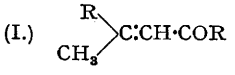
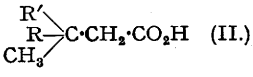
54. *Long-chain Acids containing a Quaternary Carbon Atom. Part III.*

By W. H. Hook and Sir Robert Robinson.

The general method of synthesis of derivatives of ββ-dialkylbutyric acids by reaction of Grignard reagents with substances containing catio-enoid systems has been further developed. The process has been shown to be applicable to the synthesis of βββ-trialkylpropionic acids.

The work of Adams and his collaborators (*J. Amer. Chem. Soc.*, 1929, **51**, 1261; and earlier papers) has shown that dialkylacetic acids containing from 16 to 18 carbon atoms possess some bactericidal properties against *Mycobacterium tuberculosis*. More recently Birch and Robinson (J., 1942, 488), citing a report by Stenhagen, have indicated that certain ββ-dialkylbutyric acids which they prepared are equally effective, and have the advantage that they are less irritant to living tissue. As the method used for the synthesis of ββ-di-*n*-octylbutyric acid, for example, was very laborious and gave rather low yields, the present work was undertaken in order to find a better method of synthesis of ββ-dialkylbutyric acids, so that their biological properties might be more fully investigated.

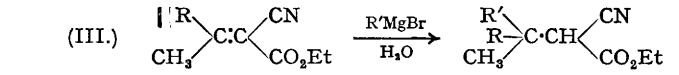
Kharasch (*J. Amer. Chem. Soc.*, 1941, **63**, 2308) has shown that the reaction of a Grignard reagent with an αβ-unsaturated ketone is substantially affected by the presence of certain metallic salts as catalysts. For instance, although the normal reaction between isophorone and methylmagnesium bromide proceeds at the carbonyl group, he has shown that in the presence of cuprous chloride the 1 : 4-addition predominates, the main product being a saturated ketone. This observation suggested that the action of a Grignard reagent on a ketone of the type (I), followed by oxidation, might yield the ββ-dialkylbutyric acids (II), but study of the

(I.)  (II.) 

reaction between 8-keto-6-methyltridec-6-ene (I, R = C_5H_{11}) and *n*-amylmagnesium bromide in the presence of cuprous bromide showed that addition occurred in the 1 : 2- and 1 : 4-positions in about equal proportions. The reaction also proved to be very sluggish, and the difficulty experienced in separating the products from unchanged starting material and from one another rendered this scheme of little practical value. During the course of this investigation it was found that the reaction between the αβ-unsaturated ketone and amylmagnesium bromide proceeded more rapidly in the presence of cuprous iodide than in that of cuprous bromide. It was also found that methylmagnesium iodide reacts with 8-keto-6-methyltridec-6-ene in the presence of a cuprous salt to give a much higher proportion of the 1 : 2-addition product than does *n*-amylmagnesium bromide. This is not surprising in view of the finding of Colonge (*Bull. Soc. chim.*, 1935, **2**, 754) that 2-keto-3-methylpent-3-ene reacted with methylmagnesium iodide in the absence of a catalyst to give only the unsaturated tertiary alcohol, but with ethylmagnesium bromide to give a mixture of tertiary alcohol and saturated ketone.

In view of the above results, it seemed of interest to test the action of Grignard reagents on suitable substances containing a more highly activated double bond as a means of building up the quaternary carbon atom in ββ-dialkylbutyric acids. Kohler and Reimer (*Amer. Chem. J.*, 1905, **33**, 333) found that phenylmagnesium bromide reacted quantitatively with ethyl α-cyanocinnamate to give ethyl α-cyano-ββ-diphenylpropionate. This method was found to be of general application, and the alkylidenecyanoacetates (III)

were converted by alkylmagnesium bromides into α-cyano-ββ-dialkylbutyrates (IV) in 66% yield (cf. Birch and Robinson, J., 1943, 501). Some reduction of the alkylidenecyanoacetate to the saturated α-cyano-β-alkyl-



butyric ester also occurred in the presence of the Grignard reagent, but the amount of reduction product was reduced to a minimum by adding the Grignard reagent slowly to the alkylidenecyanoacetate. Cuprous iodide as catalyst facilitated the reaction.

Hydrolysis of the α-cyano-ββ-dialkylbutyric ester (IV) to the ββ-dialkylbutyric acid at first presented some difficulty. αα-Dicyano-β-methyl-β-hexylglutarimide was hydrolysed by Birch and Robinson (*loc. cit.*) to β-methyl-β-hexylglutaric acid by refluxing with a mixture of sulphuric acid, acetic acid, and water, but prolonged treatment of the ethyl α-cyano-ββ-dialkylbutyrates in a similar way gave very unsatisfactory results. Vogel (J., 1928, 2010) hydrolysed a number of α-cyano-esters to the malonic acids with alcoholic potassium hydroxide, but with the present examples, prolonged treatment with aqueous and alcoholic alkali, or with alkali in high-boiling solvents such as *cyclo*hexanol (cf. B.P. 469,921; *Chem. Abstr.*, 1938, 729) proved equally ineffective. Heating with alcohol and sulphuric acid under pressure resulted in almost complete recovery of the α-cyano-ester, and keeping for several days with cold concentrated sulphuric acid yielded no useful product. The presence of the cyano-acid in some of the hydrolysis products after distillation indicated that this acid was unexpectedly stable, and experiment showed that no decarboxylation occurred below 200° except in the presence of copper powder. It seemed likely, therefore, that no decarboxylation of the cyano-acid occurred under the conditions used in the attempted acid hydrolysis.

Eventually the α-cyano-ββ-dialkylbutyric esters were hydrolysed to the cyano-acids with aqueous sodium hydroxide, and decarboxylated by heating with copper powder. Treatment of the nitriles so obtained with a mixture of sulphuric acid, acetic acid, and water then gave the ββ-dialkylbutyric acids in good yield.

β-n-*Amyl*-β-n-*heptylbutyric acid*, β-n-*butyl*-β-n-*nonylbutyric acid*, ββ-*di*-n-*heptylbutyric acid*, and β-*propyl*-ββ-*di*iso*amylpropionic acid* have been prepared by this method; they are colourless, viscous oils, which form sparingly soluble alkali-metal salts. With the exception of β-*propyl*-ββ-*di*iso*amylpropionamide*, the amides were very viscous oils which showed no tendency to crystallise.

Some difficulty was experienced throughout this work in obtaining consistent analyses of these quaternary compounds; purity of the products was therefore checked at most stages by a determination of the molecular refraction.

Specimens of the above acids have been submitted for biological tests, and preliminary results indicate that the C_{16} acids are the most active bactericidally, but they are not more active than diheptylacetic acid.

Experimental.

8-*Keto*-6-*methyl*-6-n-*amyltridecane*.—Methyl *n*-amyl ketone was condensed in the presence of methylanilinomagnesium bromide (Colonge, *Bull. Soc. chim.*, 1934, **1**, 1101), and the product dehydrated over iodine at 170° and distilled. 8-Keto-6-methyltridec-6-ene was obtained as a pale yellow oil boiling at 148—150°/19 mm. The unsaturated ketone (20 g.) in ether (30 c.c.) was slowly stirred into a cooled Grignard solution from magnesium (4·8 g.) and *n*-amyl bromide (40 g.) in ether (80 c.c.), to which cuprous bromide (0·2 g.) had been added. The mixture was refluxed for 20 hours and kept for 4 days. It was then decomposed with water and dilute hydrochloric acid, heated with iodine to dehydrate any carbinol, and distilled. The higher-boiling product was refluxed for 6 hours with 60% sulphuric acid and steam-distilled. The oily separated layer gave 4·0 g., b. p. 160—175°/18 mm. (Found: C, 82·5; H, 13·3. $C_{19}H_{38}O$ requires C, 80·8; H, 13·5. $C_{19}H_{36}$ requires C, 86·4; H, 13·6%). This product was dissolved in acetone and treated with powdered potassium permanganate (1·7 g.) with stirring, the temperature being maintained below 20°. On working up, 8-*keto*-6-*methyl*-6-n-*amyltridecane* (2·0 g.), b. p. 165—170°/19 mm., was obtained (Found: C, 81·0; H, 13·3%); the 2 : 4-dinitrophenylhydrazone was a dark red oil.

ββ-*Di*-n-*amylbutyric Acid*.—Ethyl 1-methylhexylidenecyanoacetate (29 g.), obtained by the method of Cope (*J. Amer. Chem. Soc.*, 1941, **63**, 3454), in ether (60 c.c.) was slowly added with stirring at 10—15° during ½ hour to a Grignard reagent, prepared from magnesium (5·8 g.), *n*-amyl bromide (40 g.), and ether (110 c.c.), to which cuprous iodide (0·5 g.) had been added. The mixture was refluxed for an hour, and after keeping for a further 2 hours was decomposed with ice and acetic acid (20 c.c.). The ethereal layer was washed with water, aqueous sodium bicarbonate, and with water, and dried over sodium sulphate. Fractionation by means of a heated column yielded *ethyl α-cyano-ββ-di*-n-*amylbutyrate* as a colourless oil (14 g.), b. p. 137—139°/0·3 mm. (Found: C, 72·2; H, 10·8; N, 5·1. $C_{17}H_{31}O_2N$ requires C, 72·6; H, 11·0; N, 5·0%).

A lower-boiling fraction was shaken for 10 hours with a 20% solution of sodium bisulphite to remove unchanged alkylidenecyanoacetate, and the insoluble moiety collected with benzene and distilled through a column. *Ethyl α-cyano-β-methyloctoate* was obtained as a colourless mobile oil, b. p. 90—92°/0·1 mm. (Found: C, 68·1; H, 9·9; N, 6·5. $C_{12}H_{21}O_2N$ requires C, 68·3; H, 10·0; N, 6·6%).

Ethyl cyanodiamylbutyrate (5 g.) was refluxed for 12 hours with a mixture of sulphuric acid (10 c.c.), acetic acid (20 c.c.), and water (10 c.c.). The product was poured into water, extracted with ether, and washed thoroughly with water. After drying and removal of the solvent, it was heated to 160° in a vacuum to complete decarboxylation of any amido-acid. The product was then dissolved in light petroleum, and extraction with dilute aqueous sodium hydroxide yielded *ββ-di*-n-*amylbutyric acid* (0·3 g.), b. p. 125—130°/0·3 mm. (Found: C, 74·3; H, 12·2. $C_{14}H_{28}O_2$ requires C, 73·7; H, 12·3%).

β-n-*Butyl*-β-n-*nonylbutyric Acid*.—*Ethyl* 1-*methyldecylidenecyanoacetate* (26 g.) was obtained from methyl *n*-nonyl ketone (26 g.) and ethyl cyanoacetate (17 g.) by Cope's method (*loc. cit.*) as a pale yellow oil, b. p. 146—148°/0·25 mm. (Found: C, 72·6; H, 10·3; N, 5·4. $C_{16}H_{27}O_2N$ requires C, 72·5; H, 10·2; N, 5·3%).

The Grignard solution prepared from magnesium (4·0 g.), *n*-butyl bromide (27 g.), and ether (80 c.c.) was added slowly with stirring, during 20 minutes at 15—20°, to a solution of ethyl methyldecylidenecyanoacetate (30 g.) in ether (60 c.c.)

in which was suspended cuprous iodide (0·5 g.). The mixture was refluxed for an hour and kept for a further 2 hours. *Ethyl α-cyano-β-*n*-butyl-β-*n*-nonylbutyrate* was isolated in the usual way as an almost colourless oil, b. p. 150—160°/0·2 mm. (21 g.) (Found: C, 74·4; H, 11·4; N, 4·4. $C_{20}H_{37}O_2N$ requires C, 74·3; H, 11·4; N, 4·3%); $n_D^{20°}$ 1·4537; $d^{20°}$ 0·9108; $[R_L]_D$ 95·99 (calc., 95·96).

Ethyl cyano-*n*-butyl-*n*-nonylbutyrate was hydrolysed by boiling, with stirring, for 3 hours with 5 times its weight of 10% aqueous sodium hydroxide and a little alcohol. The acidic product was isolated and heated to 180° in a vacuum with a little copper powder until decarboxylation was complete. *β-*n*-Butyl-β-*n*-nonylbutyronitrile* was a colourless mobile oil, b. p. 130—136°/0·3 mm. (Found: C, 81·1; H, 13·3; N, 5·9. $C_{17}H_{33}N$ requires C, 81·3; H, 13·1; N, 5·6%); $n_D^{20°}$ 1·4489; $d^{20°}$ 0·8364; $[R_L]_D$ 80·48 (calc., 80·45).

An intermediate fraction from the preparation of ethyl cyano-*n*-butyl-*n*-nonylbutyrate was hydrolysed and decarboxylated as above, and after distillation, a small quantity of a white solid crystallised from the distillate. This proved to be *β-methyldodecamide*; it crystallised from light petroleum in white needles, m. p. 87° (Found: C, 73·1; H, 12·7; N, 6·7. $C_{13}H_{27}ON$ requires C, 73·2; H, 12·7; N, 6·6%).

A mixture of *n*-butyl-*n*-nonylbutyronitrile (10 g.), acetic acid (40 c.c.), sulphuric acid (20 c.c.), and water (16 c.c.) was refluxed for 12 hours. The upper layer disappeared after about an hour, and after 2—3 hours the solution became cloudy, and an upper layer again began to separate. After 12 hours water was added, and the product isolated by means of ether. It was refluxed for 4 hours with methanol (50 c.c.) and sulphuric acid (2·5 c.c.). The solution was concentrated to half its volume, and the ester then separated by addition of water and extraction with ether. *Methyl β-*n*-butyl-β-*n*-nonylbutyrate* was obtained as a colourless mobile oil (5·6 g.), b. p. 116—120°/0·1 mm. (Found: C, 76·1; H, 12·7. $C_{18}H_{36}O_2$ requires C, 76·1; H, 12·7%); $n_D^{20°}$ 1·4456; $d^{20°}$ 0·8708; $[R_L]_D$ 86·89 (calc., 86·98).

The higher-boiling residue from the above hydrolysis was distilled, and *β-*n*-butyl-β-*n*-nonylbutyramide* was obtained as a very viscous, colourless oil, b. p. 165—180°/0·45 mm., which could not be induced to crystallise (Found: C, 75·9; H, 12·8; N, 5·2. $C_{17}H_{35}ON$ requires C, 75·8; H, 13·0; N, 5·2%); $n_D^{20°}$ 1·4677; $d^{20°}$ 0·8899; $[R_L]_D$ 84·06 (calc., 84·14). Hydrolysis of the amide with sulphuric and acetic acids and esterification as above yielded a further quantity of the methyl ester.

A mixture of methyl *n*-butyl-*n*-nonylbutyrate (7 g.), potassium hydroxide (5 g.), alcohol (30 c.c.), and water (20 c.c.) was refluxed for 2 hours. The alcohol was then removed, and the acidic product isolated in the known manner; *β-*n*-butyl-β-*n*-nonylbutyric acid* was obtained as a viscous, colourless oil, b. p. 155—157°/0·3 mm. (Found: C, 75·3; H, 12·6. $C_{17}H_{34}O_2$ requires C, 75·6; H, 12·6%); $n_D^{20°}$ 1·4539; $d^{20°}$ 0·8889; $[R_L]_D$ 82·25 (calc., 82·24).

*β-*n*-Amyl-β-*n*-heptylbutyric Acid.*—The Grignard solution prepared from magnesium (5·4 g.), heptyl bromide (41 g.), and ether (120 c.c.) was caused to react with ethyl 1-methylhexylidenecyanoacetate (34 g.) in ether (60 c.c.) as described for ethyl cyano-*n*-butyl-*n*-nonylbutyrate. On working up the product, *ethyl α-cyano-β-*n*-amyl-β-*n*-heptylbutyrate* was obtained as an almost colourless oil (33 g.), b. p. 155—158°/·012 mm. (Found: C, 74·0; H, 11·3; N, 4·8. $C_{19}H_{35}O_2N$ requires C, 73·8; H, 11·3; N, 4·5%); $n_D^{20°}$ 1·4522; $d^{20°}$ 0·9125; $[R_L]_D$ 91·39 (calc., 91·34).

The lower-boiling fraction was shaken with concentrated sulphuric acid, washed with water, dried, and distilled. The product was found to be *n*-tetradecane, b. p. 122—123°/14 mm., m. p. 5·5° (Kraft, *Ber.*, 1886, **19**, 2218, gives m. p. 5·5°); $n^{20°}$ 1·4293 (Found: C, 85·0; H, 15·1. Calc. for $C_{14}H_{30}$: C, 84·9; H, 15·1%).

Ethyl α-cyano-*β-n*-amyl-*β-n*-heptylbutyrate was hydrolysed to the dialkylbutyric acid as described for ethyl cyano-*n*-butyl-*n*-nonylbutyrate. *β-*n*-Amyl-β-*n*-heptylbutyronitrile* was obtained as a colourless oil, b. p. 123—126°/0·25 mm. (Found: C, 80·7; H, 13·1; N, 6·1. $C_{16}H_{31}N$ requires C, 81·0; H, 13·1; N, 5·9%); $n_D^{20°}$ 1·4475; d^{20} 0·8360; $[R_L]_D$ 75·82 (calc., 75·83).

*Methyl β-*n*-amyl-β-*n*-heptylbutyrate* had b. p. 115—117°/0·2 mm. (Found: C, 75·6; H, 12·6. $C_{17}H_{34}O_2$ requires C, 75·6; H, 12·6%); $n_D^{20°}$ 1·4437; $d^{20°}$ 0·8710; $[R_L]_D$ 82·30 (calc., 82·36).

*β-*n*-Amyl-β-*n*-heptylbutyric acid* was obtained as a colourless viscous oil, b. p. 144—149°/0·45 mm. (Found: C, 75·1; H, 12·7; *M*, 255. $C_{16}H_{32}O_2$ requires C, 75·0; H, 12·5%; *M*, 256); $n_D^{20°}$ 1·4526; $d^{20°}$ 0·8904; $[R_L]_D$ 77·65 (calc., 77·62).

*ββ-Di-*n*-heptylbutyric Acid.*—Methyl *n*-heptyl ketone was prepared by the method of Pickard and Kenyon (J., 1911, **99**, 57), b. p. 80—81°/13 mm. ($n_D^{20°}$ 1·4215); semicarbazone, m. p. 119—120°.

Ethyl 1-methyloctylidenecyanoacetate was obtained as a pale yellow oil, b. p. 165—168°/13 mm. (Found: C, 70·9; H, 9·7; N, 5·8. $C_{14}H_{23}O_2N$ requires C, 70·9; H, 9·7; N, 5·9%); $n_D^{20°}$ 1·4678; $d^{20°}$ 0·9433; $[R_L]_D$ 69·82 (calc., 67·78; exaltation, 2·04).

The Grignard solution prepared from magnesium (4·5 g.), *n*-heptyl bromide (36 g.), and ether (100 c.c.) was brought into reaction with ethyl methyloctylidenecyanoacetate (30 g.) in the usual way, and yielded *ethyl α-cyano-ββ-di-*n*-heptylbutyrate* (29 g.), b. p. 168—172°/0·5 mm. (Found: C, 74·9; H, 11·6; N, 4·1. $C_{21}H_{39}O_2N$ requires C, 74·8; H, 11·6; N, 4·1%); $n_D^{20°}$ 1·4535; $d^{20°}$ 0·9046; $[R_L]_D$ 100·78 (calc., 100·57). This α-cyano-ester was hydrolysed in the usual way, and *ββ-di-*n*-heptylbutyronitrile* was obtained as a colourless mobile oil, b. p. 145—150°/0·5 mm. (Found: C, 81·3; H, 13·3. $C_{18}H_{35}N$ requires C, 81·5; H, 13·2%); $n_D^{20°}$ 1·4499; $d^{20°}$ 0·8374; $[R_L]_D$ 85·03 (calc., 85·06).

*Methyl ββ-di-*n*-heptylbutyrate* had b. p. 135—140°/0·4 mm. (Found: C, 76·7; H, 12·7. $C_{19}H_{38}O_2$ requires C, 76·5; H, 12·8%); $n_D^{20°}$ 1·4468; $d^{20°}$ 0·8698; $[R_L]_D$ 91·52 (calc., 91·60).

*ββ-Di-*n*-heptylbutyric acid* was obtained as a colourless viscous oil, b. p. 168—172°/0·6 mm. (Found: C, 76·3; H, 12·8. $C_{18}H_{36}O_2$ requires C, 76·1; H, 12·7%); $n_D^{20°}$ 1·4548; $d^{20°}$ 0·8869; $[R_L]_D$ 86·84 (calc., 86·86).

*β-*n*-Propyl-ββ-di*isoamylpropionic Acid.*—The *iso*amyl iodide used in the following synthesis was prepared from technical *iso*amyl alcohol which contained some active amyl alcohol. The final product had a small optical activity.

n-Propyl *iso*amyl ketone (26 g.), obtained by the action of *n*-butyryl chloride on *iso*amylzinc iodide, was condensed with ethyl cyanoacetate (20 g.) and yielded *ethyl* 1-*n*-*propyl*isohexylidenecyanoacetate (27 g.), b. p. 120—125°/0·4 mm.; $n_D^{20°}$ 1·4679 (Found: C, 70·7; H, 9·7. $C_{14}H_{23}O_2N$ requires C, 70·9; H, 9·7%).

The Grignard solution prepared from magnesium (4·1 g.), *iso*amyl iodide (37 g.), and ether (80 c.c.) reacted with ethyl *n*-propyl*iso*hexylidenecyanoacetate (27 g.) in the usual way. *Ethyl α-cyano-β-*n*-propyl-ββ-di*isoamylpropionate was obtained as a colourless oil (24 g.), b. p. 140—145°/0·7 mm.; $n_D^{20°}$ 1·4542 (Found: C, 73·3; H, 11·4. $C_{19}H_{35}O_2N$ requires C, 73·8; H, 11·3%).

The cyano-ester was hydrolysed as usual, and *β-*n*-propyl-ββ-di*isoamylpropionitrile obtained as a mobile, colourless oil, b. p. 115—118°/0·8 mm.; $n_D^{20°}$ 1·4479 (Found: C, 80·4; H, 12·8. $C_{16}H_{31}N$ requires C, 81·0; H, 13·1%). *Methyl β-*n*-propyl-ββ-di*isoamylpropionate had b. p. 100—108°/0·3 mm.; $n_D^{20°}$ 1·4441 (Found: C, 75·4; H, 12·8. $C_{17}H_{34}O_2$ requires C, 75·6; H, 12·6%). *β-*n*-Propyl-ββ-di*isoamylpropionic acid was obtained as a colourless, viscous oil, b. p. 138—145°/0·3 mm.; $n_D^{20°}$ 1·4522 (Found: C, 75·2; H, 12·5. $C_{16}H_{32}O_2$ requires C, 75·0; H, 12·5%). The *amide* separated from light petroleum as greasy plates, m. p. 52—53° (Found: C, 75·2; H, 13·1. $C_{16}H_{33}ON$ requires C, 75·3; H, 12·9%).

The authors thank the Therapeutic Research Corporation of Great Britain Ltd. for grants.

DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, January 11th,* 1944.]