643. *Isomerisation of Ethyl α-2 : 3 : 4 : 5-Tetrahydrobenzoylacetoacetate.*

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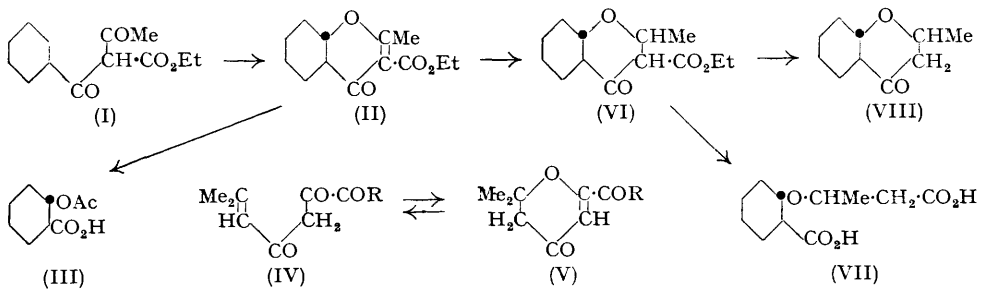
Ethyl α-2 : 3 : 4 : 5-tetrahydrobenzoylacetoacetate (I) undergoes isomerisation to give ethyl *trans*-5 : 6 : 7 : 8 : 9 : 10-hexahydro-2-methylchromone-3-carboxylate (II). The latter affords *trans*-2-acetoxy*cyclo*hexane-1-carboxylic acid on ozonolysis, thus providing proof of both its structure and configuration.

In connection with other work we have had occasion to condense 2 : 3 : 4 : 5-tetrahydrobenzoyl chloride with ethyl acetoacetate with the intention of obtaining ethyl α-2 : 3 : 4 : 5-tetrahydrobenzoylacetoacetate (I) as an intermediate. When condensation was carried out in benzene using either ethyl sodioacetoacetate or ethyl ethoxymagnesioacetoacetate the product partly crystallised. The non-crystalline portion proved to be (I) as it gave a colour with ferric chloride as well as satisfactory analytical data, and also underwent methanolysis to methyl 2 : 3 : 4 : 5-tetrahydrobenzoylacetate. The crystalline material was shown by analysis to be isomeric and, as it gave no colour with ferric chloride, was believed to be ethyl 5 : 6 : 7 : 8 : 9 : 10-hexahydro-2-methylchromone-3-carboxylate (II); this formulation was shown to be correct since ozonolysis afforded oxalic acid and 2-acetoxy-*cyclo*hexanecarboxylic acid. As the latter acid proved to be the *trans*-form (III), (II) must also have the *trans*-configuration.

The cyclisation of (I) to (II) is formally analogous with the well-established isomerisation of " mesityl oxide oxalic esters " (IV; R = OAlkyl) (Claisen, *Ber.*, 1891, **24**, 115; *Annalen*, 1896, **291**, 132; Dieckmann, *Ber.*, 1920, **53**, 1772; von Auwers and Dieckmann, *Ber.*, 1923, **56**, 1527) to derivatives of 5 : 6-dihydro-6 : 6-dimethyl-4-pyrone-2-carboxylic acid (V; R = OAlkyl), which is not, however, apparently shown by the related diethylamide (IV;

R = NEt_2) (Utzinger and Hoelle, *Helv. Chim. Acta*, 1952, **35**, 2054). It has also been shown that (IV; R = OAlkyl) and (V; R = OAlkyl) exist in equilibrium greatly favouring (V; R = OAlkyl) (Knorr and Schubert, *Ber.*, 1911, **44**, 2776) and catalysed in the forward direction by both acids and bases (Bell and Rybicka, *J.*, 1947, 24); excess of alkali alkoxide, however, gives the enol derivative of (IV; R = OBu) from (V; R = OBu) (Puetzer, Nield, and Barry, *J. Amer. Chem. Soc.*, 1945, **67**, 832). Although we have no precise evidence on this point it may well be that (I) and (II) also exist in equilibrium under suitable conditions; conversion of (I) into (II) appeared to be catalysed by hot ethanolic 0·01N-hydrochloric acid, and both acid and alkaline hydrolyses of (II) afforded acetyl*cyclo*hexene.



Catalytic hydrogenation of (II) gave ethyl *trans*-5 : 6 : 7 : 8 : 9 : 10-hexahydro-2-methylchroman-4-one-3-carboxylate (VI), which appeared from its infra-red absorption spectrum and from the slowness with which it developed a colour with ferric chloride to exist entirely in the ketonic form; this contrasts with, for example, ethyl 2-oxo-*cyclo*hexane-1-carboxylate which is extensively enolised (Dieckmann, *Ber.*, 1922, **55**, 2470) and gives evidence, corroborated by us, of a chelated conjugated carbonyl group in its infra-red spectrum (Leonard, Gutowsky, Middleton, and Petersen, *J. Amer. Chem. Soc.*, 1952, **74**, 4070). The keto-ester (VI) readily underwent "acid" rather than "ketonic" hydrolysis, to give *trans*-β-2-carboxy*cyclo*hexyloxybutyric acid (VII), although hydrolysis in the cold with dilute aqueous alkali gave some of the free β-keto-acid passing with loss of carbon dioxide at the melting point into *trans*-5 : 6 : 7 : 8 : 9 : 10-hexahydro-2-methylchroman-4-one (VIII).

Experimental

2 : 3 : 4 : 5-*Tetrahydrobenzonitrile*.—Phosphoryl chloride (338 c.c.) was added to a stirred solution of *cyclo*hexanone cyanohydrin (300 g.) in technical pyridine (1700 c.c.) at such a rate that the heat of reaction brought the mixture to the b. p. When the addition was complete, the mixture was refluxed for a further ½ hr., then cooled somewhat, and poured on ice. After extraction with benzene, the organic phase was washed twice with water and fractionated, affording 2 : 3 : 4 : 5-tetrahydrobenzonitrile (238 g., 94%), b. p. 85—90°/17 mm., n_D^{19} 1·4864. Ruzicka and Brugger (*Helv. Chim. Acta*, 1926, **9**, 399) record b. p. 81°/12 mm.

2 : 3 : 4 : 5-*Tetrahydrobenzoic Acid*.—The acid was prepared by alkaline hydrolysis of the nitrile (Boorman and Linstead, *J.*, 1935, 258, modified by Gardner and Rydon, *J.*, 1938, 48), followed by extraction with ether and distillation; it had b. p. 138—141°/18 mm., n_D^{21} 1·5010. The distillate largely solidified and the solid was freed as far as possible from adhering oil on a sintered-glass funnel. The resulting solid (crude Δ^1-isomer) was used for the preparation of the acid chloride.

2 : 3 : 4 : 5-*Tetrahydrobenzoyl Chloride*.—The tetrahydrobenzoic acid (100 g.) and thionyl chloride (66 c.c.) were mixed (endothermic reaction) and the mixture was warmed gently to keep the temperature at $\geqslant$30°. When the reaction had ceased, the mixture was rapidly fractionated (free flame); 2 : 3 : 4 : 5-tetrahydrobenzoyl chloride (112 g., 98%) passed over at 92—100°/18 mm. and had n_D^{24} 1·5100.

Ethyl* α-2 : 3 : 4 : 5-*Tetrahydrobenzoylacetoacetate (I) ***and Ethyl*** trans-5 : 6 : 7 : 8 : 9 : 10-***Hexahydro-2-methylchromone-3-carboxylate*** (II).—(*a*) Ethyl acetoacetate (19·5 g.) in dry benzene (100 c.c.) was added to alcohol-free sodium ethoxide (from 4·6 g. of sodium) and, after formation of the sodio-derivative, the last of the ethanol was removed by co-distillation with part of the benzene. Tetrahydrobenzoyl chloride (11 g.) in dry benzene (50 c.c.) was added and the mixture

was refluxed for 1·5 hr. After being shaken with 2N-hydrochloric acid (100 c.c.), the organic phase was separated and washed with water, with aqueous sodium carbonate, and again with water. Fractionation then afforded a yellow viscous oil, b. p. 124—234°/0·7 mm., which partly crystallised during several hours. The crystalline material (5·8 g.) was isolated by stirring and washing with light petroleum, and recrystallisation from the same solvent gave pure *ethyl* trans-5 : 6 : 7 : 8 : 9 : 10-*hexahydro*-2-*methylchromone*-3-*carboxylate* (II), which separated in colourless prisms, m. p. 66—67°; light absorption in EtOH: $\lambda_{max.}$ 255 mμ, log ε 4·01; $\lambda_{min.}$ 231 mμ, log ε 3·30; absorption bands (Nujol mull) in 1500—2000-cm.$^{-1}$ region at 1583, 1660, and 1720 cm.$^{-1}$ (in order of increasing strength) (Found: C, 65·4; H, 7·7. $C_{13}H_{18}O_4$ requires C, 65·5; H, 7·6%). The substance gave no colour with ferric chloride but it gave a 2 : 4-*dinitrophenylhydrazone*, which separated from ethanol–ethyl acetate in felted orange needles, m. p. 163° (Found: C, 54·5; H, 5·2; N, 13·1. $C_{19}H_{22}O_7N_4$ requires C, 54·5; H, 5·3; N, 13·4%).

The light petroleum filtrates, after removal of the above crystalline solid, were evaporated, and the residual oil (8·5 g.) was distilled, yielding *ethyl* α-2 : 3 : 4 : 5-*tetrahydrobenzoylacetoacetate* (I) as a nearly colourless oil, b. p. 120—125° (bath)/0·3 mm., n_D^{18} 1·5132; light absorption in EtOH: $\lambda_{max.}$ 244 mμ, log ε 3·95; $\lambda_{infl.}$ 264 mμ, log ε 3·80 (Found: C, 65·3; H, 7·8. $C_{13}H_{18}O_4$ requires C, 65·5; H, 7·6%). The substance gave a cherry-red colour with ferric chloride in alcoholic solution.

(*b*) Ethyl ethoxymagnesioacetoacetate * was prepared by the technique used for ethoxymagnesiomalonic ester (Lund, *Ber.*, 1934, **67**, 935) from magnesium (3·6 g.), ethanol (10 c.c.), and ethyl acetoacetate (19·5 g.) in benzene (40 c.c.) in the presence of carbon tetrachloride (1 c.c.), excess of ethanol being eventually removed by co-distillation with added benzene. Tetrahydrobenzoyl chloride (14·4 g.), dissolved in benzene, was then added slowly at 0° and reaction was completed under reflux for 1 hr. Subsequent treatment of the mixture in the manner outlined above gave ethyl *trans*-5 : 6 : 7 : 8 : 9 : 10-hexahydro-2-methylchromone-3-carboxylate (7·4 g.) and ethyl α-2 : 3 : 4 : 5-tetrahydrobenzoylacetoacetate (13 g.).

Isomerisation of Ethyl α-2 : 3 : 4 : 5-*Tetrahydrobenzoylacetoacetate* (I) *to Ethyl* trans-5 : 6 : 7 : 8 : 9 : 10-*Hexahydro*-2-*methylchromone*-3-*carboxylate* (II).—A sample of ethyl tetrahydrobenzoylacetoacetate was kept until no further separation of crystalline material took place and a portion (5 g.) of the decanted oil was refluxed for 4 hr. with ethanolic 0·01N-hydrochloric acid (50 c.c.). Removal of the solvent under reduced pressure gave a residue which partly crystallised; treatment with light petroleum as described above gave ethyl *trans*-5 : 6 : 7 : 8 : 9 : 10-hexahydro-2-methylchromone-3-carboxylate (2·35 g.), m. p. 65°, not depressed on admixture with the specimens previously obtained.

Methyl 2 : 3 : 4 : 5-*Tetrahydrobenzoylacetate*.—Ethyl tetrahydrobenzoylacetoacetate (32 g.) was added to a methanolic solution (100 c.c.) of sodium methoxide (from 3·2 g. of sodium), and the mixture was set aside at room temperature for 16 hr. The solution was acidified by being run into water simultaneously with dilute hydrochloric acid, the pH being kept at ~3·5—4·0. The product was isolated by means of ether, and fractionation gave, after a small fore-running, *methyl* 2 : 3 : 4 : 5-*tetrahydrobenzoylacetate* (14·5 g., 55%), b. p. 95°/0·4 mm., n_D^{22} 1·5009 (Found: C, 65·9; H, 7·9. $C_{10}H_{14}O_3$ requires C, 65·9; H, 7·7%). The substance gave a 2 : 4-*dinitrophenylhydrazone*, which separated from ethyl acetate–methanol in orange leaflets, m. p. 125—126° (Found: C, 52·9; H, 4·8; N, 15·1. $C_{16}H_{18}O_6N_4$ requires C, 53·0; H, 5·0; N, 15·5%), and a *phenylpyrazolone*, which crystallised from aqueous methanol in yellow needles, m. p. 120—122° (Found: C, 74·7; H, 6·7; N, 12·0. $C_{15}H_{16}ON_2$ requires C, 75·0; H, 6·7; N, 11·6%).

Ethyl trans-5 : 6 : 7 : 8 : 9 : 10-*Hexahydro*-2-*methylchroman*-4-*one*-3-*carboxylate* (VI).—Ethyl *trans*-5 : 6 : 7 : 8 : 9 : 10-hexahydro-2-methylchromone-3-carboxylate (3 g.) was hydrogenated in methanol (100 c.c.) at room temperature and atmospheric pressure in presence of palladised strontium carbonate (1 g.), one mol. of hydrogen being slowly absorbed (18 hr.). Evaporation of the filtered solution gave an oily residue which, crystallised from light petroleum, afforded pure *ethyl* trans-5 : 6 : 7 : 8 : 9 : 10-*hexahydro*-2-*methylchroman*-4-*one*-3-*carboxylate* as rosettes of fine colourless needles (2·05 g.), m. p. 67—68·5°, b. p. 85—90° (bath)/0·005 mm.; light absorption in EtOH: $\lambda_{max.}$ 262 mμ, log ε 1·71; $\lambda_{min.}$ 245 mμ, log ε 1·60; strong absorption bands (Nujol mull) in the 1500—2000-cm.$^{-1}$ region at 1700 and 1712 cm.$^{-1}$ (Found: C, 65·1; H, 8·1. $C_{13}H_{20}O_4$ requires C, 65·0; H, 8·3%). The substance gave no immediate colour with ferric chloride in alcoholic solution but a clear purple colour developed slowly. It gave a 2 : 4-*dinitrophenylhydrazone*, which separated from ethanol–ethyl acetate in orange prisms, m. p. 213—215° (Found: N, 13·0. $C_{19}H_{24}O_7N_4$ requires N, 13·3%).

* Since this reaction was carried out the method has been described as a general one for the synthesis of acylacetoacetic esters by Viscontini and Merckling (*Helv. Chim. Acta*, 1952, **35**, 2280).

Hydrolysis of Ethyl trans-5 : 6 : 7 : 8 : 9 : 10-*Hexahydro-2-methylchromone-3-carboxylate* (II).—(a) *Alkaline hydrolysis.* A solution of ethyl *trans*-5 : 6 : 7 : 8 : 9 : 10-hexahydro-2-methylchromone-3-carboxylate (5 g.) in methanolic 5% potassium hydroxide (100 c.c.) was refluxed for 1 hr. After cooling and dilution with water, extraction with ether gave an oil (1·74 g.), n_D^{16} 1·4961, shown to be acetyl*cyclo*hexene by the formation of a 2 : 4-dinitrophenylhydrazone, red needles, m. p. 194—196° not depressed on admixture with an authentic specimen.

(b) *Acid hydrolysis.* The compound (II) (1 g.) dissolved readily on warming with concentrated hydrochloric acid (5 c.c.) and was then kept at room temperature overnight. Dilution with water and extraction with ether gave an oil (0·39 g.) shown, as above, to be acetyl*cyclo*hexene.

Ozonolysis of Ethyl trans-5 : 6 : 7 : 8 : 9 : 10-*Hexahydro-2-methylchromone-3-carboxylate* (II).—The compound (II) (0·5 g.), in carbon tetrachloride (25 c.c.), was treated at 0° with a stream of ozonised oxygen for 1 hr. After removal of the solvent under reduced pressure the resultant gummy ozonide was warmed on the steam-bath with hydrogen peroxide (25 c.c. of 20-vol. solution) for ½ hr. The mixture was cooled and extracted with ether. The aqueous phase was treated with a small volume of aqueous calcium chloride; the precipitated calcium salt was collected and dissolved in a little dilute hydrochloric acid, and the solution (diluted to 5 c.c. with water) gave a positive test for oxalic acid with resorcinol and concentrated sulphuric acid (Meyer, " Nachweis und Bestimmung organischer Verbindungen," p. 131, Springer, Berlin, 1933). The ethereal solution was extracted with sodium hydrogen carbonate solution, and the acid fraction was recovered by acidification and extraction with ether. The resulting oil (190 mg.) partly solidified and gave, after two recrystallisations from ether–light petroleum, *trans*-2-acetoxy*cyclo*hexane-1-carboxylic acid (III), m. p. 101—102°, not depressed on admixture with an authentic specimen of m. p. 102—103° prepared by the method of Pascual, Sistare, and Regás (*J.*, 1949, 1943), who record m. p. 104·5—105·5° (corr.).

Hydrolysis of Ethyl trans-5 : 6 : 7 : 8 : 9 : 10-*Hexahydro-2-methylchroman-4-one-3-carboxylate* (VI).—(a) *Mild alkaline hydrolysis.* A suspension of (VI) (5 g.) in aqueous 0·5N-sodium hydroxide (100 c.c.) was shaken at room temperature overnight. The resultant clear solution was acidified (Congo-red) with dilute sulphuric acid and kept at 0° for 24 hr.; trans-5 : 6 : 7 : 8 : 9 : 10-*hexahydro-2-methylchroman-4-one-3-carboxylic acid* (2·19 g.), m. p. 139° (decomp.) then separated in rosettes of needles. Recrystallisation from chloroform–light petroleum, attended by considerable loss, raised the m. p. to 140—141° (Found : C, 61·7; H, 7·4. $C_{11}H_{16}O_4$ requires C, 62·2; H, 7·5%). The β-keto-acid gave a violet colour with ferric chloride in aqueous solution and a purple colour in methanolic solution. On heating for a minute above the m. p., it afforded trans-5 : 6 : 7 : 8 : 9 : 10-*hexahydro-2-methylchroman-4-one* (VIII) as a colourless oil, b. p. 115° (bath-temp.)/18 mm., n_D^{20} 1·4862 (Found : C, 71·2; H, 9·4. $C_{10}H_{16}O_2$ requires C, 71·4; H, 9·6%), giving a 2 : 4-*dinitrophenylhydrazone*, crystallising from methanol–ethyl acetate in yellow needles, m. p. 218° (Found : C, 55·5; H, 5·9; N, 16·0 $C_{16}H_{20}O_5N_4$ requires C, 55·1; H, 5·8; N, 16·1%).

The aqueous solution after separation of the above β-keto-acid was saturated with sodium chloride and extracted twice with ether. The combined extracts, dried and evaporated, yielded a viscous oil (2·6 g.) which slowly solidified. Crystallisation from benzene–light petroleum gave hard prisms of trans-β-2-*carboxy*cyclo*hexyloxybutyric acid* (VII) (1·6 g.), m. p. 129—130° (Found : C, 57·2; H, 8·1. $C_{11}H_{18}O_5$ requires C, 57·4; H, 7·9%).

(b) *Concentrated alkaline hydrolysis.* The compound (VI) (3 g.) was refluxed with methanolic 20% potassium hydroxide solution (50 c.c.) for 45 min., and the mixture, after cooling, was poured into an excess of dilute sulphuric acid. A precipitate appeared but quickly redissolved. After saturation with sodium chloride and extraction with ether, an acid fraction (2·4 g.) was recovered by extraction with sodium hydrogen carbonate, acidification, and re-extraction with ether. The acid slowly solidified and crystallisation from ethyl acetate–light petroleum gave *trans*-β-2-carboxy*cyclo*hexyloxybutyric acid (VII) (2·12 g., 74%), identical with that obtained above.

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