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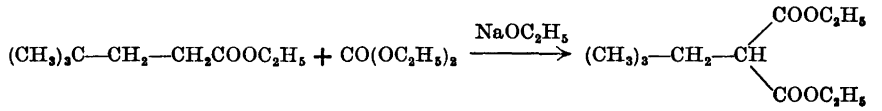
5-*neo*Pentyl-5-Allylbarbituric Acid and Related Compounds

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

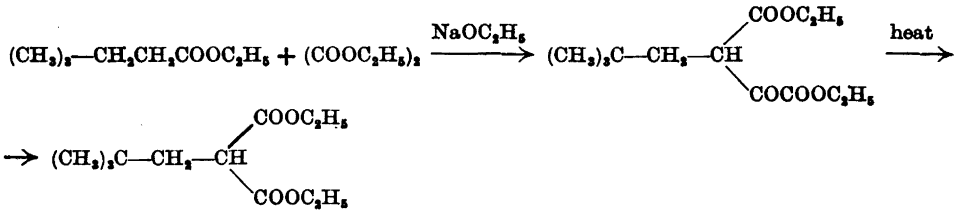


This condensation gives an excellent yield of diethyl *neo*pentylmalonate if it is performed under forcing conditions just as described by Brändström [1]. Starting with 3,3-dimethylbutyl cyanide and diethyl carbonate the same method gives ethyl *neo*pentylcyanoacetate.

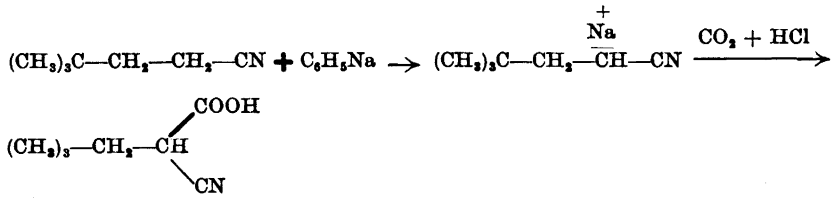
The *neo*pentyl substituted malonic and cyanoacetic esters can be alkylated just as other monoalkylated malonic and cyanoacetic esters.

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

similar to that used for the preparation of diethyl phenylmalonate [2], *viz.*

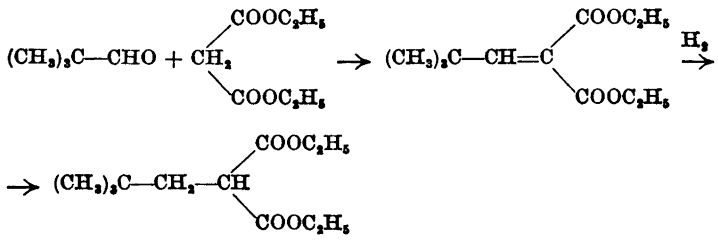


were not particularly successful. A yield of about 25 % could be obtained if the condensation was forced [3]. The following method was tried with success:



The cyano acid can be esterified to ethyl *neo*pentylcyanoacetate or to diethyl *neo*pentylmalonate, and it can be hydrolyzed to give *neo*pentylmalonic acid. The yields obtained are very good and the method is rapid but somewhat dangerous as it involves the manipulation of sodium dispersion.

Diethyl *neo*pentylmalonate can also be prepared by the following method:



This is an excellent method but trimethylacetaldehyde is not a commercially available starting material. A convenient method for a laboratory synthesis of trimethylacetaldehyde has been described by Brändström [4].

If needed in big quantities trimethylacetaldehyde might be prepared from $(CH_3)_3C-CH=CH_2$ or $(CH_3)_3C-CH=CHCl$ by oxidation with ozone [5] but as that method would probably involve many practical problems it was not tried.

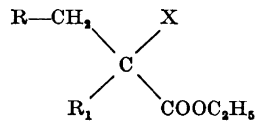
Besides the *neo*pentylderivatives a number of homologues have been prepared, *e.g.* those containing the groups β,β-dimethylbutyl and β,β,γ-trimethylbutyl.

Experimental. 1. Condensations with diethyl carbonate. 2 400 ml of diethyl carbonate are heated to boiling in a 5-litre three-necked flask provided with a stirrer, a reflux condenser and a glass stopper. The heating is then interrupted and 75 g of sodium are added at such a rate that the liquid boils vigorously. — Caution! Carbon monoxide escapes through the condenser! — When the sodium has reacted, 3 moles of the ethyl ester or the cyanide are added.

The reflux condenser is replaced by a Widmer column connected to a condenser arranged for distillation. The alcohol, which is formed in the condensation reaction, is distilled off carefully but rapidly. The temperature in the top of the column is kept below 85°. In this way about 360 ml of distillate can be obtained. The reaction mixture now contains a solution or suspension of the sodium compound of the malonic ester or cyanoester in diethyl carbonate.

The flask is cooled to room temperature and the contents are poured into a mixture of 300 ml of concentrated hydrochloric acid and ice. The mixture is shaken and separated. The ester layer is dried with anhydrous sodium sulphate and the diethyl carbonate distilled off at about 50 mm Hg, whereupon the residue is subjected to a fractional distillation *in vacuo*. The yields and boiling points are given in Table 1.

Table 1. Preparation of esters



R	R_1	X	Yield %	B. p.
$(CH_3)_3C$—	H	$COOC_2H_5$	65	109—113/ 8 mm Hg
»	CH_3-	»	61	131—134/15 » »
»	C_2H_5-	»	59	130—132/ 9 » »
»	CH_2=CH—CH_2-	»	62	136—138/ 8 » »
»	CH_2=CBr—CH_2-	»	43	165—175/ 8 » »
»	C_2H_5O—$COCH_2$-	»	60	170—180/ 8 » »
»	H	CN	65	110—114/ 8 » »
$C_2H_5C(CH_3)_2$	H	$COOC_2H_5$	65	118—128/10 » »
»	C_2H_5-	»	55	144—147/ 7 » »
»	CH_2=CH—CH_2-	»	69	150—155/15 » »
$(CH_3)_2CH$—$C(CH_3)_2$	H	»	65	130—132/ 8 » »

If a second group is to be introduced into the malonic ester or cyanoester it can be done by adding about 3.3 moles of the apropriate halide to the solution or suspension of the sodium compound mentioned above and refluxing the resulting mixture for some h (usually 1—8 h depending on the reactivity of the halide). The mixture is then cooled, poured on ice-water, acidified, separated, dried, and distilled as described above. The yields and boiling points are given in Table 1.

2. Condensations with diethyl oxalate. 3 litres of toluene and 69 g of sodium are heated to boiling in a 5-litre three-necked flask provided with a stirrer, a reflux condenser, and a dropping funnel. The stirrer is started and the heating is interrupted when the sodium begins to melt. To this mixture 180 ml of absolute alcohol are added dropwise in about 1 h. After the addition the vigorously stirred mixture is refluxed for 1 h.

The flask is cooled to 10° and the reflux condenser is replaced by a column connected to a condenser for distillation under reduced pressure. 474 g of ethyl 4,4-dimethylpentanoate and 438 g of diethyl oxalate are added. The flask is evacuated to 120 mm Hg and heated so that alcohol distills off at a temperature below 50° at the top of the column. About 800 ml of distillate are obtained. When no more alcohol distills, the flask is cooled with an ice-bath.

A mixture of 270 ml of conc. hydrochloric acid and an excess of ice is added to the contents of the flask. The mixture is effectively stirred whereupon the toluene layer is separated off, washed with water, and dried with sodium sulphate. The toluene is distilled off at reduced pressure by heating on a boiling water bath. When no more distills even if the pressure is reduced to 1 mm Hg the residue consists of ethyl 2-keto-3-carbethoxy-5,5-dimethylhexanoate, which can be purified by distillation at a pressure of at most 1 mm. B. p. 103—110/1 mm Hg.

If the crude residue is heated to boiling at ordinary pressure a vigorous evolution of carbon monoxide occurs. When this has ceased, the product is distilled under reduced pressure and thereby 175 g of diethyl *neo*pentylmalonate is obtained. B. p. 116—121/8 mm Hg.

If in the condensation above the ethyl 4,4-dimethylpentanoate is replaced by 333 g of 3,3-dimethylbutyl cyanide 210 g of ethyl 2-

keto-3-cyano-5,5-dimethylhexanoate is obtained. B. p. 140—150°/8 mm Hg. This ester does not split off carbon monoxide on heating.

3. Carboxylations of nitriles. In a 2-litre three-necked flask a dispersion of phenyl sodium is prepared from 100 g of sodium, 246 g of chlorobenzene, and 900 ml of toluene by the method given by Nobis and Moormeier [6].

The flask containing the phenyl sodium dispersion is fitted with a Hershberg stirrer [7], a thermometer, a gas inlet tube for dry nitrogen, a gas exit tube and a dropping funnel. The flask is chilled to —5° with a solid carbon dioxide-acetone bath, and a solution of 222 g of 3,3-dimethylbutyl cyanide in 200 ml of dry toluene is added at —5° to 0° during 10 min. The mixture is stirred at that temperature for 15 min and then poured into a 7-litre enamelled pan containing 1 kg of solid carbon dioxide and 100 ml of toluene. The mixture is stirred for some min and then allowed to obtain room temperature.

A few pieces of solid carbon dioxide are added (to function as a fire extinguisher), and then 2 litres of water (Caution! A considerable excess of sodium might be present!) The mixture is stirred and then separated. The aqueous layer contains the sodium salt of *neo*pentylcyanoacetic acid.

A. *Preparation of* neo*pentylmalonic acid.* 100 g of sodium hydroxide are added to the solution containing the sodium salt of *neo*pentylcyanoacetic acid. The mixture is refluxed until the evolution of ammonia ceases. The solution is cooled to room temperature and 400 ml of conc. hydrochloric acid is added while cooling so that the temperature never exceeds 30°. The solution is then extracted with three 200 ml portions of chloroform. The combined chloroform solutions are washed with 40 ml of conc. hydrochloric acid and dried with anhydrous magnesium sulphate. The chloroform is removed by distillation at reduced pressure by warming on a water-bath to 40°. The dry residue is *neo*pentylmalonic acid and weighs about 260 g. It is readily recrystallized from *cyclo*hexane, and has then a melting point of 89.5°—92°. Equiv. wt. found 86.9, calc. 87.1.

In exactly the same way the following malonic acids are prepared: β,β-dimethylbutylmalonic acid, yield of crude acid 242 g, m. p., of recrystallized product 68°—71°, equiv. wt. found 94.3, calc. 94.1; β,β,γ-trimethylbutylmalonic acid, yield of crude product 300 g, m. p. of recrystallized acid 85.5°—86.5°, equiv. wt. found 101.7, calc. 101.1.

B. *Preparation of ethyl* neo*pentylcyanoacetate.* The solution containing the sodium salt of *neo*pentylcyanoacetic acid is acidified with 250 ml of conc. hydrochloric acid at a temperature not exceeding 30°. The layers are separated and the aqueous layer is extracted with two 250 ml portions of benzene. The combined organic layers are washed with 25 ml of conc. hydrochloric acid.

To the benzene solution of *neo*pentylcyanoacetic acid 250 ml of 99.5 % alcohol and 5 ml of conc. sulphuric acid are added. The mixture is refluxed, and the water formed under the esterification removed by means of a water separator [8]. After about 8 h of reflux a second portion of 5 ml of conc. sulphuric acid is added, and the refluxing is continued until no more water is obtained (total time about 15 h). The benzene solution is cooled to room temperature, washed with 500 ml of water then with 200 ml of a 5 % sodium carbonate solution and finally dried with anhydrous magnesium sulphate. The benzene is removed by distillation and the residue is fractionated at reduced pressure. In this way 275 g of ethyl *neo*pentylcyanoacetate is obtained at 105—110°/8 mm. The forefraction contains some ethyl benzoate.

C. *Preparation of diethyl* neo*pentylmalonate.* The benzene solution containing the *neo*pentylcyanoacetic acid is concentrated by warming under reduced pressure in a water bath at a temperature not exceeding 50°. The residue weighs about 260 g. It is dissolved in 800 ml of 99.5 % alcohol, and 190 ml of conc. sulphuric acid is added whereupon the mixture is refluxed overnight with stirring. It is then cooled and poured onto ice. The layers are separated, and the aqueous layer is extracted with benzene. The combined organic layers are washed with water, then with a 5 % sodium carbonate solution, and again with water. The solution is dried with anhydrous magnesium sulphate, the benzene removed by distillation and the residue fractionated under reduced pressure. The yield is 250 g with a boiling point of 110°—115°/8 mm Hg. The forefraction contains some ethyl benzoate.

4. Introduction of a neo*pentyl group in diethyl malonate and ethyl cyanoacetate by means of trimethylacetaldehyde.* A. *Preparation of diethyl trimethylethylidenemalonate.* This ester is readily obtained by condensing trimethylacetaldehyde with diethyl malonate as described by Foreman and McElvain [9].

B. *Preparation of ethyl trimethylethylidenecyanoacetate.* If trimethylacetaldehyde is condensed with ethyl cyanoacetate by the standard method [10] ethyl trimethylethylidenecyanoacetate is obtained in a 89 % yield; b. p. 104°—111°/9 mm Hg.

C. *Preparation of diethyl* neo*pentylmalonate.* Diethyl trimethylethylidenemalonate is readily hydrogenated by means of hydrogen and pal-

ladium on charcoal. The reaction is completed in 1/2 h if alcohol is used as a solvent, and the pressure is 50 atm. The yield is quantitative. B. p. 120°—130°/11 mm Hg.

D. *Preparation of ethyl* neo*pentylcyanoacetate.* Ethyl trimethylethylidenecyanoacetate is hydrogenated as described above to ethyl *neo*pentylcyanoacetate. The yield is quantitative and the boiling point 110°—114°/8 mm Hg.

5. Alkylations of ethyl neo*pentylcyanoacetate.* A. *Preparation of ethyl ethyl*neo*pentylcyanoacetate.* 91.5 g of ethyl *neo*pentylcyanoacetate, 138 g of powdered anhydrous potassium carbonate, 275 ml of dry acetone and 94 g of ethyl iodide are refluxed with good stirring for 3 h. The resulting mixture is cooled, poured into ice-water, separated, extracted with benzene, dried and distilled under reduced pressure. In this way 100 g, 95 %, of ethyl ethyl*neo*pentylcyanoacetate is obtained. B. p. 116°—118°/7 mm Hg. This ester is recovered unchanged after refluxing with 120 ml of alcohol, and 50 ml of conc. sulphuric acid for 16 h.

B. *Preparation of ethyl allyl*neo*pentylcyanoacetate.* 41 g of ethyl *neo*pentylcyanoacetate 62 g of powdered anhydrous potassium carbonate, 125 g of dry acetone and 33 g of allylbromide are refluxed for 5 h. The mixture is then treated as above yielding 49.5 g, 99 %, of ethyl allyl*neo*pentylcyanoacetate boiling at 127°—128°/8 mm Hg.

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

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

III. On the Preparation of *neo*Pentyl-substituted Barbituric Acids

ARNE BRÄNDSTRÖM

Research Laboratory, Pharmacia Ltd., Uppsala, Sweden

Since J. von Mering in 1903 discovered the hypnotic activity of a compound he erroneously considered to be 5,5-diethylbarbituric acid [1], 5,5-disubstituted barbituric acids have been extensively studied. In Chemical Abstract Decimal Index 1917—1926 the heading "barbituric acid" covers about 5 pages, in Decimal Index 1937—1945 8 pages and in Subject Index 1956 2 pages. This shows that the interest in substituted barbituric acids is ever increasing.

In spite of the enormous interest devoted to 5,5-disubstituted barbituric acids it appears that no barbituric acid containing a *neo*pentylsubstituent in the 5 position has been described. This is still more remarkable as many very useful hypnotics are barbituric acids with a side chain in the 5 position containing five carbon atoms usually in a branched-chain arrangement.

The introduction of a *neo*pentyl group in a molecule gives often a reactivity very different from that obtained with other aliphatic groups of the same size. This is clearly demonstrated by the well-known extremely low reactivity of *neo*pentyl halides compared with that of other alkyl halides and the tendency of *neo*pentyl compounds to undergo rearrangements instead of simple substitution reactions. Therefore, it is of interest to see if the properties of *neo*pentylsubstituted barbituric acids differs from those substituted with other alkyl groups. Consequently, a number of *neo*pentylsubstituted barbituric acids have been prepared by the methods indicated in paper No. 1 in this series [2].

The chemical properties of the *neo*pentyl-substituted barbituric acids resemble those of other alkyl barbituric acids in all respects. In some cases a slight steric effect of the *neo*pentyl group could be observed resulting in a comparatively low yield in certain syntheses, but this effect is by no means as marked as that produced by a *tert*-butyl group [3].