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On the Reaction between Substituted Cyanoacetic Esters and Methylene Bromide. The Preparation of α,α′-Di-(*tert.*-butyl)-glutaric Acid

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Ethyl methyl-, ethyl-, *iso*propyl-, and *tert.*-butylcyanoacetate, in the form of their sodium compounds, react with methylene bromide with the formation of 1,3-dialkyl-1-carbethoxyglutaronitriles, *i.e.*, one carbethoxy group is eliminated during the reaction. These compounds on hydrolysis and decarboxylation give the diastereoisomers of the corresponding α,α′-dialkylsubstituted glutaric acids.

A monoalkylsubstituted malonic ester, in the form of its sodium compound, reacts with methylene bromide with the formation of a 1,3-dialkyl-1,1,3-tricarbethoxypropane [1,2]. One carbethoxy group is eliminated as diethyl carbonate. The yields of the products were dependent on the nature of the alkyl substituent in the way shown in Table 1.

Table 1. Yields of 1,3-dialkyl-1,1,3-tricarbethoxypropanes.

Alkyl group	Yield of product in %
CH_3 [1]	83
C_2H_5 [1]	61
n-C_3H_7 [1]	68
iso-C_3H_7 [1]	39 [a]
n-C_4H_9 [1]	74
iso-C_4H_9 [1]	51
tert.-C_4H_9 [1]	0 [a,b]
n-C_5H_{11} [1]	77
neo-C_5H_{11} [1]	0 [c]
$(CH_3)_3SiCH_2$ [2]	62
$C_6H_5CH_2$ [1]	77

a. The reaction was carried out in ethanol-toluene solution to attain an increased reflux temperature. b. Only unchanged starting material was obtained. c. The product was mainly ethyl α-*neo*pentylacrylate.

Thus branching at the α- or β-position in the alkyl group retards or, as for the *tert.*-butyl and *neo*pentyl derivatives, completely inhibits the reaction. It was suggested that the unreactivity of diethyl *tert.*-butylmalonate was due to its considerably reduced CH-acidity rather than the presence of the bulky *tert.*-butyl group. For the *neo*pentyl derivative the situation is another, as this compound is readily alkylated with alkyl halogenides in ethanolic solution [3] and apparently has an acidity comparable with that of *n*-alkylmalonic esters. In the reaction with methylene bromide diethyl bromomethyl-*neo*pentylmalonate consequently is formed and then split by sodium ethoxide into ethyl α-*neo*pentylacrylate, diethyl carbonate, and sodium bromide. This acrylic ester has been found to be very resistant to addition reagents and thus the reaction will stop at this stage. The unreactivity probably depends on the steric influence of the *neo*pentyl group. The difference between the rates of bromine addition to *tert.*-butylethylene and *neo*pentylethylene has been explained in the same way [4]. The great difference between the *neo*pentyl group and its silicon analogue, the trimethylsilylmethyl group [5], also manifests itself in this reaction.

As the cyano group is known to have a greater acid-strengthening effect than the carbethoxy group, the reaction between ethyl *tert.*-butylcyanoacetate and methylene bromide was studied in order to test the above hypothesis. In fact the reaction product consisted of I, R = *tert.*-butyl, formed according to the formula:

$$2\ \mathrm{R.CH(CN)COOEt} + \mathrm{CH_2Br_2} + 2\ \mathrm{OEt^-} \longrightarrow$$

$$\mathrm{R.C(CN)COOEt}\ (\mathrm{R.CH.CN}\ \text{—}\ \mathrm{CH_2}) + \mathrm{EtOH} + (\mathrm{EtO})_2\mathrm{CO} + 2\ \mathrm{Br^-}$$

I

with the elimination of one carbethoxy group, in close analogy with the behaviour of monosubstituted malonic esters. In ethanolic solution the yield was 19 %, whereas addition of toluene to the reaction mixture in order to increase the reflux temperature gave 52 % yield. Ethyl methyl-, ethyl-, and *iso*propylcyanoacetate in ethanolic solution similarly gave I, R = CH_3, C_2H_5, and *iso*-C_3H_7 in 70, 77, and 58 % yield, respectively.

I, R = *tert.*-C_4H_9 was purified by distillation *in vacuo* and then solidified on standing, m.p. 75—80°. Recrystallization from 80 % methanol gave m.p. 79—81°. The small change in m.p. indicates that the substance which is capable of existing in two diastereoisomeric forms either is produced in preponderantly one form or that the solid consists of the eutectic mixture. The formation of both forms of α,α'-di-(*tert.*-butyl)-glutaric acid is no conclusive evidence, as the drastic conditions necessary for hydrolysis are likely to affect the asymmetric centra. Recrystallization from several solvents and solvent pairs had no effect upon the m.p.

Zelinsky [6] and Auwers and Thorpe [7] carried out the same reaction with ethyl methylcyanoacetate and methylene iodide and claimed that 1,3-dimethyl-

1,3-dicarbethoxyglutaronitrile was formed in about 50 % yield. However, as their analyses did not agree well with this formula and the substance was stated to be difficult to purify owing to decomposition during distillation, it seems probable that their compound actually was I, R = CH_3. This is also indicated by the b.p. reported, 165—170°/12 mm. For comparison it should be mentioned that 1,3-dicarbethoxyglutaronitrile has b.p. 195°/20 mm [8].

I, R = *tert.*-C_4H_9, was very resistant to hydrolysis in acid or alkaline solution. Sulphuric acid of various strengths was either without effect or caused decomposition due to oxidation. Boiling ethanolic potassium hydroxide also left the substance unchanged. However, boiling with excess potassium hydroxide in ethylene glycol containing some water (boiling temperature about 175°) converted it into a mixture of the monoamides of α,α'-di-(*tert.*-butyl)-glutaric acid, which could be separated by fractionated crystallization from acetic acid, m.p. 242—243° and 214—216°, respectively. Apparently the carbethoxy group (or one of the cyano groups) was eliminated directly during this procedure, as evidenced by the evolution of large amounts of carbon dioxide on acidification. In order to hydrolyze the remaining amide group the monoamides were dissolved in a mixture of concentrated hydrochloric acid and acetic acid and treated with sodium nitrite. This method gave the two forms of α,α'-di-(*tert.*-butyl)-glutaric acid in almost quantitative yields, m.p. 221—222° and 213—214°. The eutectic m.p. was 189°. The amide with m.p. 242—243° corresponded to the acid with m.p. 213—214°.

1,3-Dimethyl-, 1,3-diethyl-, and 1,3-di*iso*propyl-1-carbethoxyglutaronitrile (I, R = CH_3, C_2H_5, and *iso*-C_3H_7) were hydrolyzed and decarboxylated in acid media as described in the experimental part. The acid mixtures obtained were separated into diastereoisomers according to known procedures. [1,9,10]

EXPERIMENTAL

The preparation of 1,3-di-(tert.-*butyl*)*-1-carbethoxyglutaronitrile (I, R =* tert.-C_4H_9*) in ethanolic solution.* Sodium, 4.6 g (0.2 mole), was dissolved in 70 ml of absolute ethanol, and 33.8 g (0.2 mole) of ethyl *tert.*-butylcyanoacetate were added followed by 17.4 g (0.1 mole) of methylene bromide. The reaction mixture was allowed to boil for 24 h after which time it reacted almost neutrally. After neutralization with acetic acid the ethanol was distilled off and the residue treated with water. The organic layer was taken up in ether and the ether solution washed with water and finally dried with anhydrous magnesium sulphate. Fractionation yielded besides unchanged starting material 5.7 g of I, R = *tert.*-C_4H_9, b.p. 113—114°/1 mm, which solidified upon standing, m.p. 75—80°. After recrystallization from 80 % aqueous methanol 5.2 g of the pure compound were obtained, m.p. 79—81°. Further recrystallizations from 80 % aqueous methanol, 80 % aqueous ethanol, petroleum ether, benzene-petroleum ether, or ethyl acetate-petroleum ether did not change the m.p. (Found: C 68.9; H 9.3; N 10.0. Calc. for $C_{16}H_{26}O_2N_2$: C 69.0; H 9.4; N 10.1). The yield was 19 %.

The preparation of I, R = tert.-C_4H_9*, in ethanol-toluene solution.* Sodium, 11.5 g (0.5 mole), was heated under 200 ml of toluene until the metal had melted. A mixture of 40 ml of absolute ethanol and 84.5 g (0.5 mole) of ethyl *tert.*-butylcyanoacetate was added during a period of 10 min whereby a vigorous reaction occurred. To the resulting yellow solution were added 43.5 g (0.25 mole) of methylene bromide, and the mixture was kept at reflux temperature for 36 h, after which time it reacted neutrally. Water was added and the product was isolated and purified as above, b.p. 150—152°/4 mm, m.p. after recrystallization from 80 % aqueous methanol 79—81°. The yield was 29.8 g (52 %), based on unrecovered starting material (69.3 g).

The monoamides of a,a'-di-(tert.-*butyl*)-*glutaric acid.* 1,3-di-(*tert.*-butyl)-1-carbethoxyglutaronitrile, 13.9 g (0.05 mole), was slowly heated together with 28.0 g (0.5 mole) of potassium hydroxide, 80 ml of ethylene glycol, and 5 ml of water. A vigorous reaction occurred, and when it had subsided the solution was refluxed for 20 h. After cooling it was poured into 150 ml of water. On acidification with concentrated hydrochloric acid large amounts of carbon dioxide were evolved and a solid was obtained. The latter was very difficult to filter owing to contamination with silicon dioxide from the reaction vessel. After drying it weighed 15.7 g. A small amount was treated with boiling ethyl acetate, filtered from insoluble matter, and the solution allowed to cool slowly. Crystals with m.p. 235—240° separated, m.p. after another recrystallization from ethyl acetate 242—243°. The mother liquor from the first filtration was freed from solvent and the residue recrystallized twice from aqueous acetic acid, m.p. 214—216°. (Found for the monoamide with m.p. 242—243°: C 64.0; H 10.2; N 5.8; equiv. wt. 243.5. Found for the monomide with m.p. 214—216°: C 64.2; H 10.4; N 5.8; equiv. wt. 242.3. Calc. for $C_{13}H_{25}O_3N$: C 64.2; H 10.4; N 5.8; equiv. wt. 243.3).

a,a'-Di-(tert.-*butyl*)-*glutaric acid.* Crude mixture of the monoamides, 3.0 g, was dissolved in 50 ml of glacial acetic acid and filtered from insoluble matter. Concentrated hydrochloric acid, 10 ml, was added and the solution cooled in an ice-bath. When the temperature was below 5°, a solution of 3.0 g of sodium nitrite in a few ml of water was added slowly. The mixture was cautiously heated in a water-bath whereby evolution of nitrogen began at about 40°. When the gas evolution had ceased, the solution was boiled for 10 min and then diluted with 300 ml of water. The solid was filtered and dried (1.4 g). It was dissolved in a mixture of ethyl acetate and benzene (1:1) and the solution allowed to cool. The crystals were filtered, m.p. 220—222°, and recrystallized once from glacial acetic acid, m.p. 221—222° (0.5 g). The mother liquor was evaporated to dryness and the residue recrystallized twice from aqueous acetic acid, m.p. 213—214° (0.45 g). The eutectic mixture melted at 189°. (Found for the acid with m.p. 221—222°: C 63.8; H 9.9; equiv. wt. 121.8. Found for the acid with m.p. 213—214°: C 63.7; H 9.9: equiv. wt. 122.7. Calc. for $C_{13}H_{24}O_4$: C 63.9; H 9.9; equiv. wt. 122.2).

When small amounts of the pure monoamides were treated in the same way, almost quantitative yields of the respective acids were obtained. The amide with m.p. 242—243° corresponded to the acid with m.p. 213—214°.

1,3-Dimethyl-1-carbethoxyglutaronitrile (*I*, $R = CH_3$). This compound was prepared from 0.2 mole of sodium dissolved in 70 ml of ethanol, 0.2 mole of ethyl methylcyanoacetate, and 0.1 mole of methylene bromide. The reflux time was 24 h. The product was isolated as above, b.p. 137—138°/4 mm, n_D^{20} 1.4438, d_4^{20} 1.0354, yield 70 %. (Found: C 61.4; H 7.3; N 14.0; r_D 0.2564. Calc. for $C_{10}H_{14}O_2N_2$: C 61.8; H 7.3; N 14.4; r_D 0.2560).

a,a'-Dimethylglutaric acid. 1,3-Dimethyl-1-carbethoxyglutaronitrile was hydrolyzed and decarboxylated by boiling with concentrated hydrochloric acid for 20 h. The yield of crude acid mixture was almost quantitative and it was separated into the diastereoisomers according to Möller [9], m.p. 140—141° and 125—127°, respectively.

1,3-Diethyl-1-carbethoxyglutaronitrile (*I*, $R = C_2H_5$). This compound was prepared in the same way as the methyl derivative in a 0.2 mole run, b.p. 151—153°/4 mm, n_D^{20} 1.4468, d_4^{20} 1.0088, yield 77 %. (Found: C 64.6; H 8.1; N 12.5; r_D 0.2648. Calc. for $C_{12}H_{18}O_2N_2$: C 64.8; H 8.2; N 12.6; r_D 0.2655).

a,a'-Diethylglutaric acid. 1,3-Diethyl-1-carbethoxyglutaronitrile was hydrolyzed and decarboxylated by boiling with 50 % sulphuric acid for 12 h. The yield of crude acid mixture was almost quantitative and it was separated into the diastereoisomers according to Berner and Landmark [10], m.p. 119—121° and 92—94°, respectively.

*1,3-Di*iso*propyl-1-carbethoxyglutaronitrile* (*I*, R = iso-C_3H_7). This compound was prepared in the same way as the methyl derivative in a 0.5 mole run, b.p. 136—142°/2 mm, n_D^{20} 1.4523, d_4^{20} 0.9992, yield 58 %. (Found: C 67.0; H 8.9; N 11.3; r_D 0.2701. Calc. for $C_{14}H_{22}O_2N_2$: C 67.2; H 8.9; N 11.2; r_D 0.2728).

*a,a'-Di*iso*propylglutaric acid.* 1,3-Di*iso*propyl-1-carbethoxyglutaronitrile was hydrolyzed and decarboxylated by boiling with 80 % sulphuric acid for 20 min. The yield of crude acid mixture was 90 %, and it was separated into diastereoisomers according to Eberson [1], m.p. 141—142° and 119—120°, respectively.

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REFERENCES

1. Eberson, L. *Acta Chem. Scand.* **12** (1958) 314.
2. Eberson, L. *Acta Chem. Scand.* **9** (1955) 1711.
3. Brändström, A. *Private communication.*
4. Newman, M. S. *Steric Effects in Organic Chemistry.* John Wiley & Sons, Inc. New York 1956, p. 244.
5. Whitmore, F. C. and Sommer, L. H. *J. Am. Chem. Soc.* **68** (1946) 481.
6. Zelinsky, N. *Ber.* **22** (1889) 2823.
7. Auwers, K. and Thorpe, J. F. *Ann.* **285** (1895) 310.
8. Higson, A. and Thorpe, J. F. *J. Chem. Soc.* **89** (1906) 1458.
9. Möller, E. *Kgl. Fysiograf. Sällskap. Lund. Förh.* **30** (1918) Ns. 6.
10. Berner, E. and Landmark, L. H. *Acta Chem. Scand.* **7** (1953) 1347.

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