arranged for distillation under reduced pressure. The receiver is kept below —30° and the flask evaporated to about 120 mm Hg. A solution of 770 ml of conc. sulphuric acid in 1.4 litres of water is added at such a rate that the temperature in the flask can be kept at 35—40° by cooling with ice-water. The trimethylacetaldehyde distills during this addition. When the acid has been added, the flask is heated to 45° and the vacuum broken. The aldehyde in the receiver is melted and decanted from the ice. It weighs 1.06 kg and is pure enough for most purposes. If a pure product is desired, it can be obtained by distillation. In this way 950 g of pure trimethylaldehyde, b. p. 71—74°, is obtained.

From the water layer most of the sodium periodate can be recovered by treating the solution containing the sodium iodate with sodium hydroxide and chlorine [2].

Even pure trimethylacetaldehyde is slowly decomposed on standig into gaseous products, and it is advisable to release the pressure developed in the flask at intervals, and to keep it in a dark and cold place.

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# 5-*neo*Pentyl-5-Allylbarbituric Acid and Related Compounds

## I. On the Preparation of β-*tert*-Alkylpropionic Acids and Derivatives

ARNE BRÄNDSTRÖM

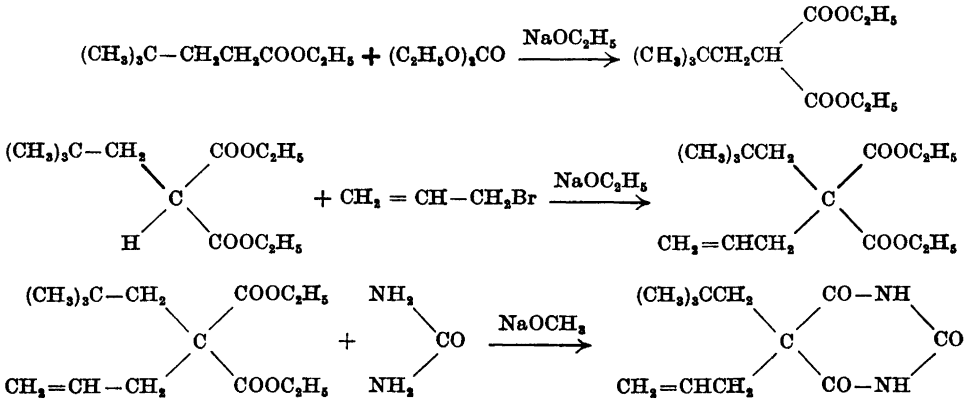
*Research Laboratory, Pharmacia Ltd., Uppsala, Sweden*

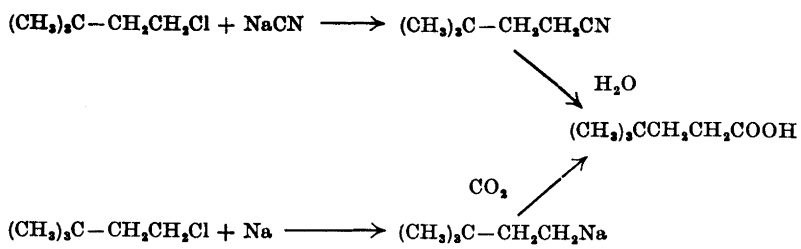
In this laboratory it has been found that *neo*pentylallylbarbituric acid is a very good sedative drug. In order to make this compound available in commercial quantities an investigation of the methods to prepare this barbiturate has been performed and in this connection some intermediates containing a branched chained structure have been prepared. Some of these compounds and methods will be described in this and the two following papers.

For this and similar methods 4,4-dimethylpentanoic acid was needed as a starting material. This compound has been prepared by Moreau and Delange [1] and later by Spindt, Stevens and Bladwin [2]. None of these methods are convenient for a large scale preparation of 4,4-dimethylpentanoic acid or the ethyl ester.

The following methods are, however, very satisfactory. They start with the readily available 1-chloro-3,3-dimethylbutane (obtainable from ethylene and *tert*-butyl chloride).

The method for the conversion of primary alkyl chlorides into cyanides has






recently been studied by Brändström [4] who found that polyethylene glycol-300 is an excellent solvent for the reaction. 3,3-Dimethylbutyl cyanide is obtained in excellent yield by this method and can easily be converted into the corresponding acid or ethyl ester by standard methods.

The preparation of carboxylic acids from alkyl chlorides *via* alkyl sodium compounds has been investigated by Morton *et al.*[5] The yields are usually somewhat low due to the fact that malonic acids are obtained as by-products. When this method is applied to the synthesis of 4,4-dimethylpentanoic acid a very good yield is obtained, probably because the *tert*-butyl group prevents the side reaction to the corresponding malonic acid.

The 4,4-dimethylpentanoic acid can also be prepared from *β-tert*-butylacrylic acid by hydrogenation.

In connection with the preparation of 4,4-dimethylpentanoic acid some homologues have been prepared by the same methods. All alkyl chlorides used in the following preparations are obtained from the reaction of *tert*-butyl chloride with ethylene [6].

*Experimental. Preparation of cyanides.* The method given by Brändström is followed and for the following cyanides the yields and boiling points are:

| | | |
|---|---|---|
| 3,3-dimethylbutyl cyanide | 94 % | 57°— 59°/8 mm Hg |
| 3,3-dimethylamyl cyanide | 93 » | 76°— 80°/8 mm Hg |
| 3,3,4-trimethylamyl cyanide | 91 » | 88°— 89°/8 mm Hg |
| 3,3,6,6-tetramethylheptyl cyanide | 80 » | 107°—110°/8 mm Hg |

*Preparation of acids.* A 2 litre three-necked flask is fitted with a high speed stirrer (about 10 000 r.p.m.) a thermometer, a dropping funnel, a gas inlet tube and a gas exit tube. A slow stream of dry nitrogen is passed through the flask. 54 g of clean sodium and 800 ml of dry kerosene (free from aromatics, olefins and sulphurous compounds) are heated to 110°C. The mixture is now stirred at that temperature for 10 min. The stirrer is stopped and the flask chilled to —5° (Danger! The flask must not crack!)

The stirrer is started again. 10 ml of a solution containing 120 g of 1-chloro-3,3-dimethylbutane and 100 ml of pure kerosene are added. In some cases the reaction soon starts, which is indicated by a rapid rise in temperature and a darkning of the contents in the flask. In other cases 2 ml of butanol must be added to start the reaction. When the reaction has started, the flask is chilled in a solid carbon dioxide-acetone bath, and the rest of the chloride solution is added to the *very dark* contents in the flask at such a rate that the temperature is kept between 0° and —10°. The mixture is stirred at that temperature for 15 min after the addition.

*Warning!* It is very dangerous to add large quantities of the chloride solution to the sodium dispersion before the reaction has started!

The high speed stirrer is changed to an ordinary stirrer and the nitrogen replaced by pure carbon dioxide. The temperature is kept between 0° and —10° by cooling and adjusting the rates of stirring and addition of carbon dioxide. When the temperature begins to decrease, even if the rate of stirring and the stream of carbon dioxide are increased, the cooling bath is removed. If the temperature now only slowly rises, the reaction is finished.

700 ml of water is cautiously added to destroy the excess of sodium and dissolve the salts formed. The layers are separated. The aqueous layer is acidified with conc. hydro-

chloric acid, and the acid, which is liberated, is extracted with benzene. The benzene solution is dried with anhydrous sodium sulphate and then distilled under reduced pressure. The yield is 100 g or 77 % of the theoretical. The boiling point of the 4,4-dimethylpentanoic acid is 104—105°/8 mm Hg.

In exactly the same way the following acids are prepared: 4,4-Dimethylhexanoic acid, b.p. 112—120°/10 mm Hg, yield 46 %; 4,4,5-Trimethylhexanoic acid, b. p. 129—135°/8 mm Hg, yield 50 %.

*Hydrolysis of cyanides.* The same acids as mentioned above are conveniently prepared from the corresponding cyanides in the following way.

One mole of the cyanide is refluxed with two moles of sodium hydroxide, and 800 ml of water for 24 h or until the evolution of ammonia ceases. The resulting alkaline solution is cooled, extracted with benzene and then treated as above. The yields are almost quantitative.

*Hydrogenation of β-tert-butylacrylic acid.* *β-tert*-Butylacrylic acid is dissolved in 5 parts of alcohol and hydrogenated with palladium on charcoal as a catalyst at a hydrogen pressure of 50 kg/cm². The hydrogenation is rapid and an almost quantitative yield of 4,4-dimethylpentanoic acid is obtained on distillation of the filtered solution.

*Preparation of esters.* 475 g of 3,3-dimethylbutyl cyanide are dissolved in 1 080 ml of 99.5 % alcohol in a 5-litre flask fitted with a stirrer, a reflux condenser, and a dropping funnel. 465 ml of conc. sulphuric acid are added during one h. The mixture is then refluxed for 8 h. After cooling the mixture is poured on ice. Water is added to dissolve the salts, and the layers are then separated. The aqueous layer is extracted with benzene, and the combined organic layers are washed with a sodium carbonate solution, dried and distilled. The yield is 580 g of ethyl 4,4-dimethylpentanoate (86 %). The boiling point is 60—62°/8 mm Hg.

In exactly the same way the other cyanides could be converted into the corresponding esters.

The author is indebted to his colleagues and assistants at Pharmacia for good help with this project.

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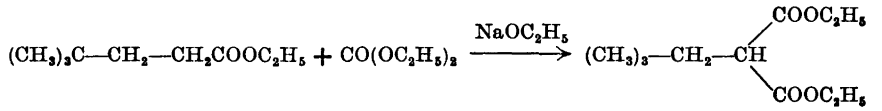
# 5-*neo*Pentyl-5-Allylbarbituric Acid and Related Compounds

## II. On the Preparation of Diethyl *neo*Pentylmalonate and Related Compounds

ARNE BRÄNDSTRÖM

*Research Laboratory, Pharmacia Ltd., Uppsala, Sweden*

Diethyl *neo*pentylmalonate is an important intermediate in the synthesis of 5-*neo*-pentyl-5-allylbarbituric acid. Due to the very low reactivity of *neo*pentyl halides it cannot be prepared by alkylation of diethyl malonate but other methods must be tried. The most convenient method seems to be the following




This condensation gives an excellent yield of diethyl *neo*pentylmalonate if it is performed under forcing conditions just as described by Brändström [1]. Starting with 3,3-dimethylbutyl cyanide and diethyl carbonate the same method gives ethyl *neo*pentylcyanoacetate.

The *neo*pentyl substituted malonic and cyanoacetic esters can be alkylated just as other monoalkylated malonic and cyanoacetic esters.

Attempts to prepare diethyl *neo*pentylmalonate from ethyl 4,4-dimethylpentanoate and diethyl oxalate by a process