

703. *Terpene Compounds. Part VII.* The Synthesis and Reactions of 5-Keto-2-isopropylhexanoic † (γ -Acetyl- α -isopropylbutyric) Acid.*

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The synthesis of 5-keto-2-isopropylhexanoic acid,† based on a method described earlier (Bardhan, *J.*, 1940, 848), is reported. Sodium ethoxide converts the corresponding ethyl ester into the cyclic dione (II), which on treatment with phosphorus trichloride and ethyl sodiocyanoacetate, followed by hydrolysis, affords (\pm)-piperitone. The unsaturated cyano-ester (X) resulting from the action of ethyl 5-keto-2-isopropylhexanoate with ethyl cyanoacetate furnishes, on catalytic hydrogenation and hydrolysis, a crystalline modification, m. p. 87—88°, of β -methyl- α' -isopropylpimelic acid. This on ketonisation gives mainly (\pm)-isomenthone. The ester (X) and potassium cyanide give β -carboxy- β -methyl- α' -isopropylpimelic acid, m. p. 135—136°.

IN connexion with our studies in the terpene series we required appreciable quantities of 5-keto-2-isopropylhexanoic * (γ -acetyl- α -isopropylbutyric) acid (cf. I; R = H). This acid has been obtained previously (Schimmel and Co., Report, 1910, Oct., p. 97; Simonsen, *J.*, 1921, 119, 1653) by oxidation of piperitone with alkaline potassium permanganate. Obviously, this

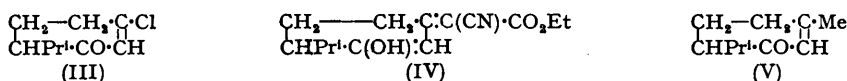
* Part VI, *J.*, 1949, 197. † Geneva nomenclature ($\text{CO}_2\text{H} = 1$) is used throughout.

method is not suitable for the preparation of even moderately large quantities and the present communication reports a more convenient route, and also some reactions of this acid.

Following earlier work (Bardhan, *J.*, 1940, 848) we treated ethyl sodioisopropylmalonate with 4-diethylaminobutan-2-one methiodide, obtaining diethyl 6-keto-2-methylheptane-3 : 3-dicarboxylate (I; R = CO₂Et) in excellent yield. On alkaline hydrolysis followed by decarboxylation, this yielded 5-keto-2-isopropylhexanoic acid as a colourless liquid which readily formed a semicarbazone, m. p. 157°. The derived ethyl ester, on treatment with

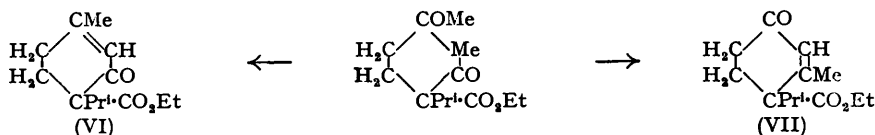


alcoholic sodium ethoxide, afforded the cyclic dione (II), m. p. 106—107°. When allowed to react with phosphorus trichloride according to the general method of Crossley and Le Sueur (*J.*, 1903, 83, 117; 1902, 81, 675, 821) (II) gave the corresponding unsaturated chloro-ketone (III) as an apparently homogeneous liquid, which was hydrogenated over palladium to 2-isopropylcyclohexanone, identified by comparison with an authentic specimen (Kötz and Michels, *Annalen*, 1906, 350, 204). The structure of (III) is, moreover, in accord with the behaviour of dihydro-1 : 1 : 2-trimethylresorcinol towards phosphorus trichloride (Crossley and Renouf, *J.*, 1911, 99, 1102).



3-Chloro-6-isopropylcyclohex-2-enone (III) and ethyl sodiocyanoacetate readily afford a crystalline acidic product, to which the enolic structure (IV) is assigned by analogy with other substances of this class (cf. Crossley and Gilling, *J.*, 1910, 97, 526). On being heated with an excess of concentrated hydrochloric acid the unsaturated cyano-ester (IV) decomposes almost quantitatively, giving an unsaturated ketone (V) the physical constants of which, as well as of several derivatives, closely corresponded with those of (±)-piperitone and its derivatives (Read and Smith, *J.*, 1922, 1871; Simonsen, *loc. cit.*). Incidentally, the formation of piperitone as the sole product of the above series of reactions provides further proof of the correctness of the structure of (III).

Walker (*J.*, 1935, 1585) has effected a simple synthesis of (±)-piperitone by condensing 2-chloroethyl methyl ketone with ethyl sodioisopropylacetoacetate and has interpreted the reaction as proceeding through the intermediate (VI). The formation of an isomeric product



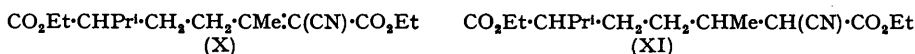
(VII) can however not be precluded, especially since in all such reactions the latter type of product is more frequently encountered. Thus, according to Barrett, Cook, and Linstead (*J.*, 1935, 1067) ethyl sodioacetoacetate and acetylcyclohexene give the keto-ester (VIII), and Mannich and Fourneau (*Ber.*, 1938, 71, 2090) have prepared (IX) by the action of sodium



ethoxide on a mixture of ethyl acetoacetate and 4-diethylaminobutan-2-one. However, we find that ethyl sodioisopropylacetoacetate and diethylaminobutanone methiodide readily yield a product hydrolysed to (±)-piperitone (V), with no trace of the isomeric ketone corresponding to (VII); this unexpected behaviour is probably due to the presence of the substituent which greatly reduces the tendency of the adjacent carbonyl group to participate in ring formation in the usual way. Further work will be necessary to clear up this point.

Ethyl 5-keto-2-isopropylhexanoate (I; R = H) readily condensed with ethyl cyanoacetate in presence of ammonium acetate-acetic acid (cf. Cope and his co-workers, *J. Amer. Chem. Soc.*, 1941, 63, 3452), to give diethyl 1-cyano-2 : 6-dimethylhept-1-ene-1 : 5-dicarboxylate (X). This on hydrogenation in alcohol over Adams's platinum oxide furnished the saturated ester

(XI) and, on hydrolysis with an excess of concentrated hydrochloric acid, (XI) yielded β -methyl- α -isopropylpimelic acid, m. p. 87—88° (hitherto reported as an oil; Kötze and Schwarz, *Annalen*, 1907, 357, 209; Kötze and Hesse, *ibid.*, 1905, 342, 306). The acid on distillation in



presence of small amounts of barium hydroxide at 310—330° afforded mainly (\pm)-isomenthone (semicarbazone, m. p. 222—223°) (cf. Hughesdon, Smith, and Read, *J.*, 1923, 123, 2922).

The unsaturated cyano-ester (X) and alcoholic potassium cyanide (Lapworth and McRea, *J.*, 1922, 121, 2752) gave a product which on hydrolysis and elimination of carbon dioxide



yielded 2 : 6-dimethylheptane-1 : 2 : 5-tricarboxylic acid (XII), m. p. 135—136°. We hope to deal with the reactions of (XII) in a later communication.

EXPERIMENTAL.

Diethyl 6-Keto-2-methylheptane-3 : 3-dicarboxylate (I; R = CO₂Et).—Ethyl isopropylmalonate (60.6 g.) was added to a solution of sodium (6.9 g.) in absolute alcohol (120 ml.) and, to the mixture, cooled in ice, 4-diethylaminobutan-2-one methiodide (from 43 g. of ketone, prepared according to Wilds and Shunk, *J. Amer. Chem. Soc.*, 1943, 65, 472, and 22.5 ml. of methyl iodide), dissolved in a little absolute alcohol, was gradually introduced. After 5 hours at 0°, the mixture was kept at room temperature overnight and then refluxed on the steam-bath for 4 hours. On cooling it was diluted with water, slightly acidified with dilute hydrochloric acid, and repeatedly extracted with benzene. The benzene layer was washed, dried, and evaporated, and the residue distilled under diminished pressure. *Diethyl 6-keto-2-methylheptane-3 : 3-dicarboxylate* (53.6 g.) formed an almost colourless oil having a characteristic odour and b. p. 140°/4 mm. (Found: C, 61.7; H, 8.8. C₁₄H₂₄O₅ requires C, 61.8; H, 8.8%). The *semicarbazone*, on recrystallisation from dilute alcohol formed minute prisms, m. p. 146° (Found: C, 54.8; H, 8.3. C₁₄H₂₇O₅N₃ requires C, 54.7; H, 8.3%).

5-Keto-2-isopropylhexanoic Acid (as I; R = H).—The foregoing ester (82.5 g.) was boiled under reflux with potassium hydroxide (44 g.) in water (36 ml.) and alcohol (186 ml.) for 1 hour, the alcohol was removed as completely as possible, the residue diluted with water and extracted with ether, and the extract discarded. The alkaline solution was acidified with dilute hydrochloric acid and again extracted with ether. After removal of the ether the residue was heated in an oil-bath at 130—140° until evolution of carbon dioxide ceased (2—3 hours). *5-Keto-2-isopropylhexanoic acid* was obtained as a colourless somewhat viscous liquid, b. p. 139—140°/5 mm. (Found: C, 62.7; H, 9.4. C₉H₁₆O₃ requires C, 62.8; H, 9.3%). The *semicarbazone* (from alcohol) had m. p. 157° (Found: C, 52.6; H, 8.3. C₁₀H₁₈O₃N₃ requires C, 52.4; H, 8.3%). The *ethyl ester*, prepared by refluxing the acid with an excess of 3% alcoholic hydrogen chloride for 6 hours, formed a colourless oil, having a characteristic sweet smell and b. p. 103—104°/3 mm. (Found: C, 65.9; H, 9.9. C₁₁H₂₀O₃ requires C, 66.0; H, 10.0%). The *semicarbazone*, separate from aqueous alcohol in shining plates, m. p. 124° (Found: C, 55.9; H, 8.9. C₁₂H₂₃O₃N₃ requires C, 56.0; H, 9.0%).

4-Isopropylcyclohexane-1 : 3-dione (II).—The foregoing hexanoate (22 g.), mixed with a solution of sodium (2.8 g.) in absolute alcohol (90 ml.), was refluxed on the steam-bath for 20 hours. On cooling it was diluted with water, excess of alcohol was removed on the steam-bath as completely as possible, and the clear alkaline solution was washed with ether, separated, and acidified with dilute sulphuric acid. The product which at first separated as an oil quickly solidified. This was collected, washed with water, and dried. The *diketone* crystallises from benzene—light petroleum (b. p. 60—80°) in colourless, compact prisms (17 g.), m. p. 106—107° (Found: C, 69.9; H, 9.3. C₉H₁₄O₂ requires C, 70.1; H, 9.1%). It has acidic character, and its solution in alcohol gives a pink colour with ferric chloride.

3-Chloro-6-isopropylcyclohex-2-enone (III).—A mixture of the diketone (II) (22.5 g.), dry chloroform (45 ml.), and phosphorus trichloride (4.5 ml.) was heated under reflux for 3 hours. The chloroform was distilled off, and the viscous residue treated with water and extracted with ether. The ethereal solution was washed with 4% sodium hydroxide solution, then with water, dried, and evaporated. *3-Chloro-6-isopropylcyclohex-2-enone* distilled constantly as a colourless, highly refractive oil (14 g.), b. p. 93°/4 mm. (Found: Cl, 20.8. C₉H₁₃OCl requires Cl, 20.6%).

The chloro-ketone (5 g.) was shaken in alcohol (30 ml.) in an atmosphere of hydrogen in the presence of gum arabic (0.1 g.), dissolved in a little water, and palladium chloride (0.1 g.) until the calculated amount of hydrogen (2 mols.) was absorbed (cf. France, Heilbron, and Hey, *J.*, 1939, 1290). The solution was filtered, and treated with an excess of semicarbazide acetate solution. After being kept overnight the crystalline precipitate, purified from dilute alcohol, m. p. 187—188° (Found: C, 60.6; H, 9.7. Calc. for C₁₀H₁₅ON₃: C, 60.9; H, 9.6%), showed no depression when mixed with the semicarbazone (m. p. 187°) of *2-isopropylcyclohexanone* (Kötze and Michels, *loc. cit.*). The regenerated ketone had b. p. 63—65°/4 mm. and proved to be *2-isopropylcyclohexanone* (Found: C, 77.1; H, 11.5. Calc. for C₉H₁₆O: C, 77.1; H, 11.4%).

Ethyl α -Cyano- α -(3-hydroxy-4-isopropylcyclohex-2-enylidene)acetate (IV).—To a solution of sodium (2.5 g.) in alcohol (dried over calcium) (34 ml.) ethyl cyanoacetate (12.4 ml.) was added, the solution cooled, and chloroisopropylcyclohexenone (III) (9.4 g.) gradually added, care being taken to avoid rise of temperature. Next morning the reaction mixture was heated on the water-bath for 6 hours, poured

into water, and extracted with ether. The aqueous alkaline liquid was then acidified with dilute sulphuric acid and repeatedly extracted with ether, and the ethereal solution washed, dried, and evaporated. The solid residual *ester*, on recrystallisation from chloroform–light petroleum (b. p. 60–80°), formed minute colourless prisms, m. p. 124° (10 g.) (Found: C, 67.3; H, 7.5. $C_{11}H_{16}O_3N$ requires C, 67.5; H, 7.7%). It is moderately soluble in most organic solvents and almost insoluble in light petroleum. It dissolves in sodium carbonate solution with effervescence and gives with ferric chloride in alcoholic solution a fine emerald-green colour.

(±)-*Piperitone* (V).—The cyano-ester (IV) (12 g.) was refluxed (sand-bath) with concentrated hydrochloric acid (120 ml.) for 6 hours. The solid gradually disappeared with evolution of carbon dioxide, and an oil separated. On cooling the liquid was diluted with water and extracted with ether, the ethereal solution washed, dried, and evaporated, and the residue distilled under diminished pressure; nearly the whole boiled at 104–106°/8 mm. The yield was 5.5 g. The semicarbazone is best prepared by boiling the ketone with aqueous-alcoholic semicarbazide acetate for 6 hours. The insoluble product which separated, on recrystallisation from acetic acid, formed minute leaflets, m. p. 226–227° (Found: C, 63.1; H, 9.1. Calc. for $C_{11}H_{16}ON_3$: C, 63.2; H, 9.1%). The mother-liquor yielded a small quantity of a more soluble semicarbazone, which on repeated crystallisation from alcohol (charcoal) afforded microscopic needles, m. p. 174–175° (Found: C, 63.3; H, 9.0. Calc. for $C_{11}H_{16}ON_3$: C, 63.2; H, 9.1%). There can be little doubt that these are identical with the α - (m. p. 226–227°) and the β -semicarbazone (m. p. 174–176°) respectively of (±)-piperitone (cf. Read and Smith, *loc. cit.*, p. 1868; Simonsen, *loc. cit.*). The ketone regenerated from the semicarbazone (m. p. 226–227°) on distillation in a vacuum formed a colourless transparent oil having b. p. 78°/4 mm., d_4^{20} 0.9295, n_D^{20} 1.4822, $[R_L]_D$ 46.63 (Calc., 45.72) (Found: C, 78.9; H, 10.5. Calc. for $C_{10}H_{16}O$: C, 78.9; H, 10.5%). Read and Smith (*loc. cit.*) give b. p. 113°/18 mm.; d_4^{20} 0.9331, n_D^{20} 1.4845, $[R_L]_D$ 46.70. The substance has a pronounced odour reminiscent of peppermint. The piperonylidene derivative, prepared according to Earl and Read (*J.*, 1926, 2075), had m. p. 128° (Found: C, 75.9; H, 7.1. Calc. for $C_{15}H_{20}O_3$: C, 76.0; H, 7.1%).

Action of Ethyl Sodiosisopropylacetoacetate on 4-Diethylaminobutan-2-one Methiodide.—A solution of ethyl isopropylacetoacetate (34.4 g.) in alcoholic sodium ethoxide (4.6 g. of sodium in 80 ml. of alcohol) was cooled in ice, and diethylaminobutanone methiodide (Mannich base, 28.1 g.; methyl iodide, 14.2 ml.) in alcohol (20 ml.) gradually added. After being kept overnight the solution was refluxed for 4 hours, cooled, diluted with water, acidified with hydrochloric acid, and extracted with ether. After removal of the solvent from the dried ethereal layer the residue on distillation afforded 32 g. of a liquid, b. p. 95–160°/12 mm. This was refluxed with acetic acid (100 ml.) and concentrated hydrochloric acid (50 ml.) for 30 hours. On cooling, the solution was diluted with water, saturated with ammonium sulphate, and extracted with ether. The ethereal solution was washed, dried, and distilled, giving (i) a colourless liquid having a characteristic ketonic odour (12.5 g.) and b. p. 104–105°/8 mm., and (ii) a somewhat viscous liquid (4 g.), b. p. 110–140°/8 mm. Fraction (i) on further purification through the semicarbazone (m. p. 226–227°) had b. p. 77–78°/3 mm., d_4^{25} 0.9290, n_D^{25} 1.4822, $[R_L]_D$ 46.66 (Found: C, 78.7; H, 10.4. Calc. for $C_{10}H_{16}O$: C, 78.9; H, 10.5%). The piperonylidene derivative, by which (±)-piperitone can be most readily characterised, had m. p. 127–128° as stated by Earl and Read (*loc. cit.*). Fraction (ii) above was not further examined.

Ethyl 1-Cyano-2:6-dimethylhept-1-ene-1:5-dicarboxylate (X).—Following Cope and his co-workers (*loc. cit.*), ethyl 5-keto-2-isopropylhexanoate (20 g.), ethyl cyanoacetate (11.3 ml.), ammonium acetate (3.8 g.), acetic acid (12 ml.), and benzene (50 ml.) were refluxed (oil-bath) at 150–160° for 4 hours. On cooling, the benzene layer was separated, washed with water, dried, and distilled. The unsaturated *ester* formed an almost colourless oil (23 g.), b. p. 175°/5 mm. (Found: C, 64.8; H, 8.5. $C_{16}H_{25}O_4N$ requires C, 65.0; H, 8.5%).

Ethyl 1-Cyano-2:6-dimethylheptane-1:5-dicarboxylate (XI).—The unsaturated ester (X) (31 g.) was shaken in alcohol (30 ml.) at the room temperature with pallidised charcoal (*Org. Synth.*, 26, 32) (1 g.) in an atmosphere of hydrogen until the required amount (2680 ml.) had been absorbed. The solution was filtered, excess of alcohol was distilled off at the water-pump, and the residue fractionated at diminished pressure to give the saturated *ester* (XI) as a colourless oil (30.5 g.), b. p. 168–170°/3 mm. (Found: C, 64.7; H, 9.3. $C_{16}H_{27}O_4N$ requires C, 64.6; H, 9.2%).

β -*Methyl- α' -isopropylpimelic* (2:6-Dimethylheptane-1:5-dicarboxylic) *Acid*.—The ester (XI) (29 g.) was heated with potassium hydroxide (16.8 g.), water (10 ml.), and alcohol (45 ml.) under reflux for 1 hour. The acidic material (24 g.), isolated in the usual way, was boiled for 10 hours with a mixture of sulphuric acid (40 ml.), acetic acid (53 ml.), and water (53 ml.), and, on cooling, the product was collected in ether. On evaporation of the solvent a dark brown oil remained which on storage in an evacuated desiccator over sulphuric acid gradually solidified to a crystalline mass (18 g.). This was esterified by heating it with alcohol (65 ml.) and sulphuric acid (5 ml.) for 6 hours. Ethyl β -methyl- α' -isopropylpimelate was obtained as a colourless liquid (17 g.), b. p. 128–129°/4 mm. (Found: C, 66.3; H, 10.4. Calc. for $C_{15}H_{23}O_4$: C, 66.2; H, 10.3%). Kötze and Schwarz (*loc. cit.*) give b. p. 151–152°/9 mm. This on hydrolysis with a 10% solution of alcoholic potassium hydroxide gave the acid as an oil which when rubbed with light petroleum (b. p. 60–80°) quickly solidified, and on repeated crystallisation from the same solvent formed aggregates of prisms, m. p. 87–88° (Found: C, 61.1; H, 9.2. Calc. for $C_{11}H_{20}O_4$: C, 61.1; H, 9.4%). The acid (2 g.) when heated with barium hydroxide (0.2 g.) at 310–330° (air-bath) yielded an oily distillate, which readily formed a semicarbazone, m. p. 222–223° (from alcohol) (Found: C, 62.3; H, 9.8. Calc. for $C_{11}H_{21}ON_3$: C, 62.56; H, 10.05%). The mother-liquor on evaporation afforded small quantity of an impure semicarbazone, which was not further examined. The ketone probably consists chiefly of (±)-isomenthone (Hughesdon, Smith, and Read, *loc. cit.*, give m. p. 225° and state that the m. p. is dependent on the rate of heating).

2:6-Dimethylheptane-1:2:5-tricarboxylic Acid (XII).—The unsaturated ester (X) (29.6 g.), dissolved in alcohol (125 ml.), was mixed with a solution of 98% potassium cyanide (11 g.) in water (25 ml.). The

solution, which became warm, was kept at the ordinary temperature for 4 days, then evaporated on the water-bath almost to dryness, concentrated hydrochloric acid (250 ml.) was added, and the whole heated under reflux (sand-bath) for 30 hours. The crude acid (25 g.) recovered from the ethereal extract was heated with absolute alcohol (50 ml.) and concentrated sulphuric acid (5 ml.) at 110–115° in a current of alcohol vapour for 6 hours. *Triethyl 2 : 6-dimethylheptane-1 : 2 : 5-tricarboxylate* thus obtained distilled constantly at 176°/4 mm. as a colourless mobile oil (Found: C, 62.9; H, 9.3. $C_{16}H_{32}O_6$ requires C, 62.8; H, 9.3%). Hydrolysis with alcoholic potassium hydroxide [4 g. in water (4 ml.) and alcohol (30 ml.)] for 1 hour yielded the corresponding *acid* as an oil which when rubbed with a little concentrated hydrochloric acid readily solidified. It crystallised from concentrated hydrochloric acid, in which it is sparingly soluble, in short prisms, m. p. 135–136° [Found: C, 55.3; H, 7.7%; equiv. (by titration), 87.0. $C_9H_{17}(CO_2H)_3$ requires C, 55.4; H, 7.7%; equiv., 86.7].

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