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THE PREPARATION  
of the  
FOUR-MONO-BROM-NORMAL-VALERIC ACIDS.

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BY

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A Thesis submitted for the Degree of  
MASTER OF ARTS  
in the  
DEPARTMENT OF CHEMISTRY.

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THE UNIVERSITY OF BRITISH COLUMBIA.

APRIL, 1928.

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## THE PREPARATION OF THE FOUR MONO-BROM-NORMAL VALERIC ACIDS.

INTRODUCTION.

In certain work undertaken in this laboratory the four mono-brom derivatives of normal valeric acid were required, that is - the  $\alpha$ ,  $\beta$ ,  $\gamma$ , and  $\delta$  compounds. Only one of these, the  $\alpha$ -compound, could be bought. Therefore the preparation of the other three was undertaken here.

Search in the literature yielded a suitable method for but one of these three, the  $\gamma$ -acid. For the other two, the methods given were not practicable for the amount of the acids needed for the further work.

For the sake of completeness in this research, some of the  $\alpha$ -acid was also prepared. Analogous cases of the direct bromination of normal-butyric acid<sup>1</sup> and iso-valeric acid<sup>2</sup> to give the corresponding  $\alpha$ -acids suggested a similar procedure in the case of the normal-valeric acid. Experiment confirmed this. A second method was suggested by the common method of using red phosphorus and bromine<sup>3</sup> in the making of this class of compounds. This was also confirmed by experiment, and later much the same method was found in a recent paper<sup>4</sup>.

The  $\beta$ -acid presented a difficult problem, and finally a combination of former methods had to be used. The ester of the  $\alpha$ -acid was made into the unsaturated  $\alpha$ - $\beta$  "penten"-acid<sup>5</sup> and on treating this with hydro-bromic acid the  $\beta$ -brom valeric was



obtained<sup>6</sup>. An attempt to make the  $\alpha$ -brom-valeric ester from the corresponding acid by the silver salt method of making esters was not very successful.

The  $\gamma$ -acid was made according to a procedure given in the literature<sup>7&8</sup>. This was, in brief, the formation of allyl-acetic acid and the addition of hydrogen bromide to this to yield the required valeric acid<sup>9</sup>. A comparison of two ways of making the allyl-acetic acid was made, and some slight improvements made in the procedures. A small quantity of the valeric acid was also made from  $\gamma$ -valero-lactone<sup>10</sup>.

The methods given for the making of  $\delta$ -brom-n-valeric acid were too costly to allow the preparation of any considerable amount of the acid. The first possible method that suggested itself was to make one bromine only of the symmetrical I-4 dibrom-butane undergo a Grignard's reaction. From this last-named compound have been made adipic and sebacic acids by the use of sufficient magnesium to form the metal complex with both ends of the compound<sup>11</sup>. Since I-4 dibrom-butane could not be obtained a start was made last year in its manufacture. It was hoped, by Fittig's reaction, adding one mole of sodium to two molecular weights of ethylene dibromide, to obtain the desired compound. Repeated experimenting gave no results. Next was attempted the making of the same compound starting with butadiene, which was to be made from ethylene and acetylene<sup>12</sup>. I-4 dibrom-butadiene had previously been made from butadiene<sup>13,14</sup><sub>15</sub>. It seemed quite probable that this compound could be reduced to the corresponding I-4 dibrom-butane. The description for



the manufacture of butadiene along the proposed lines being very meagre, it was soon found that too long a time would be required for the study of proper conditions, so that attempt<sup>p</sup> was dropped.

The lactone being used often in the making of brom-acids by addition of hydrogen bromide, it was decided to use  $\delta$ -valero lactone in the formation of the  $\delta$ -acid.<sup>16</sup> The required lactone was made by the aceto-acetic ester synthesis from 3-chlor-n-propyl alcohol. Treatment of this with concentrated hydrogen bromide solution yielded the  $\delta$ -acid.

As a matter of interest, an attempt to make  $\beta$ -brom-propionic acid from ethylene dibromide was made, this being analagous with the procedure tried in the case of  $\delta$ -brom-valeric acid.

## EXPERIMENTAL.

### A.

#### $\alpha$ -brom-n-valeric Acid.

As already stated in the introduction,  $\alpha$ -brom-butyric acid has been prepared by the direct bromination of n-butyric acid.<sup>1</sup> One molecular weight of the acid was sealed up in a glass tube with one molecular weight of bromine. The tube was then heated. The products of the reaction were  $\alpha$ -brom-valeric acid and hydrogen bromide.

10 grams of n-valeric acid were sealed with 16 grams of bromine in a tube. The tube was heated in a furnace for several hours at 110°C. The tube, after cooling, was carefully opened, since a considerable volume of gas would be formed by the reaction-



The bromine remaining was expelled by heating and the acids fractionated. Some unchanged n-valeric acid was recovered, and a small amount of  $\alpha$ -brom-n-valeric acid, boiling-point -about 135° at 30 mm. pressure.

$\alpha$ -brom-n-butyric acid has been prepared by the action of bromine on the n-acid in the presence of red phosphorus, and the subsequent hydrolysis of the  $\alpha$ -brom-n-butyryl bromide so formed with the exact amount of water required.<sup>3</sup>

10 grams of n-valeric acid were placed in a flask provided with a reflux condenser. 2 grams of phosphorus were added and then bromine, gradually, until finally the mixture

remained reddish in colour on heating. The phosphorus oxy-bromide formed was filtered off and just enough water added to decompose the  $\alpha$ -brom-n-valeryl bromide. The mixture was then boiled for a few minutes. After drying over concentrated sulphuric acid and solid potassium hydroxide in desiccators, the oil was fractionated, and as before a small amount of both the original acid and  $\alpha$ -brom-n-valeric acid was obtained.

The method later found<sup>4</sup>, which corresponds very closely with this last, is, briefly, as follows. The n-valeric acid is brominated, as before, in the presence of red phosphorus. The mixture is poured into ethyl alcohol and the ester of the brom-acid is formed.

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## B.

### $\beta$ -brom-n-valeric Acid.

No method could be worked out which would be better than those already in the literature for the preparation of the  $\beta$ -acid. Therefore, since the  $\alpha$ -acid was easily procurable, it was decided to try to make this into the corresponding  $\alpha$ - $\beta$  acid with alcoholic potassium hydroxide, and then, by treatment of this unsaturated acid with hydrogen bromide solution, to get the  $\beta$ -brom-valeric acid. However, it was not known whether the potassium salt of the  $\alpha$ -brom-acid would readily split off hydrogen bromide, so that this method was given up for one already tried out elsewhere<sup>5</sup>. In this one,  $\alpha$ -brom-n-valeric ester was refluxed with quinoline, when the ester of the required unsaturated acid was obtained. Accordingly, some of this acid was so prepared by this method and subsequent



saponification with potassium hydroxide and acidification with sulphuric acid. After extraction and purification, the acid was shaken for several days with hydrogen bromide solution saturated at 0°C. One layer finally resulted from which the  $\beta$ -brom acid formed was recovered by diluting the solution. The acid was extracted with ether and dried as was the  $\alpha$ -compound.

An attempt to make the  $\alpha$ -brom-valeric ester required by the silver salt method was not so successful as this is said to be. To 25 grams of acid was added a water solution of 43 grams of silver nitrate. The silver salt was filtered off and dried. It was then refluxed with 50 grams of ethyl iodide, but the yield of the  $\alpha$ -ester was very poor. The method was therefore discarded for the one described immediately before this.

(Note:- This acid was made by Mr. Guy Waddington.)

### C.

#### $\gamma$ -brom-n-valeric Acid.

After consideration of methods which presented themselves and of such as were found in the literature, it was decided to make the  $\gamma$ -acid by a method already well-tried. By the malonic ester synthesis allyl bromide was converted to allyl-acetic acid<sup>7</sup>, and this treated with hydrogen bromide yielded the  $\gamma$ -acid.

23 grams of sodium metal were dissolved in 300 grams of absolute ethyl alcohol, distilled over lime. Through a reflux water condenser was added just one mole (160 grams) of malonic ester. A pasty, white mass was produced.



Slightly more than the calculated amount (120 grams) of allyl bromide was then added. The reaction was accompanied by the evolution of considerable heat.



The reaction mixture was then heated a short time on the steam bath, refluxing, and it was found to be neutral. The excess allyl bromide and the alcohol were distilled off on the steam bath. (If all the alcohol was not removed here, it caused difficulty in the drying of the ester later.) Sufficient water was added to dissolve the sodium bromide, and the ester was extracted with ether. The ethereal solution was dried, the ether distilled off, and the ester fractionated, the portion boiling from 218-225° being retained. (Yield-70% theoretical).

The ester was treated with twice the theoretical amount of concentrated potassium hydroxide solution (1.2 gram alkali to 1 gram of water). After two hours heating on the steam-bath, the ester was completely saponified.



Here a departure was made from the method of the literature in that a step was left out. Precipitation of barium allyl-malonate, as advised, caused trouble, as the barium hydroxide also formed caused much trouble. So the alkali solution was neutralized with the calculated amount of sulphuric acid.

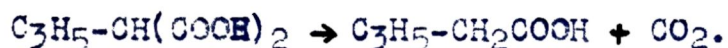


Since allyl-malonic acid is soluble in water, the solution was extracted upwards of ten times. Even with this, the amount of acid obtained was only 20% of the amount calculated from the



ester used. The acid was dried over potassium hydroxide after recrystallization from ether. Melting-point of crystals -  $103^{\circ}\text{C}$ .

The allyl-malonic acid was then heated on an oil-bath to  $180^{\circ}$ , or, as was found equally satisfactory, with a small flame, thermometer in the liquid, until no more gas was generated. Finally the liquid was fractionated, the fraction between  $182^{\circ}$  &  $184^{\circ}$  being collected separately, - this is allyl-acetic acid.



A solution of hydrogen bromide, saturated at  $0^{\circ}\text{C}$ , was prepared. Two volumes of this were shaken for several days with one volume of allyl-acetic acid. Gradually the two merge into one.



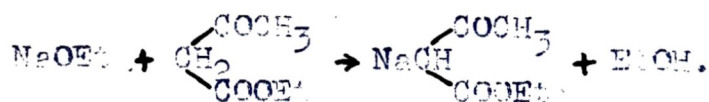
The  $\gamma$ -brom-valeric acid was obtained by diluting the solution and extracting with ether. The ether being distilled off, the acid was washed with water, and dried over concentrated sulphuric acid. On standing, the acid became quite black, but this colour can be removed with animal charcoal. When the fractionation of the acid was attempted, it was found that this could not be effected, even at 30 mm. pressure. In spite of all precautions, the liquid bumped. A very fine jet of air was introduced beneath the surface of the liquid by means of a capillary tube, and glass  $\bar{\text{A}}$ s were also used, but to no purpose. Since no boiling-point is given in the literature, this same difficulty has probably been encountered before.

In general, the malonic ester synthesis gives a better yield than does the aceto-acetic synthesis, but recent work has

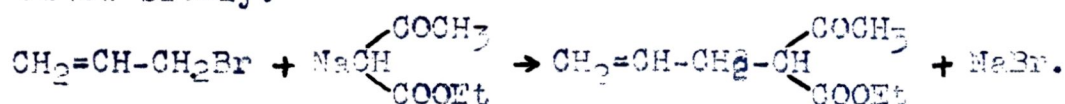


given with the latter very good yields, so that its use was tested in the making of allyl-acetic acid.

5.7 grams of sodium were dissolved in 70 grams of absolute ethyl alcohol. With cooling, 32.5 grams of aceto-acetic ester were added slowly.



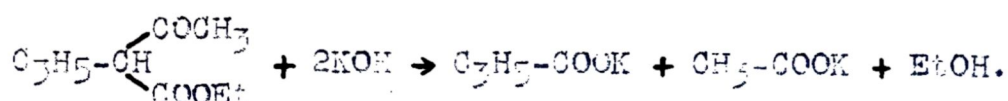
Through a reflux water condenser 30 grams of allyl bromide were added slowly.



The mixture was then refluxed until it showed a neutral reaction. The alcohol was distilled off on a steam-bath, water was added to dissolve the sodium bromide formed in the reaction and the allyl aceto-acetic ester extracted with ether. After the ethereal extract had been dried with anhydrous potassium acid carbonate, the ether was distilled off, and the ester fractionated. The portion boiling between 200° and 213° C. was collected, being almost pure ester. Yield - 70%.

The procedure next followed in the literature was to reflux the ester with 3-4 times the theoretical amount of potassium hydroxide in a little water. This was tried and it yielded no allyl acetic acid when the mixture was further treated, but only a mixture of other, undesired products. Next was tried a modification of this method. 40 grams of potassium hydroxide were dissolved in 15 grams of 50% alcohol, two layers resulting. The allyl aceto-acetic ester was added gradually, when the top layer of ester and alcohol slowly dissolved

The mixture was then refluxed for four hours.



The reaction was poured into 250 c.c. of water and the whole extracted with ether to remove any allyl <sup>acetone</sup> that might have been formed and any unchanged ester. The aqueous solution was acidified with sulphuric acid and the allyl acetic acid then extracted with ether. Yield-50%, calculated on ester used. The acid was dried and treated as in the previous method.

Since it had been decided to use one of the methods of the literature to make the  $\gamma$ -brom-valeric acid, an attempt was made to obtain it through the use of the  $\gamma$ -lactone. A brief summary of the combination of various procedures<sup>10</sup> in this synthesis follows:-

100 grams of cane-sugar were heated for twenty-four hours with 500c.c. of 1:4 hydrochloric acid on a steam-bath. The mixture was filtered and 35 grams of sodium hydroxide added gradually. The whole was then evaporated "in vacuo" to 100c.c. and the sodium chloride which separated out filtered off. The laevulinic acid was extracted with ether and fractionated- B.P.- 140°-170° at 15-30 mm.

34 grams of acid were dissolved in 12 grams of sodium hydroxide in 100 c.c. of 95% ethyl alcohol, in a flask with a reflux condenser attached. During an hour, 13.3 grams of sodium metal in fine slices were introduced into the mixture with continual stirring. After all the sodium had been added, 30 c.c.

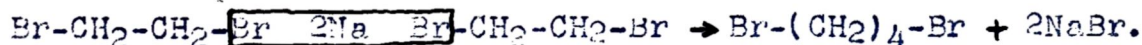
of the alcohol were distilled off. The residue was treated with 25c.c. of water to decompose the sodium ethylate formed in the reaction and the alcohol resulting removed by distillation. After cooling, the mixture remaining was acidified with 75.5c.c of dilute sulphuric acid. The yellow oil floating on top was removed, the aqueous solution neutralized with sodium carbonate and extracted repeatedly with ether. The oil obtained was fractionated and the lactone, B.P.-115-135° at 60mm., collected. On heating this lactone with saturated hydrobromic acid in a sealed tube at 100°C, the  $\gamma$ -brom-n-valeric acid was obtained. The yields all through were very poor.

#### D.

##### $\delta$ -brom-n-valeric Acid.

As has already been stated, it was hoped to make the  $\delta$ -acid from 1:4 dibrombutane. However, no method could be evolved which would yield sufficient of this last compound for the purpose in view.

Theoretically, the easiest way of making the butane seemed to be by Fittig's reaction, according to the equation-



A number of trials, made under varying conditions of temperature and dilution gave no results. The use of methyl cyanide as a catalyst did no good. It may be that the lack of expected results is accounted for by Bischoff's "Dynamic Hypothesis".

A second possible way of making 1:4 dibrombutane is the reduction of dibrombutadien. This last compound had already



been made by what seemed a simple method, so an attempt was made to reduplicate the experiment.<sup>12</sup>

Ethylene was prepared by passing ethyl alcohol vapours over anhydrous aluminium sulphate, contained in a combustion-tube heated to  $350^{\circ}\text{C}$ . (This procedure gives about 99% yield of ethylene. Acetylene was made from calcium carbide. Any ammonia present in it was removed by bubbling it through water. It was then freed from any hydrogen phosphides by passing through a suspension of calcium hypochlorite in water. At this point, the ethylene and acetylene were mixed by bubbling them into a flask containing more water, thus allowing the admixture of the gases in equal volumes. The mixed gases then passed over granular calcium oxide in a tube into a porcelain combustion-tube heated to  $500^{\circ}\text{--}600^{\circ}\text{C}$  which was full of fragments of pumice-stone. The outflowing gases were cooled in a spiral condenser in a freezing mixture ( $-20^{\circ}\text{C}$ ). A small yield of butadien, B.P.  $-5^{\circ}\text{C}$ , was obtained, but not sufficient to be of use. For lack of time the attempt was abandoned.

The method finally used for the  $\delta$ -acid was the treatment of the  $\delta$ -lactone with assaturated solution of hydrobromic acid. The lactone was made from 3-chlor-n-propyl alcohol by both the malonic ester and aceto-acetic ester syntheses.

The required chlor-propanol was made by a method which proved quite satisfactory<sup>17</sup>. Redistilled trimethylene glycol was saturated in the cold with dry hydrochloric acid gas. The increase in volume amounted to about one-fourth of the original volume of the liquid. At first the mixture was sealed in tubes

and then heated on a steam-bath, but later it was found that so little pressure was developed that ordinary reagent bottles with rubber corks wired in were quite strong enough. The heating was continued for four hours, the containing vessel cooled and opened. The liquid, now viscous, was again saturated with hydrogen chloride, and heated as before for two hours longer. It was then distilled. There was a great tendency towards bumping, even with glass beads. This was best remedied by gently tapping the side of the fractionating-flask until all the hydrogen chloride had come off, when the bumping ceased. The fraction boiling from  $160^{\circ}$ - $162^{\circ}$  was collected, being the chlor-propyl alcohol.

The procedure from here on was, in both the malonic ester and the aceto-acetic ester syntheses, exactly the same as that followed in the making of the  $\gamma$ -acid, the chlor-propanol being substituted for the allyl bromide. In neither case, after the addition of the halide to the mono-sodium ester, was the purification of the resulting compound attempted, since no information could be obtained about either of them. They were used in the following reactions as if pure and were found to act fairly well. The final product of each reaction was  $\delta$ -hydroxy-n-valeric acid. On distillation, this yielded, by the loss of one molecule of water,  $\delta$ -n-valero-lactone. This was heated with saturated hydrobromic acid in a sealed tube to  $145^{\circ}\text{C}$ . The mixture was diluted and the  $\delta$ -brom-n-valeric acid extracted with ether. M.P. of the acid -,  $39^{\circ}$ - $40^{\circ}\text{C}$ .<sup>16</sup>  
B.P.  $215-220^{\circ}$  at  $760\text{ mm}$ .

## E.

 *$\beta$* -brom-propionic Acid.

In order to get an idea as to how the proposed synthesis of  *$\delta$* -brom-valeric acid from the dibrom-butane might go, an attempt was made to obtain  *$\beta$* -brom-propionic acid by Grignard's reaction from ethylene dibromide.

To 90 grams of ethylene dibromide in 200c.c. of dry ether was added one-half mole of magnesium, in the form of ribbon, through a reflux condenser. When all the metal had dissolved, the flask was put in an ice-bath, and a stream of carbon dioxide bubbled through the liquid. At the end of 50 minutes the temperature rose suddenly from 2° to 15°C, and a solid settled out. The carbon dioxide was passed in until no more solid precipitated. The two reactions were presumably as follows:-



Three times the theoretical amount of 25% sulphuric acid, cooled, was added, since just exactly the theoretical amount did not dissolve the solid. When extraction of the expected acid was attempted, three distinct layers of liquid resulted. The top one consisted of ether plus a small amount of ethylene dibromide. The middle layer contained some ether and a pure liquid which boiled entirely at 73°-73°C at 8-10cm. This liquid was perfectly miscible with ether, soluble in water. its freezing-point was -40°, and boiling-point 123° at 760mm. Its density, determined by depression of freezing-point of water, was 1.78.



I wish to express my appreciation of the many suggestions and the help given me by Dr. Clark, which have lent much impetus to this research. To Dr. Roger Adams, Head of the Department of Chemistry at the University of Illinois, also, I am indebted for information in regard to the manufacture of 1:4 dibrom-butane, as well as to Dr. Johnston, now at Cornell, who supplied me with information in the same line. Lack of time prevented the use of this information.

*Fred B. Johnston.*



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