isocyanate and the alcohol and allowing them to stand at room temperature for twenty-four hours. Purification was accomplished in the same manner as described for the phenylurethane.

2,2-dimethyl-butanol-1: The alcohol was first prepared by Bouveault and Blanc (15) who utilized their reduction process by treating the ethyl ester of 2,2-dimethyl-butyric acid with sodium and absolute alcohol. They did not report the yield of the reaction.

Favorski and Ssakara (16) also made 2,2-dimethyl-butanol-1 by reacting ethyl formate with tert.-amyl magnesium chloride. They were able to obtain yields of nearly sixty per cent based on the ethyl formate added. They made the acetate of the alcohol and found the boiling point to be 152-153° C. The phenylurethane was also reported. It had a melting point of 65-66° C.

2-ethyl-2-methyl-butanol-1: Favorski and Zalesskii-Kibardine (17) prepared this alcohol by treating diethyl-methyl-carbinyl magnesium chloride with formaldehyde. They also identified 3-methylpentane and 3-methyl-

2-pentene as products of the reaction. The phenylurethane did not crystallize.

2,2-diethyl-butanol-1: The formation of this compound was reported by Whitmore and Badertscher (18) from the reaction of triethylcarbinyl magnesium chloride and formaldehyde. B.P. 75-78° C. at 12 mm. pressure. The yield was ten per cent based on the Grignard reagent used.

## PART I

## EXPERIMENTAL

## Preparation of Ether for Grignard Reactions

Large quantities of anhydrous, alcohol-free ether were necessary for carrying out the Grignard reactions explained below. The following method was found to produce a satisfactory product and was the one finally adopted after trials of other procedures.

Two 2-liter portions of commercial ether were each extracted with five 100-cc. portions of cold distilled water in order to remove most of the alcohol present and the two portions poured together in a 5-liter flask containing 100 Gm. of anhydrous calcium chloride in large lumps. The flask was shaken frequently during the next two hours then placed in the refrigerator overnight. The partially dried ether was then poured off into another 5-liter flask and powdered, anhydrous calcium chloride added in ten Gm. portions. The addition was continued until after shaking the liquid a quantity of finely divided calcium chloride remained suspended for about a minute. It was found that as long as water was present in the ether it reacted at once with the calcium chloride particles to form a hydrate which sank immediately after shaking was discontinued.

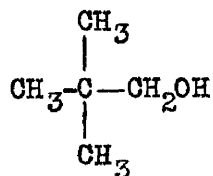
The flask was then connected to a distilling apparatus fitted with an efficient condenser and the ether distilled at as rapid a rate as the condenser would allow, the distillate being collected in a dry flask of suitable capacity containing about fifteen grams of freshly cut sodium in thin shavings and protected from the air by a tube of calcium chloride. When distillation was complete, the ether was refluxed over the sodium

for five hours then placed in the refrigerator and let stand over night after which a few pieces of freshly cut sodium were added and watched carefully for any evidence of reaction with the ether. If drying was not complete, five more grams of sodium shavings were added and refluxing continued three hours longer. This treatment was sufficient to completely dry all the runs made.

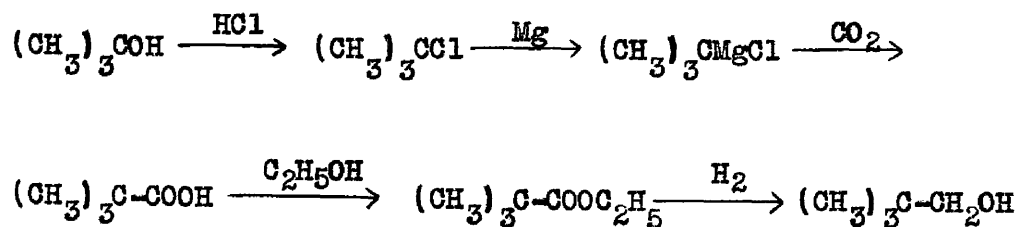
The ether was then distilled slowly in a completely dry apparatus and collected in a container in which was placed about five grams of sodium shavings. The last 200 cc. of residue was not distilled but used to preserve the sodium for use in future dryings. The ether thus obtained measured about 3300 cc. and was stored in the refrigerator in tightly stoppered containers over sodium until ready for use. This procedure was also found satisfactory for purifying ether recovered from the Grignard reactions.

The dry ether was transferred into reaction flasks and containers by means of an atomizer bulb connected to a glass-tubing system similar to a wash bottle, the air pumped in being dried by passing it through a tube of calcium chloride.

2,2-dimethyl-propanol-1



Two methods were tried for the preparation of this compound. The first method was carried out according to the following reactions:



Tertiary-butyl Chloride: This compound was made according to the method of Norris and Olmsted (19). In a 1-liter separatory funnel was placed 200 cc. of tert.-butyl alcohol (Eastman practical) and 500 cc. of C.P. concentrated hydrochloric acid. After shaking for about fifteen minutes, the layers were allowed to separate and the upper layer drawn off and washed with a saturated solution of sodium bicarbonate until it was no longer acid to litmus paper. The chloride was then dried over twenty Gm. calcium chloride and distilled through a 20-cm. glass bead column over a water bath. The fraction distilling at 51-52° C. was collected and kept over anhydrous sodium carbonate until ready for use. The yield was 120 - 130 Gm. or 77-83 per cent.

Trimethylacetic acid: The procedure of Puntambeker and Zoellner (20) was followed. Sixty-one grams of magnesium powder was placed in a 3-liter, three-necked flask fitted with a mechanical stirrer and mercury seal, a 300-cc. separatory funnel and reflux condenser. The magnesium was covered with 200 cc. of anhydrous ether. Five cc. of ethyl bromide and a crystal of iodine was added to start the reaction. Stirring was then started and a solution of 227 Gm. of tert.-butyl chloride in 1100 cc. of anhydrous ether was dropped slowly on the magnesium during a period of about six hours. The rate of addition was regulated so that slow refluxing continued throughout the reaction. After complete addition of the halide solution, the mixture was stirred for fifteen minutes to complete the reaction.

Note: When this reaction was first tried, considerable difficulty was experienced in starting it without the formation of a large amount of bulky white precipitate which increased as the addition of tert.-butyl chloride continued and resulted in a low yield of the Grignard reagent. It was found that by using a small quantity of ethyl bromide to produce a vigorous initial reaction and adding the tert.-butyl chloride fast enough to maintain gentle refluxing none of the white precipitate separated and the yield was greatly increased.

The flask was then surrounded with ice and salt and the separatory funnel replaced by a two-hole stopper containing a thermometer and a glass tube, the outer end of which was connected with a mercury trap. When the temperature had reached 0° C., the condenser was replaced by a tube leading to a tank of carbon dioxide, the end of the tube in the flask being adjusted about five cm. above the surface of the liquid. Carbon dioxide was then passed in while the mixture was stirred rapidly at such a rate that the temperature did not exceed 8° C. until passage of the gas no longer produced an increase in temperature.

Note: This reaction with carbon dioxide was carried out by pouring the solution of trimethyl-carbinyl magnesium chloride into a 2-liter beaker and slowly adding one pound of solid carbon dioxide previously broken into pieces about a cubic inch in volume. The extremely cold mixture resulting was placed in the ice box for two hours then hydrolyzed as described below. Although the method is much faster and easier to carry out, the yields of trimethylacetic acid were so reduced that the above method of reaction with carbon dioxide gas was preferred.

The resulting mixture was hydrolyzed by pouring it slowly with vigorous stirring onto 1200 Gm. of crushed ice and 600 cc. of 50 per cent

sulfuric acid. The water layer was extracted with four 100-cc. portions of ether and these ether extracts together with the original ether portion extracted with four 100-cc. portions of 25 per cent sodium hydroxide solution. This alkaline solution was then heated to 100° C. to remove ether and other volatile impurities and cooled in ice and acidified with 25 per cent sulfuric acid. The trimethylacetic acid which separated as an oily layer on top of the liquid was removed and the aqueous portion distilled until no more oil came over with the distillate. The distillate was saturated with sodium chloride and the trimethylacetic acid which separated was drawn off and added to the original portion. The crude acid was then distilled and the fraction coming over at 163-165° C. collected. The product slowly solidified and melted at 34-35° C. The yield was 150-157 Gm. or about 66 per cent. It had an unpleasant odor resembling that of butyric acid.

Ethyl Ester of Trimethylacetic Acid: The procedure of Richard (10) was followed in which 10 Gm. of the acid, 10 Gm. of absolute alcohol and 5 Gm. of concentrated sulfuric acid were heated for two hours on the water bath under a reflux condenser. At the end of the time the liquid had separated into two layers. It was poured into ice water and the ester layer which separated was washed with sodium bicarbonate solution until free from acid. It was then dried over anhydrous sodium sulfate and distilled. The yield of ester B.P. 117-122° C. was 11.0 Gm. or 80 per cent. The yield from a run starting with 50 Gm. of trimethylacetic acid was 58 Gm. or about 90 per cent.

Reduction of the Ethyl Ester of Trimethylacetic Acid: This reduction was attempted by following the general procedure of Bouveault and Blanc

for reducing esters of fatty acids to their corresponding alcohols (11). Twenty-eight grams of sodium in pieces about one centimeter on a side was placed in a 1-liter flask equipped with a mechanical stirrer and mercury seal, reflux condenser and dropping funnel. A solution of 24 Gm. of the ethyl ester of trimethylacetic acid in 120 Gm. of absolute alcohol was then dropped slowly onto the sodium. Reaction became so violent at times that it was necessary to cool the flask in ice water. After all the solution had been added and no more reaction was apparent, the mixture was heated on a water bath for two hours. The product obtained was poured slowly into water and gave a very dark brown solution from which no product of constant boiling point could be isolated even after repeated fractionations. This result led to the trial of another method for the preparation of the alcohol.

Method II for Preparing 2,2-dimethyl-propanol-1: Tert.-butyl magnesium chloride prepared in the manner described above was allowed to react with gaseous formaldehyde as follows: The yield of Grignard reagent was first obtained by the method of Gilman (21) in which a 20-cc. aliquot portion of the solution of the reagent was dissolved in an excess of half-normal sulfuric acid solution, heated to about 60° C. to remove the ether and the excess sulfuric acid titrated with half-normal sodium hydroxide solution. This procedure showed 80-85 per cent yields of the trimethylcarbinyl magnesium chloride. A ten per cent excess of formaldehyde was then passed in over a period of 6-8 hours by heating the correct quantity of paraformaldehyde (previously dried over sulfuric acid for ten days) in a large test tube connected to the reaction flask by a large-bore delivery tube, the mixture being stirred and allowed to reflux gently. It was

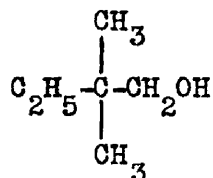


found most satisfactory to use a short delivery tube for the formaldehyde gas and protect the reaction flask from the heat of the hot plate used to depolymerize the formaldehyde by an asbestos board in order to prevent as much as possible repolymerization of the formaldehyde and consequent clogging of the tube. After all the formaldehyde had passed in, the flask was warmed over a water bath and refluxing and stirring continued for two hours longer.

Note: An attempt was made to dry the paraformaldehyde in a vacuum desiccator over phosphorous pentoxide for several days for this reaction but at the end of this time the paraformaldehyde had become sticky and it had developed a very sharp odor which indicated that some change had taken place to make it unsatisfactory for use.

The resulting product was hydrolyzed by pouring it over a mixture of 1500 Gm. of cracked ice, 300 cc. of water and 300 Gm. of ammonium chloride with frequent stirring. After separating the ether layer, the aqueous portion was extracted with three 100-cc. portions of ether and the combined ether solutions were distilled until all ether was removed. The residue was then dried for several hours over anhydrous sodium sulfate. Subsequent fractionation yielded 88-95 Gm. of product B.P. 111-113° C. M.P. 49° C.

Note: This yield was obtained by starting with four moles of magnesium and tert.-butyl chloride. The melting point and boiling point agree with those found by other workers although somewhat conflicting values have been reported (9, 10, 12). The 2,2-dimethyl-propanol-1 is a white crystalline solid having a high vapor pressure and an agreeable camphoraceous odor.

2,2-dimethyl-butanol-1

This compound was prepared by essentially the same procedure as described for preparing 2,2-dimethyl-propanol-1.

Dimethyl-ethyl-carbinyl Chloride: This substance was prepared from tert.-amyl alcohol (Eastman-practical) by two different methods:

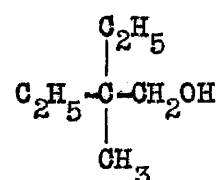
(a) 400 cc. of tert.-amyl alcohol was shaken with one liter of concentrated hydrochloric acid for about fifteen minutes and the chloride layer separated and cooled in ice water. It was then washed with small portions of ice-cold sodium bicarbonate solution until all the acid had been removed. The resulting product was placed over anhydrous potassium carbonate for twelve hours to dry. Distillation of the product at such reduced pressure that the vapor temperature never exceeded 55° gave 332 Gm. of product or an 83 per cent yield.

(b) The second method was that of Halse (22) which consisted in passing dry hydrogen chloride gas into three moles (264 Gm.) of tert.-amyl alcohol at such a rate that the temperature could be kept at 0° C. or less by immersing the flask in ice and salt. The reaction was continued until a slight excess of the theoretical amount of hydrogen chloride had been taken up. The water formed in the reaction was separated and the product dried over anhydrous sodium sulfate and potassium carbonate after it had been washed free of acid with sodium bicarbonate solution. Distillation in the manner described above yielded 230 Gm. of product or a 71 per cent yield.

Both methods resulted in a colorless liquid of characteristic odor.  
B.P. 84-86° C.  $n_D^{20}$  1.4045

2,2-dimethyl-butanol-1: The tert.-amyl chloride was allowed to react with magnesium to form its Grignard reagent in the manner described above and this Grignard reagent treated with formaldehyde. One run was made under an atmosphere of nitrogen and the yield of reagent was found to be increased about five per cent. In consequence of this result all subsequent reactions for preparing Grignard reagents were run in this manner. Yields of tert.-amyl magnesium chloride varied from 65-75 per cent. Hydrolysis of the product after treatment with formaldehyde and fractionation of the ethereal solution thus obtained produced 90-95 Gm. of 2,2-dimethyl-butanol-1. It is a colorless, somewhat viscous liquid having an agreeable aromatic odor. B.P. 134-135° C.  $n_D^{20}$  1.4203

2-ethyl-2-methyl-butanol-1

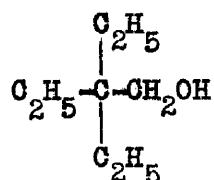


Diethyl-methyl-carbinyl Chloride: This substance was prepared by the two methods used for making dimethyl-ethyl-carbinyl chloride which were explained above. When it was prepared by shaking the carbinol with concentrated hydrochloric acid, a yield of pure dry product of 316 Gm. was obtained from 410 Gm. of the carbinol or 77 per cent. By saturating diethyl-methyl carbinol with hydrogen chloride at 0° C. a yield of 54 per cent was obtained. The product from either method had the constants,

B.P. 115-117° C.  $n_D^{20}$  1.4123

Diethyl-methyl-carbinyl Magnesium Chloride: This was prepared according to the procedure for making trimethyl-carbinyl magnesium chloride described above with slight modifications. Two and one-half moles of magnesium were used in place of four moles and two and one-half moles of the halide were diluted with 1000 cc. of anhydrous ether and dropped slowly on the magnesium after the reaction had been initiated by adding five cc. of ethyl bromide. Yields of the Grignard reagent were 60-65 per cent. After the usual treatment with formaldehyde, hydrolysis and distillation of this product produced 80-85 Gm. of the 2-ethyl-2-methyl-butanol-1. B.P. 59-61° C. at 15 mm. pressure or 150-151° C. at atmospheric pressure.  $n_D^{20}$  1.4261

2,2-diethyl-butanol-1



This compound was made in the usual manner by the reaction of triethyl-carbinyl magnesium chloride with gaseous formaldehyde followed by hydrolysis and distillation.

Triethyl Carbinol: The procedure of Moyer and Marvel (23) was followed. In a 3-liter, three-necked flask equipped with a mechanical stirrer and mercury seal, dropping funnel and reflux condenser was placed 98 Gm. of magnesium turnings and 300 cc. of anhydrous ether. The reaction was started by adding a crystal of iodine and five cc. of ethyl bromide.

When reaction was pronounced, the stirring was begun and a solution of 480 Gm. of ethyl bromide in one liter of ether was dropped in at such a rate that vigorous refluxing continued throughout the reaction. Stirring was continued for fifteen minutes after all the halide solution had been added. Titration of yields showed 90-95 per cent of the desired product.

The ethyl magnesium bromide thus obtained was treated in two ways in order to prepare triethyl carbinol. (a) Two hundred and six grams (2 moles) of ethyl propionate diluted with an equal volume of anhydrous ether was dropped in as fast as possible so that refluxing did not become too vigorous and after complete addition, stirring and refluxing were continued for two hours. The resulting product was hydrolyzed by pouring it over 1500 Gm. of crushed ice, 300 cc. of water and 300 Gm. of ammonium chloride.

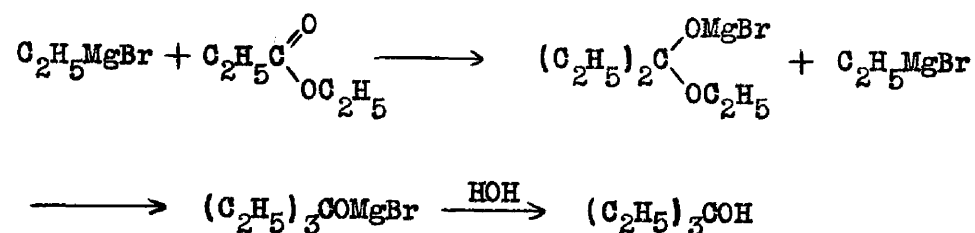
The aqueous layer obtained was extracted with three 300-cc. portions of ether and these washings added to the original ether layer. After distilling off the ether, the residue was dried over ten grams of anhydrous potassium carbonate and fractionated at reduced pressure. An average yield was 175 Gm. of product B.P. 140-145° C. or 43-45° C. at 10 mm. pressure.  $n_D^{20} 1.4295$

(b) The Grignard reagent prepared as above was treated with 145 Gm. of diethyl carbonate dissolved in an equal volume of anhydrous ether. The diethyl carbonate had a boiling point of 125-127° C. and was distilled from the Eastman technical product. The average yield was 125 Gm. of triethyl carbinol.

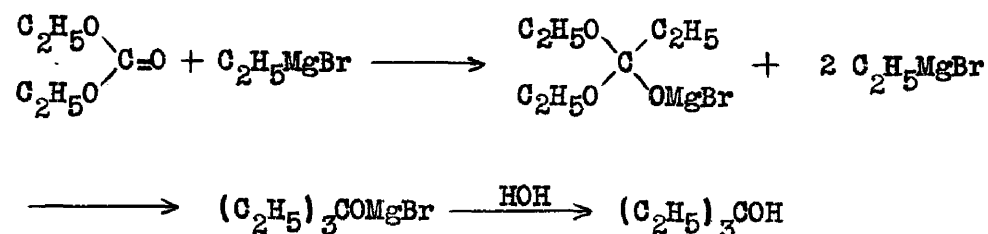
Note: Although 175 Gm. of the triethyl carbinol was obtained by the first procedure and only 125 Gm. by the second, the per cent yields were 75 and 81 respectively. This may be explained by consideration of the

reactions taking place in each case.

(a)



(b)



In other words two moles of ethyl bromide are required to react with one of ethyl propionate, the other being lost, while three moles of the bromide are necessary for each mole of ethyl carbonate, two of them being lost. However, since ethyl carbonate is available at a much lower price than ethyl propionate, the ultimate cost of the final product is about the same.

Triethyl-carbinyl Chloride: The compound was prepared according to the method of Halse (22) in which the carbinol was cooled to  $-10^\circ \text{C}$ . and saturated with dry hydrogen chloride. The halide layer was separated, dried and freed from hydrogen chloride by allowing it to stand in a vacuum desiccator with sodium hydroxide overnight. The product was then purified by one of two methods: (a) that of Gilman (24) in which it was washed with half its volume of C.P. concentrated sulfuric acid, the acid separated and the chloride layer centrifuged until clear, then let stand for twelve hours at  $0^\circ \text{C}$ . with anhydrous sodium sulfate and sodium carbonate. The resulting chloride was filtered and preserved in well-stoppered bottles

kept in the refrigerator. (b) The chloride layer after being separated from the water formed in the reaction was washed several times with ice-cold five per cent sodium bicarbonate solution then dried for at least twelve hours over anhydrous sodium sulfate and sodium carbonate. This product was distilled at about two hundred mm. pressure and the distillate preserved as above. Both methods resulted in 85-88 per cent yields of the chloride.

A second method of preparation found to result in a somewhat lower yield was tried. Two hundred and fifty grams of triethyl carbinol was mixed with one liter of concentrated hydrochloric acid and shaken for fifteen to twenty minutes. The chloride layer was separated, washed with cold five per cent sodium bicarbonate solution, dried over anhydrous sodium sulfate and sodium carbonate, then distilled at reduced pressure. The yield from such a reaction was 219 Gm. or 75 per cent. Triethylcarbinyl chloride prepared by any of these methods was found to have a boiling point of 142-143° C.  $n_D^{20} 1.4330$ . These constants agree with those reported by Schreiner (25).

Triethyl-carbinyl Magnesium Chloride: A typical run serves to describe the method used in this case. 52.4 Gm. (2.23 moles) of magnesium powder was placed in a 3-liter, three-necked flask equipped with a mechanical stirrer and mercury seal, reflux condenser and dropping funnel and covered with 500 cc. of anhydrous ether. To this was added a crystal of iodine and three cc. of ethyl bromide to start the reaction. Stirring was begun and a mixture of 300 Gm. (2.23 moles) of triethyl-carbinyl chloride in 800 cc. of anhydrous ether was added at the rate of about one drop per second or fast enough to keep the reaction flask slightly warm to the

touch. Stirring was continued for fifteen minutes after complete addition of the halide solution. Yields of the Grignard reagent varied widely being from 30-50 per cent.

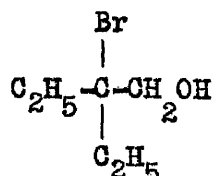
Note: The reaction was run approximately seven times to find the method giving the best yield of Grignard reagent. Such factors as the rate of addition of halide, the temperature of reaction and the size of the magnesium used were varied to find their effect upon the yield. It was necessary to add the halide fast enough to maintain a temperature of about 35° C. in order to get any reaction, and reactions in which magnesium powder was used instead of the turnings produced a somewhat better yield. In all cases, however, the formation of a white precipitate took place, usually after about half of the halide solution had been added and this precipitate continued to increase slowly until complete addition of halide had been accomplished. Whitmore and Badertscher (18) reported a 58 per cent yield by essentially this same procedure.

2,2-diethyl-butanol-1: A ten per cent excess over the calculated amount of formaldehyde gas was allowed to react with the Grignard reagent as prepared above by heating the paraformaldehyde in the manner previously described. The product was refluxed an hour over a water bath, then hydrolyzed by pouring it on to 1 Kgm. of crushed ice and 200 Gm. of ammonium chloride. The ether layer was then separated and the aqueous portion extracted three times with 200-cc. portions of ether. The ether was then distilled off, the residue dried and finally distilled under reduced pressure. Yields of product, B.P. 76-77° C. at 11 mm. pressure, were from 12.5 to 16 Gm. (8.5 - 11 per cent)  $n_D^{20}$  1.4400. It is a colorless, somewhat viscous liquid having a characteristic camphoraceous odor. The

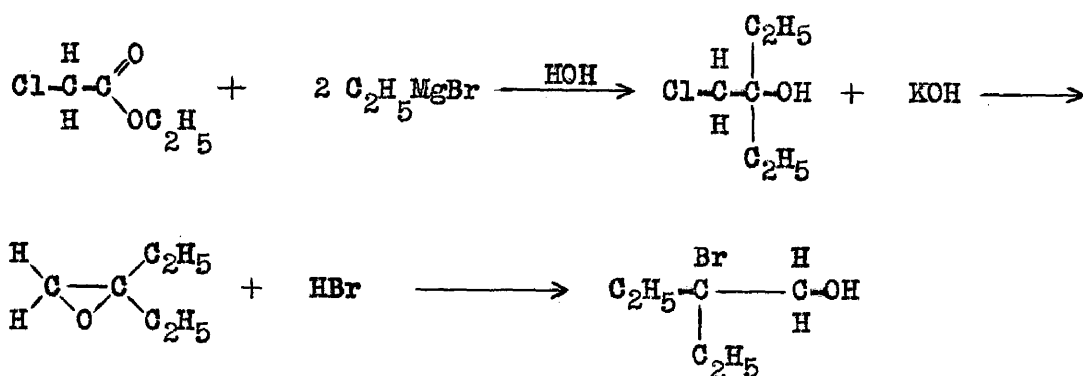


The boiling point and refractive index agree with those found by Whitmore and Badertscher (18).

At attempt to Prepare 2-bromo-2-ethyl-butanol-1



It was planned to carry out the following reactions to obtain the desired alcohol:



Ethyl Chloroacetate: The method of Conrad (26) was used. 400 Gm. of monochloroacetic acid were dissolved in 190 Gm. of 95 per cent ethyl alcohol by the aid of gentle heat and to the mixture was added slowly 50 Gm. of concentrated sulfuric acid. The product was then heated on a water bath under a reflux condenser for five hours and poured into an equal volume of ice water. The ester layer was separated, washed with cold distilled water then sodium bicarbonate solution until free from acid and finally dried over anhydrous sodium sulfate and distilled. Two such runs gave an average of 350 Gm. of ethyl chloroacetate or 68 per cent. B.P. 141-142° C. The ester is a colorless liquid having a characteristic but very irritating odor.

Chloro-methyl-diethyl carbinol: Ethyl magnesium bromide prepared in the manner previously described by treating 107 Gm. (4.4 moles) of magnesium in 800 cc. of anhydrous ether with 480 Gm. (4.4 moles) of ethyl bromide was allowed to react with 225 Gm. (2 moles) of ethyl chloroacetate diluted to 400 cc. with anhydrous ether. The reaction was very vigorous and required about five hours for addition of all the ethyl chloroacetate solution and upon standing the product separated into two distinct layers, a behavior which was unexplained. This mixture was hydrolyzed by pouring it slowly onto 1500 Gm. of crushed ice, 300 Gm. of ammonium chloride and 150 cc. of water. The ethereal layer was separated and the aqueous portion extracted with three 300-cc. portions of ether, these extractions being added to the original ether layer and the whole subjected to distillation. After recovery of the ether, 82-90 Gm. of product boiling at 62-63° C. at 12 mm. pressure or 70-72° C. at 18 mm. pressure was obtained. A residue of approximately 60 Gm. of black tarry residue of undetermined composition remained in the distilling flask. The chloro-methyl-diethyl carbinol obtained was found to darken rapidly on standing even in the refrigerator, a product which was colorless at distillation becoming deep brown on standing overnight. Because of this fact the material was used as soon as possible after its preparation.

$\alpha,\alpha$ -diethyl-ethylene oxide: (a) Eighty-two grams of chloro-methyl-diethyl carbinol and 32 Gm. (0.56 moles) of powdered potassium hydroxide were mixed together and placed in a distilling flask. Upon mixing there was considerable evolution of heat. Distillation was carried out slowly over an oil bath until the residue remaining had become solid. The distillate consisted of two immiscible layers, the lower one being the water formed in the reaction. The upper layer was fractionated in a 30-cm.

glass bead column but no product of constant boiling point could be isolated. Dalebroux and Wuyts (27) describe  $\alpha,\alpha$ -diethyl-ethylene oxide as a mobile liquid with a mint-like odor B.P.  $107^{\circ}$  C. The above distillate had a distinct mint-like odor but distilled over a wide range which was below  $107^{\circ}$  C.

Treatment of the distillate with hydrogen bromide: The distillate was cooled to  $0^{\circ}$  C. in ice and salt and saturated with dry hydrogen bromide, the resulting product being a dark brown viscous oil. This oil was diluted with an equal volume of benzene and washed with cold sodium bicarbonate solution until free from acid. Distillation resulted only in recovery of the benzene. No other product of constant boiling point could be obtained.

(b) A second attempt was made to prepare the  $\alpha,\alpha$ -diethyl-ethylene oxide in appreciable yields. 110 Gm. of chloro-methyl-diethyl carbinol was dissolved in an equal volume of absolute alcohol and 40 Gm. of powdered potassium hydroxide added. This mixture was refluxed for five hours on a water bath, then filtered to remove the solid residue. The alcohol in the filtrate was removed by distillation leaving a solid residue. This residue was treated with water and the mixture steam distilled but only a trace of oil was obtained.

Because of the failure to obtain any of the desired  $\alpha,\alpha$ -diethyl-ethylene oxide and lack of more time to continue this investigation the preparation of 2-bromo-2-ethyl-butanol-1 was discontinued.

TABLE I

PREPARATION OF SUBSTITUTED ETHANOLS				
Alcohol	Chloride used and per cent yield	Yield of Grig. reagent	Yield of alcohol from Grig. reagent	Overall yield
2,2-dimethyl-propanol-1	$(\text{CH}_3)_3\text{C}-\text{Cl}$ 80%	83%	35%	25%
2,2-dimethyl-butanol-1	$(\text{CH}_3)_2(\text{C}_2\text{H}_5)-\text{C}-\text{Cl}$ 80%	70%	33%	23%
2-ethyl-2-methyl-butanol-1	$(\text{CH}_3)(\text{C}_2\text{H}_5)_2-\text{C}-\text{Cl}$ 77%	62%	40%	25%
2,2-diethyl-butanol-1	$(\text{C}_2\text{H}_5)_2\text{C}-\text{Cl}$ 85%	50%	10%	5%

## PREPARATION OF THE ACETATES OF THE SUBSTITUTED ETHANOLS

Acetate of 2,2-dimethyl-propanol-1: To 8.8 Gm. of the alcohol was added slowly with frequent shaking 8 Gm. of acetyl chloride. Large quantities of hydrogen chloride were evolved during this procedure. After standing for one half hour at room temperature, the mixture was warmed up slowly on a water bath to the maximum temperature and heated under a reflux condenser until no more hydrogen chloride was given off. The resulting product was poured into 25 cc. of ice water and the acetate layer separated. It was washed with cold water then with sodium bicarbonate solution and finally dried over anhydrous sodium sulfate. Distillation gave 8 Gm. of product boiling at 124-125° C.  $n_D^{20}$  1.3959. It is a colorless product of fragrant odor, insoluble in water and miscible with the common organic solvents.

Analysis: (a) 10.58 cc. of 1 N potassium hydroxide were required to saponify 1.3814 Gm. of the acetate. The calculated quantity

is 10.62 cc. Per cent purity - 99.62

(b) 10.61 of 1 N potassium hydroxide were required to saponify 1.3802 Gm. of the acetate. The calculated quantity is 10.61 cc.

Per cent purity - 100.00

Acetate of 2,2-dimethyl-butanol-1: 10.2 Gm. of the alcohol and 8 Gm. of acetyl chloride were treated in the manner previously described. Distillation yielded 8 Gm. of product B.P. 152-153° C.  $n_D^{20}$  1.4098

Analysis: (a) 1.4859 Gm. of the acetate required 9.68 cc. of 1 N potassium hydroxide for saponification. The calculated quantity is 10.31 cc. Per cent purity - 93.90

(b) 1.4923 Gm. of the acetate required 9.73 cc. of 1 N potassium hydroxide solution for saponification. The calculated quantity is 10.35 cc. Per cent purity - 94.00

Acetate of 2-ethyl-2-methyl-butanol-1: 11.6 Gm. of the alcohol and 8 Gm. of acetyl chloride were treated in the usual manner, distillation producing 7 Gm. of product. B.P. 51-52° C. at 8 mm. pressure or 170-171° C. at 757 mm. pressure.  $n_D^{20}$  1.4140.

Analysis: (a) 1.7166 Gm. of acetate required 10.56 cc. of 1 N potassium hydroxide for saponification. The calculated quantity is 10.85 cc. Per cent purity - 97.32

(b) 1.6977 Gm. of acetate required 10.44 cc. of 1 N potassium hydroxide for saponification. The calculated quantity is 10.73 cc. Per cent purity - 97.30

Acetate of 2,2-diethyl-butanol-1: 5.3 Gm. of the alcohol were treated with 4.0 Gm. of acetyl chloride as previously described. The product

obtained was distilled twice at 20 mm. pressure resulting in 3.5 Gm. of product B.P. 70-71° C.  $n_D^{20}$  1.4331

Analysis: (a) 0.5851 Gm. of acetate required 2.97 cc. of 1 N potassium hydroxide for saponification. The calculated quantity is 3.40 cc. Per cent purity - 87.35

(b) 0.8396 Gm. of the acetate required 4.25 cc. of 1 N potassium hydroxide for saponification. The calculated quantity is 4.87 cc. Per cent purity - 87.27

#### PREPARATION OF PHENYLURETHANES OF THE SUBSTITUTED ETHANOLS

Phenylurethane of 2,2-dimethyl-propanol-1: 2.2 Gm. of the alcohol and 3.0 Gm. of phenyl isocyanate were mixed together and heated on a water bath until the mixture solidified to an almost white mass. The product was crystallized twice from ligroin and was found to melt at 114-114.5° C.\* Nitrogen analysis by the Kjeldahl method: 6.60 per cent. Calc. - 6.70 per cent.

Phenylurethane of 2,2-dimethyl-butanol-1: 5.2 Gm. of the alcohol and 6.0 Gm. of phenyl isocyanate were mixed together and heated on a water bath for half an hour and upon cooling and stirring the mixture solidified to a nearly white mass. After two crystallizations from ligroin a product of constant melting point at 63-64° C. was obtained. Nitrogen analysis: 6.09; 6.23 per cent. Calc. - 6.33 per cent.

Phenylurethane of 2-ethyl-2-methyl-butanol-1: 5.8 Gm. of the alcohol

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\* There are conflicting data on the melting point of this urethane. Richard (10) reports 114-115° while Gordon found his product to melt at 45°. The constant found here agrees with that of Richard.

and 6.0 Gm. of phenyl isocyanate were heated together for an hour on a water bath. The product was cooled and stirred in ice and salt but no crystallization took place. It was heated for another hour on the water bath but no solid product could be obtained. An attempt to purify the product by distillation at 5 mm. pressure produced only decomposition. Due to the fact that a considerable quantity of heat was given off as was characteristic in the formation of the other phenylurethanes, it was concluded that the reaction between the alcohol and phenyl isocyanate had taken place but the phenylurethane formed is a thick viscous liquid unsuited for analysis or characterization of the 2-ethyl-2-methyl-butanol-1.

Phenylurethane of 2,2-diethyl-butanol-1: 2.6 Gm. of the alcohol and 2.4 Gm. of phenyl isocyanate were treated in the manner described above and in this case again a viscous oil impossible to crystallize was formed. It was concluded that the phenylurethane of 2,2-diethyl-butanol-1 is a liquid unsuitable for characterization of the alcohol.

#### $\alpha$ -NAPHTHYLURETHANES OF THE SUBSTITUTED ETHANOLS

$\alpha$ -Naphthylurethane of 2,2-dimethyl-propanol-1: 2.2 Gm. of the alcohol and 4.2 Gm. of  $\alpha$ -naphthyl isocyanate were heated together for a short time then stirred until crystallization was complete and a hard mass resulted. After two crystallizations from ligroin, a product of M.P. 99-100° was obtained and on analysis was found to contain 5.40 and 5.28 per cent nitrogen in two analyses.\* Calculated per cent - 5.45

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\* Gordon (14) reported a melting point of 71° C. No analysis of his compound was given.

$\alpha$ -Naphthylurethane of 2,2-dimethyl-butanol-1: 5.1 Gm. of the alcohol heated with 8.4 Gm. of  $\alpha$ -naphthyl isocyanate resulted in a product having a melting point of 81-82° C. after two crystallizations from ligroin. Nitrogen analysis: 5.06 and 5.26 per cent. Calc. - 5.16

$\alpha$ -Naphthylurethane of 2-ethyl-2-methyl-butanol-1: 3.7 Gm. of the alcohol heated with 5.5 Gm. of  $\alpha$ -naphthyl isocyanate in the usual manner resulted in a viscous product impossible to crystallize. It was therefore concluded that the  $\alpha$ -naphthylurethane of 2-ethyl-2-methyl-butanol-1 is a liquid and is not suitable for purification and analysis.

$\alpha$ -Naphthylurethane of 2,2-diethyl-butanol-1: 1.5 Gm. of the alcohol was heated with 2.5 Gm. of  $\alpha$ -naphthyl isocyanate for a short time, then stirred and let cool to room temperature. A white mass resulted which was recrystallized twice from ligroin and gave a M.P. of 135-136° C. Nitrogen analysis: 4.57 and 4.53 per cent. Calc. - 4.63 per cent

#### ACID-PHTHALATES OF THE SUBSTITUTED ETHANOLS

Acid-phthalate of 2,2-dimethyl-propanol-1: (a) A mixture of 5.0 Gm. of the alcohol, 9.0 Gm. of phthalic anhydride and 50 cc. of benzene was refluxed together for two hours, then cooled and allowed to crystallize. The crystals obtained had a melting point of 128-129° C. which was unchanged when a mixed melting point with phthalic anhydride was taken. It was concluded that either no reaction or incomplete reaction had taken place so a modified procedure was adopted.

(b) Five grams of the alcohol and 9.0 Gm. of phthalic anhydride were heated and stirred frequently on a water bath for three hours, the resulting product being a colorless viscous mass which crystallized



only after long standing in the refrigerator and stirring. After four crystallizations from ligroin and ether, a product of constant melting point  $70-71^{\circ}$  C. was obtained.

Analysis: (a) 1.2475 Gm. of the ester required 10.67 cc. of 1 N potassium hydroxide solution for neutralization and saponification. The calculated quantity is 10.57 cc. Per cent purity - 100.97

(b) 1.4425 Gm. of the ester required 12.32 cc. of 1 N potassium hydroxide solution for neutralization and saponification. The calculated quantity is 12.21 cc. Per cent purity - 100.90

Acid-Phthalate of 2,2-dimethyl-butanol-1: 10.2 Gm. of the alcohol were heated with 14.8 Gm. of phthalic anhydride on a water bath for four hours. The resulting colorless, viscous mass was crystallized by allowing it to stand in the refrigerator over night, then stirring vigorously. After five crystallizations from ligroin and ether, a product of constant melting point at  $68-69^{\circ}$  C. was obtained.

Analysis: (a) 1.6385 Gm. of the ester required 13.17 cc. of 1 N potassium hydroxide solution for neutralization and saponification. The calculated quantity is 13.10 cc. Per cent purity - 100.53

(b) 1.4729 Gm. of the ester required 11.82 cc. of 1 N potassium hydroxide solution for neutralization and saponification. The calculated quantity is 11.77 cc. Per cent purity - 100.42

Acid-Phthalate of 2-ethyl-2-methyl-butanol-1: 20.4 Gm. of the alcohol and 44.0 Gm. (1.5 times the calculated amount) of phthalic anhydride were heated on an oil bath at  $130-140^{\circ}$  C. for 4-5 hours. The resulting product was cooled in ice and salt and stirred until crystallization took

place, then dissolved in ether and filtered to separate the unreacted phthalic anhydride. The ether solution was extracted with cold five per cent sodium hydroxide solution and the alkaline aqueous portion was then made distinctly acid with 6 N hydrochloric acid. The oily layer which separated crystallized upon cooling and stirring. These crystals were then dried in a vacuum desiccator and recrystallized twice, first from petroleum benzin and ether then from petroleum benzin alone. The product had a melting point of  $44.5-45.5^{\circ}\text{C}$ .

This method was found to give better yields of the pure product than those described above for the formation of the other esters.

Analysis: (a) 1.6978 Gm. of ester required 12.79 cc. of 1 N potassium hydroxide solution for neutralization and saponification. The calculated quantity is 12.85 cc. Per cent purity - 99.53  
(b) 1.6450 Gm. of ester required 12.40 cc. of 1 N potassium hydroxide solution for neutralization and saponification. The calculated quantity is 12.45 cc. Per cent purity - 99.60

Acid-Phthalate of 2,2-diethyl-butanol-1: 6.5 Gm. ( $1/20$  mole) of the alcohol and 7.4 Gm. ( $1/20$  mole) of phthalic anhydride were heated together on a water bath for four hours. A transparent viscous liquid was formed which crystallized after cooling and stirring in ice and salt for some time. This product was recrystallized once from ligroin and twice from petroleum ether and melted at  $84-85^{\circ}\text{C}$ .

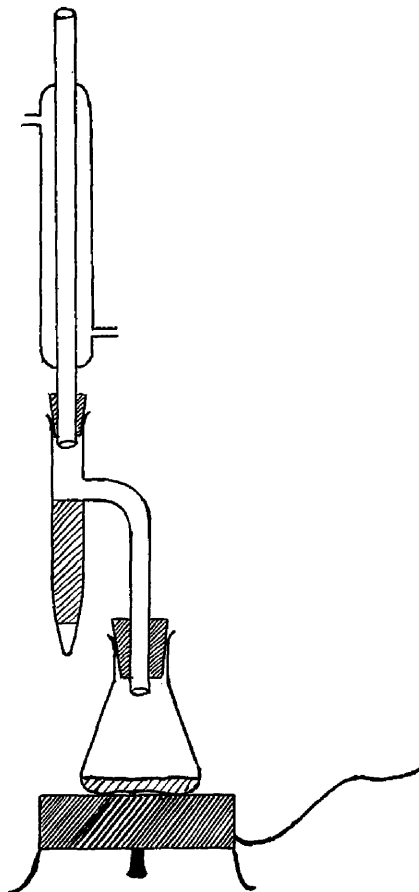
Analysis: (a) 0.5805 Gm. of ester required 4.20 cc. of 1 N potassium hydroxide solution for neutralization and saponification. The calculated quantity is 4.26 cc. Per cent purity - 98.59  
(b) 0.6766 Gm. of ester required 4.89 cc. of 1 N potassium hydroxide solution for neutralization and saponification. The

calculated quantity is 4.97 cc. Per cent purity - 98.39

These acid-phthalates are all white crystalline compounds insoluble in water but soluble in dilute alkali solution. They are very soluble in the common organic solvents and sparingly soluble in petroleum benzin.

#### ACID-TETRACHLOROPHTHALATES OF THE SUBSTITUTED ETHANOLS

Tetrachlorophthalic acid dried at  $110^{\circ}$  C. for two hours was heated with a slight excess of the alcohol in benzene solution for five hours using the apparatus shown below.



The water formed in the reaction being heavier than the solvent (benzene) settled out of the distillate into the side-arm-tube connected to the condenser thus allowing the reaction to go to completion. At the

same time the solvent ran back into the flask and prevented any concentration of the mixture through loss of solvent.

Acid-Tetrachlorophthalate of 2,2-dimethyl-propanol-1: 12.2 Gm. (1/25 mole) of tetrachlorophthalic acid and 4 Gm. of 2,2-dimethyl-propanol-1 were placed in the flask with 60 cc. of benzene and heated as described above. The resulting solution was filtered while hot and placed in the refrigerator overnight. 6.5 Gm. of product were recovered by filtering off the mother liquor. The mother liquor was evaporated to dryness and heated about thirty minutes on a water bath to volatilize the excess alcohol present. The residue weighed 6.5 Gm.

The first fraction was recrystallized from benzene and yielded a product of M.P. 140-141° C. and the second fraction was recrystallized from this mother liquor. It also melted at 140-141° C. The combined yield was 8.7 Gm.

Analysis: (a) 0.2320 Gm. of ester yielded 0.3497 Gm. of silver chloride corresponding to 0.0865 Gm. of chlorine. Per cent chlorine - 37.72

(b) 0.2168 Gm. of ester yielded 0.3306 Gm. of silver chloride corresponding to 0.0818 Gm. of chlorine. Per cent chlorine 37.72. The calculated value is 37.93 per cent.

Acid-Tetrachlorophthalate of 2,2-dimethyl-butanol-1: 12.2 Gm. of tetrachlorophthalic acid and 5.0 Gm. of the alcohol were heated together in 60 cc. of benzene for five hours. The resulting solution was filtered and evaporated to dryness, then heated on the water bath for thirty minutes to volatilize the excess alcohol. The residue weighed 13.2 Gm. and was recrystallized twice from benzene to give a product melting at 150-151° C.

Analysis: (a) 0.2710 Gm. of ester yielded 0.4029 Gm. of silver chloride corresponding to 0.0998 Gm. of chlorine. Per cent chlorine = 36.82

(b) 0.2873 Gm. of ester yielded 0.4262 Gm. of silver chloride corresponding to 0.1054 Gm. of chlorine. Per cent chlorine = 36.69. The calculated per cent is 36.54

Acid-Tetrachlorophthalate of 2-ethyl-2-methyl-butanol-1: 12.2 Gm. of tetrachlorophthalic acid and 6.0 Gm. of the alcohol were heated in 60 cc. of benzene for five hours. The resulting solution was filtered and cooled in ice water giving 7.5 Gm. of precipitate when dried. Evaporation of the mother liquor yielded 6.0 Gm. of residue. The first fraction was recrystallized from benzene, filtered on a Buchner funnel with the aid of suction and washed with petroleum benzin. The second fraction was recrystallized from the above mother liquor and treated in a similar manner. The two fractions were then combined and crystallized once more from benzene and washed with petroleum benzin. M.P. 144-145°

Analysis: (a) 0.5021 Gm. of ester yielded 0.7210 Gm. of silver chloride corresponding to 0.1784 Gm. of chlorine. Per cent chlorine = 35.53

(b) 0.3029 Gm. of ester yielded 0.4336 Gm. of silver chloride corresponding to 0.1073 Gm. of chlorine. Per cent chlorine = 35.42. The calculated per cent is 35.28.

Acid-Tetrachlorophthalate of 2,2-diethyl-butanol-1: 6.1 Gm. of tetrachlorophthalic acid and 3.5 Gm. of the alcohol were heated in the usual manner in 60 cc. of benzene for five hours. The product was filtered while hot and allowed to crystallize. This first crop of crystals weigh-

ing 2.1 Gm. melted at  $245-247^{\circ}$  C. so it was concluded that it was mostly unreacted tetrachlorophthalic acid. The filtrate was diluted with an equal volume of petroleum benzin, cooled in an ice bath and stirred. A white crystalline precipitate weighing 2.6 Gm. was obtained which melted at  $137-140^{\circ}$  C. Recrystallization of this fraction from benzene and petroleum benzin gave 2.1 Gm. of substance, M.P.  $138-139^{\circ}$  C.

Analysis: (a) 0.1875 Gm. of ester yielded 0.2593 Gm. of silver chloride corresponding to 0.0642 Gm. of chlorine. Per cent chlorine = 34.24.

(b) 0.2584 Gm. of ester yielded 0.3596 Gm. of silver chloride corresponding to 0.0890 Gm. of chlorine. Per cent chlorine = 34.44. The calculated per cent is 34.10.

#### p-NITROBENZOATE OF 2,2-DIMETHYL-PROPANOL-1

Several methods were employed before any yield of the ester was obtained.

(a) 4.0 Gm. of the alcohol was dissolved in 30 cc. of absolute ethyl alcohol in which 1 Gm. of sodium had previously been dissolved. An alcoholic solution of 8.4 Gm. of p-nitrobenzoyl chloride was then added and the mixture shaken for some time and cooled frequently, then set aside in the refrigerator overnight. It was found impossible to isolate a pure crystalline product from this mixture so another method was tried.

(b) Claisen method - 2.2 Gm. of the alcohol and 4.6 Gm. of p-nitrobenzoyl chloride were placed in 5 cc. of ether and 3 Gm. of anhydrous sodium carbonate added to the mixture. After standing for twelve

hours it was apparent that no reaction had taken place from the fact that the p-nitrobenzoyl chloride was still present unchanged so that still another method was triad.

(c) Schö<sup>"</sup>otten-Baumann method - 2.2 Gm. of the alcohol and 4.6 Gm. of p-nitrobenzoyl chloride were placed in a flask and 30 cc. of ten per cent sodium hydroxide solution added. The mixture was shaken vigorously with cooling from time to time for one-half hour then let stand overnight in the refrigerator. The crystalline precipitate was filtered off and recrystallized three times from alcohol and water. This gave a product of constant melting point 56-57° C. Nitrogen analysis by the Kjeldahl method - 5.87 per cent. Calculated per cent - 5.90.

TABLE II

## DERIVATIVES OF THE SUBSTITUTED ETHANOLS PREPARED

Alcohol	Acetate	Phenylurethane	$\alpha$ -naphthylurethane	Acid-phthalate	Acid-tetrachloro-phthalate
B.P.	B.P. and analysis	M.P. and nitrogen analysis	M.P. and nitrogen analysis	M.P. and analysis	M.P. and chlorine analysis
2,2-dimethyl-propanol-1 B.P.- 111-113° M.P.- 49°	124-125° 99.8%	114-115° Calc.-6.70 Found-6.60	99-100° Calc.- 5.45 Found- 5.66	70-71° 100%	140-141° Calc.- 37.93 Found- 37.72
2,2-dimethyl-butanol-1 B.P.- 134-135°	153-154° 93.9%	63-64° Calc.- 6.33 Found- 6.23	80-81° Calc.- 5.16 Found- 5.16	68-69° 100%	149.5-150.5° Calc.- 36.54 Found- 36.69
2-ethyl-2-methyl-butanol-1 B.P.- 150-151°	170-171° 97.2%	Liquid	Liquid	44.5-45.5° 99.5%	144-145° Calc.- 35.28 Found- 35.42
2,2-diethyl-butanol-1 B.P.- 76-77° at 11 mm.	70-71° at 20 mm. 85.7%	Liquid	135-136° Calc.- 4.67 Found- 4.50	84-85° 98.4%	138-139° Calc.- 34.10 Found- 34.34



## PART II

## PHARMACOLOGICAL

2,2-dimethyl-propanol-1; 2,2-dimethyl-butanol; 2 ethyl-2-methyl-butanol-1 and 2,2-diethyl-butanol-1 were compared with respect to their physiological properties with 2,2,2-tribromoethanol obtained through the courtesy of the Winthrop Chemical Company. Each of the five compounds was used in two media (a) a ten per cent or a one per cent solution in olive oil and (b) a ten per cent or a one per cent solution in 95 per cent ethyl alcohol. Pharmacological studies were made upon mice, rats, guinea pigs and cats.

When 1-2 cc. doses of the one per cent alcohol solution were administered by rectum to rats and guinea pigs, 2,2,2-tribromoethanol was the only one found to produce complete narcosis. 2,2-diethyl-butanol-1 in doses of 3 cc. of the alcohol solution produced only a partial narcosis in guinea pigs while 4 cc. doses of 2,2-dimethyl-propanol-1 solution caused only a mild depression.

One per cent solutions of the compounds in olive oil were injected intraperitoneally in mice and the relative dosage required to produce narcosis or depression was determined. It was found that administration of 0.75 cc. of the one per cent solution of 2,2,2-tribromoethanol to mice weighing about twenty grams would produce complete narcosis which lasted about ten hours and sometimes resulted in death. One cc. of 2,2-diethyl-butanol-1 solution, 1.2 cc. of 2-ethyl-2-methyl-butanol-1, 1.5 cc. of 2,2-dimethyl-butanol-1 and 2.1 cc. of 2,2-dimethyl-propanol-1 produced unconsciousness but of a shorter duration than the halogenated ethanol.

A dose of about eight cc. of 95 per cent ethyl alcohol was necessary to produce this same result.

Cats anesthetized with ether were injected through the femoral vein with the respective solutions and the blood pressure taken from the carotid artery. A ten per cent solution of the compound to be tested in 95 per cent ethyl alcohol was injected slowly in doses of 0.5 cc. diluted to 10 cc. with normal saline solution. In this dose 2,2,2-tribromoethanol produced a partial paralysis of the respiration and depression of the circulation, followed by slow recovery. 2,2-diethyl-butanol; 2-ethyl-2-methyl-butanol-1 and 2,2-dimethyl-propanol-1 produced a similar result but in a progressively lesser degree. Most peculiarly 2,2-dimethyl-butanol-1 in the same dose was very toxic causing complete paralysis of the respiration and stoppage of the heart. Control solutions of 5 per cent ethyl alcohol had very little effect upon the circulation and produced only a slight depression of the respiration.

A very interesting observation was made in regard to the absorption of these compounds through the skin. When one cc. of a ten per cent solution of 2,2,2-tribromoethanol was placed on the intact skin of mice, it was rapidly absorbed to produce anesthesia lasting over twelve hours followed by recovery. 2,2-diethyl-butanol-1; 2-ethyl-2-methyl-butanol-1; 2,2-dimethyl-butanol-1 and 2,2-dimethyl-propanol-1 were all absorbed but as found in other experiments, their effects became increasingly less as more methyl groups replaced the ethyl groups of the substituted ethanol. Ninety-five per cent ethyl alcohol (the dilution medium used above) produced no effect other than slight discomfort due to the cooling of the skin as the alcohol evaporated.

## SUMMARY

1. A study has been made of the methods for the preparation of 2,2-dimethyl-propanol-1; 2,2-dimethyl-butanol-1; 2-ethyl-2-methyl-butanol-1 and 2,2-diethyl-butanol-1.
2. In order to characterize these alcohols, their phenylurethanes,  $\alpha$ -naphthylurethanes, acid-phthalates and acid-tetrachlorophthalates have been prepared and analyzed.
3. A preliminary comparison has been made between the pharmacological action of these substituted ethanols and that of 2,2,2-tribromo-ethanol.

## CONCLUSIONS

1. The chlorides of tert.-butyl alcohol, tert.-amyl alcohol, dimethylethyl carbinol and triethyl carbinol may be prepared rapidly and in good yields by shaking them with concentrated hydrochloric acid.
2. Various 2,2,2-trialkyl ethanols may be prepared by the action of formaldehyde upon the proper Grignard reagent followed by hydrolysis.
3. The yields of some Grignard reagents may be appreciably increased by excluding the oxygen of the air from the reaction system.
4. Reaction between tertiary chlorides and magnesium to form various Grignard reagents may be initiated satisfactorily in the cases studied by the addition of a small amount of ethyl bromide and a crystal of iodine before the tertiary halide is introduced.
5. The acetates of the alkylated ethanols studied may be prepared by treatment of the alcohol with acetyl chloride.
6. The phenylurethanes of 2-ethyl-2-methyl-butanol-1 and 2,2-diethyl-butanol-1 and the  $\alpha$ -naphthylurethane of 2-ethyl-2-methyl-butanol-1 are liquids unsuited for characterization of these alcohols.
7. The acid-phthalates of the alcohols studied may be prepared by heating them with phthalic anhydride.
8. The acid-tetrachlorophthalates of the alcohols studied may be formed by treating them with tetrachlorophthalic acid in benzene solution using the apparatus shown.
9. Eleven compounds have been prepared and analyzed which have not been previously reported in the literature.

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