614. *Experiments on the Synthesis of Carbonyl Compounds. Part V.* β-Keto-esters and -nitriles.*

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β-Keto-esters and -nitriles may be prepared by hydrogenolysis and subsequent decarboxylation of benzyl ethyl acylmalonates and benzyl acylcyanoacetates respectively.

THE debenzylation process using dibenzyl esters of substituted acylmalonic esters has been used for the synthesis of ketones (Bowman, *J.*, 1950, 325). We now report the use of monobenzyl esters for the synthesis of β-keto-esters and -nitriles.

Benzyl ethyl malonate was readily obtained by alcoholysis of the diethyl ester with benzyl alcohol in the presence of a catalytic amount of sodium ethoxide. Reaction of its sodio-derivative (I; R′ = H, 2 mols.) with an acid chloride and subsequent hydrogenolysis and decarboxylation furnished the β-keto-esters (II; R = C_7H_{15} and $C_{11}H_{23}$, R′ = H) in 70% yield.

$$\mathrm{R{\cdot}COCl} + \underset{\text{(I.)}}{\mathrm{CH_2Ph{\cdot}O_2C{\cdot}CR'Na{\cdot}CO_2Et}} \longrightarrow \mathrm{R{\cdot}CO{\cdot}CR'(CO_2{\cdot}CH_2Ph){\cdot}CO_2Et} \xrightarrow[-\mathrm{CO_2}]{\mathrm{H_2}\text{-}\mathrm{Pd}} \underset{\text{(II.)}}{\mathrm{R{\cdot}CO{\cdot}CHR'{\cdot}CO_2Et}}$$

For α-substituted β-keto-esters the requisite benzyl ethyl alkylmalonates were prepared by interaction of the crude sodium salt of the half acid-ester and benzyl chloride or, more conveniently, by partial alcoholysis. Reaction as before gave the β-keto-esters (II; R = $C_{11}H_{23}$, R′ = CHMeEt·CH_2, and R = C_8H_{17}·CH·OMe, R′ = Me), in the latter case accompanied by the ketone (III) and the ester (IV) formed by trans-esterification.

(III.) C_8H_{17}·CH(OMe)·CO·C_2H_5 C_8H_{17}·CH(OMe)·CO·CMe·$(CO_2Et)_2$ (IV.)

A trans-esterification equilibrium was realised experimentally in boiling benzene and limits the yield of β-keto-ester.

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* Part IV, preceding paper.

For the preparation of β-keto-nitriles, the requisite benzyl sodiocyanoacetate was generated *in situ* (cf. *J.*, 1950, **177**, 325), ester-interchange being highly satisfactory although ethyl

$$\mathrm{CN{\cdot}CHR'{\cdot}CO_2Et} \xrightarrow[\mathrm{CH_2Ph{\cdot}OH}]{\mathrm{Na-}} \mathrm{CN{\cdot}CR'Na{\cdot}CO_2{\cdot}CH_2Ph} \xrightarrow[\mathrm{H_2\text{-}Pd;\ -CO_2}]{\mathrm{R{\cdot}COCl;}} \underset{\text{(V.)}}{\mathrm{R{\cdot}CO{\cdot}CHR'{\cdot}CN}}$$

sodiocyanoacetate and the corresponding benzyl ester were sparingly soluble. Subsequent hydrogenation and decarboxylation furnished (V; $R = C_9H_{19}$ and Ph, $R' = H$) in 80% yields. α-Substituted β-keto-nitriles may be prepared in a similar manner, *e.g.*, (V; $R = C_8H_{17}$, $R' = CHMe{\cdot}C_6H_{13}$; $R = C_8H_{17}$ or $C_{11}H_{23}$, $R' = Bu$).

It may be noted that the sodio-derivatives of the α-substituted keto-nitriles are more stable in boiling ethanol than are the parent β-keto-esters (cf., *inter al.*, Renfrew, *J. Amer. Chem. Soc.*, 1944, **66**, 144) since the keto-nitrile (V; $R = C_8H_{17}$, $R' = Bu$) and *n*-octyl bromide in the presence of ethanolic sodium ethoxide gave the disubstituted product (VI) in 82% yield. Hydrolysis of the substituted keto-nitrile with aqueous sulphuric acid gives the corresponding ketone, whereas attempts to obtain the derived β-keto-ester from the keto-nitrile (V; $R = C_8H_{17}$, $R' = Bu$) by means of ethanolic hydrogen chloride were unsuccessful, the corresponding amide (VII) being formed (cf. Dorsch and McElvain, *ibid.*, 1932, **54**, 2960).

(VI.) $C_8H_{17}{\cdot}CO{\cdot}CBu(C_8H_{17}){\cdot}CN$ $C_8H_{17}{\cdot}CO{\cdot}CHBu{\cdot}CO{\cdot}NH_2$ (VII.)

Experiments on the synthesis of carbonyl compounds without the use of hydrogenation are in progress.

EXPERIMENTAL.

Benzene (AnalaR) and ether were dried by sodium.

Unless otherwise specified, the techniques were as described in Part II (*loc. cit.*), catalytic debenzylation being carried out in ethyl methyl ketone by use of palladised strontium carbonate either at room temperature with subsequent decarboxylation (method A; Part II) or at the b. p. with simultaneous decarboxylation of the keto-acids (method B; see Part IV, preceding paper).

Benzyl Ethyl Malonate.—A mixture of ethyl malonate (320 g., 2 mols.), benzyl alcohol (108 g., 1 mol.), and benzene (200 ml.) was distilled slowly through a Fenske column fitted with a variable reflux-head until any water present was removed and, after slight cooling, sodium ethoxide in ethanol (20 ml. of 10%) was added. Benzene–ethanol azeotrope (b. p. 68—69°) was then distilled off until interchange was complete, and the cooled mixture was washed with dilute sulphuric acid, then water, and dried (Na_2SO_4). Fractionation through a short Fenske column *in vacuo* yielded ethyl malonate (b. p. 55—60°/1·5 mm.; 120 g.), an intermediate fraction (b. p. 60—123°/1·5 mm., 40 g.), and benzyl ethyl malonate, a colourless oil, b. p. 123—125°/1·5 mm. (mainly 124/1·5 mm.) (165 g., 74%). A residue of *ca.* 30 g. was presumably the dibenzyl ester; the use of less malonic ester gave more of the dibenzyl ester but caused no difficulty in isolation of the product.

Acylacetic Esters, $R{\cdot}CO{\cdot}CH_2{\cdot}CO_2Et$.—Benzyl ethyl malonate (0·2 mol.) was added in ether (100 ml.) to powdered sodium (0·2 mol.) under ether (200 ml.) in the usual manner and, when dissolution of the metal was complete, the acid chloride (0·1 mol.) was added dropwise with stirring. After 0·5 hour's refluxing the cooled suspension of sodio-derivative was filtered off and the residue washed with dry ether and then decomposed by shaking a suspension of it in ether with dilute sulphuric acid. The dried organic extract was evaporated and the residue hydrogenated and decarboxylated (method A). Distillation then yielded the keto-ester in 60—70% yield. In this manner, octanoyl and dodecanoyl chloride furnished ethyl 3-ketodecanoate, b. p. 82—84°/0·3 mm., and 3-ketotetradecanoate, b. p. 128—130°/0·3 mm., respectively, identical with specimens prepared previously (Part I; *J.*, 1950, 322).

Benzyl Ethyl iso*Amylmalonate.*—Potassium hydroxide (13 g.) and ethyl *iso*amylmalonate (46 g., 0·2 mol.) in ethanol (200 ml.) were left overnight and the product was then evaporated to dryness under reduced pressure. Benzyl chloride (26 g., 0·2 mol.) was added, together with sodium iodide (2 g.) and pyridine (1 ml.), the mixture was heated under reflux at 160° for 6 hours, cooled, and poured into water, and the resulting oil extracted with benzene. After being washed with sodium hydrogen carbonate solution, then water and dried, the organic extract was distilled, giving the *ester* as a colourless oil, b. p. 126—128°/0·1 mm., n_D^{20} 1·4822 (30 g., 52%) (Found: C, 70·1; H, 8·6. $C_{17}H_{24}O_4$ requires C, 69·9; H, 8·3%).

Ethyl 2-iso*Amyl*-3-*ketotetradecanoate.*—The foregoing ester (22 g., 0·075 mol.) in dry ether (100 ml.) was converted into its sodio-derivative with sodium (1·73 g.; 0·075 mol.) under ether as above, and decanoyl chloride (16·4 g., 0·074 mol.) added. After 0·5 hour's refluxing the cooled reaction mixture was washed with aqueous acid and then evaporated *in vacuo*. The product obtained after hydrogenation and decarboxylation (method A) was dissolved in light petroleum (b. p. 40—60°; 150 ml.) and washed with water and dilute aqueous potassium hydrogen carbonate. Distillation gave, after a forerun, the *keto-ester* as a colourless oil, b. p. 151—152°/0·2 mm., n_D^{20} 1·4471 (15·5 g., 60%) (Found: C, 73·7; H, 11·7. $C_{21}H_{40}O_3$ requires C, 74·1; H, 11·8%).

Benzyl Ethyl Methylmalonate.—Prepared from methylmalonic ester (155 g.; *Org. Synth.*, 1937, **17**, 56) and benzyl alcohol (48 g.) as was the unmethylated analogue, the *ester* had b. p. 134—136°/1 mm., n_D^{20} 1·4892 (75 g., 70%) (Found: C, 66·3; H, 7·0%; sap. equiv., 119. $C_{13}H_{16}O_4$ requires C, 66·1; H, 6·8%; sap. equiv., 118).

Ethyl 3-*Keto*-4-*methoxy*-2-*methyldodecanoate*.—By interaction of 2-methoxydecanoyl chloride (37 g., 0·16 mol.) and benzyl ethyl sodiomethylmalonate (0·2 mol.) as in the previous experiment and subsequent hydrogenation and decarboxylation (method A), an oil (50 g.) of b. p. 85—155°/0·3 mm. was obtained. Fractionation yielded fractions, (*A*) b. p. 50—84°/0·3 mm., (*B*) b. p. 120—130°/0·3 mm., and (*C*) b. p. 134—142°/0·3 mm.

Fraction (*A*) was a mixture of ester (22% as diethyl methylmalonate) and ketone. The former was removed by an excess of boiling ethanolic potassium hydroxide; after removal of ethanol in steam, the ketone was isolated in the usual manner. 3-*Keto*-4-*methoxydodecane* thus obtained, b. p. 81—82°/0·4 mm., n_{D}^{20} 1·4361 (Found : C, 72·5; H, 11·9. $C_{13}H_{26}O_2$ requires C, 72·9; H, 12·1%), formed a *semicarbazone*, short prisms (from aqueous methanol), m. p. 118° (Found : N, 15·3. $C_{14}H_{29}O_2N_3$ requires N, 15·5%).

Fraction (*B*) on refractionation yielded the *keto-ester*, b. p. 122—124°/0·2 mm., n_{D}^{20} 1·4430 (12 g., 26%) (Found : C, 66·7; H, 10·6. $C_{16}H_{30}O_4$ requires C, 67·1; H, 10·5%), which gave a deep red colour with aqueous-ethanolic ferric chloride. The derived *pyrazolone* formed colourless plates, m. p. 75° (Found : N, 8·55. $C_{20}H_{30}O_2N_2$ requires N, 8·48%).

Fraction (*C*) on redistillation gave *diethyl* 3-*keto*-4-*methoxydodecane*-1 : 1-*dicarboxylate*, b. p. 142—144°/0·3 mm., n_{D}^{20} 1·4478 (Found : C, 63·7; H, 9·8. $C_{19}H_{34}O_6$ requires C, 63·7; H, 9·5%).

Acylacetonitriles, $R{\cdot}CO{\cdot}CH_2{\cdot}CN$.—A mixture of benzyl alcohol (0·25 mol.) and ethyl cyanoacetate (0·25 mol.) was added in benzene (200 ml.) to "foamed" sodium ethoxide (0·25 mol.; *J*., 1950, 325) under benzene (400 ml.) and the resulting suspension distilled (oil-bath) through a Fenske column until ester interchange was complete (see Part II). The acid chloride (0·125 mol.) was then added and the mixture refluxed for 0·5 hour. If the resulting sodio-derivative was insoluble it was filtered off and treated as in the case of the unsubstituted β-keto-ester; if the sodio-derivative was soluble, the cooled mixture was shaken with ice-cold dilute sulphuric acid and after removal of solvent was hydrogenated and distilled as before.

From *n*-decanoyl chloride, by method (B), 1-*cyanoundecan*-2-*one* was obtained; it had b. p. 111—113°/0·3 mm. and solidified readily and then separated from methanol in plates, m. p. 58—58·5° (80%) (Found : C, 73·5; H, 11·0. $C_{12}H_{21}ON$ requires C, 73·8; H, 10·8%). It gave a deep red ferric reaction and formed a 2 : 4-*dinitrophenylhydrazone* which separated from ethanol in orange-yellow needles, m. p. 66° (Found : C, 57·6; H, 6·4. $C_{18}H_{25}O_4N_5$ requires C, 57·6; H, 6·7%).

Phenylacetyl chloride gave similarly (method B; 80%) 1-*cyano*-3-*phenylacetone*, b. p. 116°/0·5 mm., n_{D}^{20} 1·5370, which gave a deep red colour with aqueous-ethanolic ferric chloride (Found : C, 75·4; H, 6·0. $C_{10}H_9ON$ requires C, 75·5; H, 5·7%) and a 2 : 4-*dinitrophenylhydrazone*, yellow needles (from ethanol), m. p. 130° (Found : C, 56·1; H, 3·5. $C_{16}H_{13}O_4N_5$ requires C, 56·5; H, 3·8%).

a-Substituted β-Ketonitriles, $R{\cdot}CO{\cdot}CHR'{\cdot}CN$.—The procedure was that used in the previous experiments, except that the reactants were benzyl alcohol (1 mol.), ethyl alkylcyanoacetate (1 mol.), sodium (1 mol.), and the acid chloride (0·95 mol.); none of the products gave a ferric reaction.

5-*Cyanotetradecan*-4-*one*. Pelargonyl chloride and benzyl sodio-*n*-butylmalonate gave the *keto-nitrile*, b. p. 122—123°/0·5 mm., n_{D}^{20} 1·4526 (method A; 63%) (Found : C, 75·7; H, 11·1. $C_{15}H_{27}ON$ requires C, 75·9; H, 11·4%). It formed an *oxime*, glistening colourless needles [from light petroleum (b. p. 80—100°)], m. p. 54—54·5° (Found : N, 10·6. $C_{15}H_{28}ON_2$ requires N, 11·1%), and was hydrolysed by refluxing it (5 g.) with sulphuric acid (20N.) and propionic acid (15 ml.) for 10 hours to give tetradecan-6-one, m. p. 24° (3·5 g.) undepressed on admixture with an authentic specimen (see Part IV, *loc. cit.*).

9-*Butyl*-9-*cyano-octadecan*-10-*one*. The foregoing nitrile (5 g.) was added to a solution of sodium ethoxide (from 0·5 g. of metal) in ethanol (20 ml.), and *n*-octyl bromide (8 g.) was added. The mixture was refluxed for 4 hours whereafter most of the ethanol was removed by distillation and the cooled residue treated with cold dilute sulphuric acid. The product was isolated with benzene and distilled, giving the *ketone*, b. p. 174—176°/0·5 mm., n_{D}^{20} 1·4590 (6 g., 82%) (Found : C, 78·8; H, 12·1. $C_{23}H_{43}ON$ requires C, 78·9; H, 12·3%).

2-*Butyl*-3-*ketoundecanoamide*. A solution of 5-cyanotetradecan-4-one (5 g.) in absolute ethanol (4 ml.) was saturated with dry hydrogen chloride and set aside at room temperature for 7 days. The mixture was then poured into water, giving the *keto-amide* which was filtered off. It separated from boiling benzene in prisms, m. p. 113° (Found : C, 70·3; H, 11·1; N, 5·7. $C_{15}H_{29}O_2N$ requires C, 70·6; H, 11·4; N, 5·5%).

5-*Cyanoheptadecan*-6-*one*. From benzyl sodio-*n*-butylcyanoacetate and decanoyl chloride, the *keto-nitrile* was obtained having b. p. 146—147°/0·1 mm.; it rapidly solidified and had f. p. 34° (Found : C, 77·1; H, 11·4. $C_{18}H_{33}ON$ requires C, 77·2; H, 11·7%).

8-*Cyano*-7-*methylheptadecan*-9-*one*. This *keto-nitrile* was prepared from nonanoyl chloride and benzyl sodio-1′-methylheptylcyanoacetate (method A; 80%); it had b. p. 154—156°/0·5 mm., n_{D}^{20} 1·4550 (Found : C, 77·9; H, 11·9; N, 4·5. $C_{19}H_{35}ON$ requires C, 77·8; H, 11·9; N, 4·8%). The product was recovered unchanged after being treated with boiling ethanolic sodium ethoxide (1 mol.) for 8 hours.

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