366. *Synthesis of* cyclo*Hexenones.*

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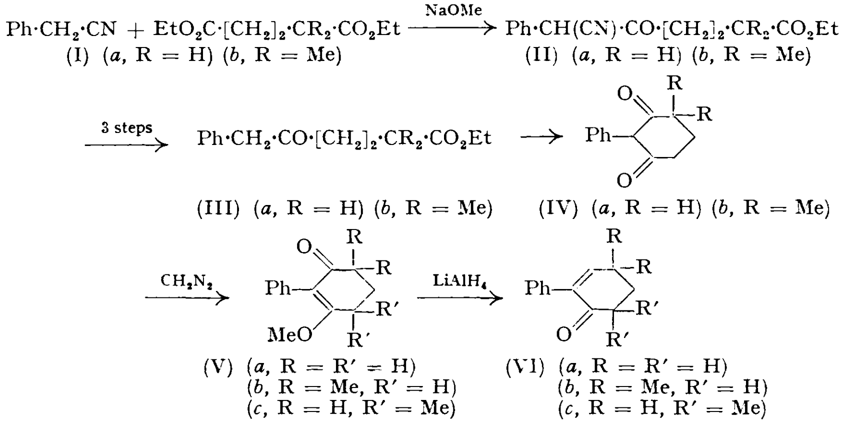
Reduction of *cyclo*hexane-1 : 3-diones with lithium aluminum hydride opens a satisfactory route to the series of *cyclo*hex-2-enones. The reaction has been utilized for the preparation of a number of intermediates of current interest.

When enol ethers of *cyclo*hexane-1 : 3-diones are reduced with lithium aluminum hydride and the reaction products decomposed under acidic conditions, *cyclo*hex-2-enones are obtained. Frank and Hall (*J. Amer. Chem. Soc.*, 1950, **72**, 1645) thus prepared 5 : 5-dimethyl- and 5-*iso*propyl-*cyclo*hex-2-enone from the enol ethyl ethers and Blanchard and Goering (*ibid.*, 1951, **73**, 5863) synthesized 5-methyl*cyclo*hex-2-enone. Seifert and Schinz (*Helv. Chim. Acta*, 1951, **34**, 728) obtained aldehydes from alkyl ethers of hydroxymethylene-*cyclo*hexanone or -*cyclo*pentanone.

We find that the enol methyl ether of *cyclo*hexane-1 : 3-dione gives, on successive reduction and acid treatment, *cyclo*hex-2-enone in 85% yield overall from the diketone, which compares very favourably with that of the methods previously reported (Paquot, *Bull. Soc. chim.*, 1941, **8**, 695; Birch, *J.*, 1944, 430; Oppenauer and Oberrauch, *Anal. Asoc. Quím. Argentina*, 1949, **37**, 246; for other references, see Bartlett and Woods, *J. Amer. Chem. Soc.*, 1940, **62**, 2933). Analogously, 2-methyl*cyclo*hexane-1 : 3-dione was converted into 2-methyl*cyclo*hex-2-enone (Butz, Davis, and Gaddis, *J. Org. Chem.*, 1947, **12**, 122) in 95% yield, and the corresponding 2-phenyl compound (VI*a*) (Ginsburg and Pappo, *J.*, 1951, 516) was obtained in 45% yield.



$\mathrm{Ph{\cdot}CH_2{\cdot}CN + EtO_2C{\cdot}[CH_2]_2{\cdot}CR_2{\cdot}CO_2Et \xrightarrow{NaOMe} Ph{\cdot}CH(CN){\cdot}CO{\cdot}[CH_2]_2{\cdot}CR_2{\cdot}CO_2Et}$

(I) (*a*, R = H) (*b*, R = Me) (II) (*a*, R = H) (*b*, R = Me)

$\mathrm{\xrightarrow{3\ steps} Ph{\cdot}CH_2{\cdot}CO{\cdot}[CH_2]_2{\cdot}CR_2{\cdot}CO_2Et \longrightarrow}$

(III) (*a*, R = H) (*b*, R = Me) (IV) (*a*, R = H) (*b*, R = Me)

$\xrightarrow{CH_2N_2}$ (V) $\xrightarrow{LiAlH_4}$ (VI)

(V) (*a*, R = R′ = H)
(*b*, R = Me, R′ = H)
(*c*, R = H, R′ = Me)

(VI) (*a*, R = R′ = H)
(*b*, R = Me, R′ = H)
(*c*, R = H, R′ = Me)

The diketone (IV*a*) was synthesized as follows. Benzyl cyanide was condensed with ethyl glutarate (I*a*) in the presence of sodium methoxide to give ethyl 6-cyano-5-keto-6-phenylhexanoate (II*a*). Hydrolysis, decarboxylation, and re-esterification afforded ethyl 5-keto-6-phenylhexanoate (III*a*), cyclized by sodium ethoxide or sodium hydride in ether to (IV*a*). The diketone with diazomethane afforded 3-methoxy-2-phenyl*cyclo*hex-2-enone (V*a*), whilst ethyl orthoformate gave the corresponding ethyl ether.

Employing benzyl cyanide and αα-dimethylglutarate (I*b*) gave 6 : 6-dimethyl-2-phenyl-*cyclo*hexane-1 : 3-dione (IV*b*) *via* (III*b*). The intermediates (II*b*) and (III*b*) might have the isomeric structures that would arise if the condensation with benzyl cyanide were to involve the quaternary ester group. The structures (II*b*) and (III*b*) appear, however, to be preferable on steric grounds, but no attempt has been made to elucidate this point, as the formula of the cyclization product (IV*b*) is the same for both reaction mechanisms. Reaction of (IV*b*) with diazomethane gave a mixture of 3-methoxy-6 : 6- (V*b*) ($\lambda_{\text{max.}}$ 268 mμ; *E* 13,700) and 3-methoxy-4 : 4-dimethyl-2-phenyl*cyclo*hex-2-enone (V*c*) ($\lambda_{\text{max.}}$ 263 mμ; *E* 12,000). (V*c*) is hydrolyzed more slowly than (V*b*) by boiling 5% aqueous sodium hydroxide (Doering and Knox, *J. Amer. Chem. Soc.*, 1951, **73**, 828) and also shows a hypsochromic shift in the ultra-violet spectrum.

Reduction of (V*b*) with lithium aluminum hydride gave 4 : 4-dimethyl-2-phenyl*cyclo*hex-2-enone (VI*b*) as an oil which was characterized as the red dinitrophenylhydrazone ($\lambda_{max.}$ 380 mμ; *E* 63,000), and reduction of (V*c*) gave 6 : 6-dimethyl-2-phenyl*cyclo*hex-2-enone (VI*c*) which afforded an orange dinitrophenylhydrazone ($\lambda_{max.}$ 375 mμ; *E* 67,000). As expected, (VI*c*) shows a hypsochromic shift in the ultra-violet spectrum (cf. the spectrum of the dinitrophenylhydrazone of 2-phenyl*cyclo*hex-2-enone for which Ginsburg and Pappo, *loc. cit.*, reported $\lambda_{max.}$ 380 mμ; *E* 25,800).

EXPERIMENTAL

Ultra-violet spectra were determined by Dr. S. Pinchas and Mr. Ch. Eger using a Beckman spectrophotometer, model DU. Ethanol was the solvent.

cyclo*Hex-2-enone*.—Dihydroresorcinol (15 g.) (*Org. Synth.*, **27**, 21) was added to an excess of ethereal diazomethane. The solution was evaporated; the residue afforded on distillation a colourless oil (15·4 g.), b. p. 73°/0·5 mm., m. p. 37° (Found: C, 66·8; H, 8·1. Calc. for $C_7H_{10}O_2$: C, 66·6; H, 8·0%).

Hydrolysis with N-hydrochloric acid at 60° for 1 hr. reversed the reaction and gave dihydroresorcinol.

The reduction with lithium aluminum hydride, carried out as usual, gave a 93% yield of material, b. p. 70°/26 mm. ($\lambda_{max.}$ 225 mμ; *E* 11,270). The dinitrophenylhydrazone melted at 167° (Bartlett, *loc. cit.*; Dimroth and Resin, *Ber.*, 1942, **75**, 322; Dimroth and Stockstrom, *Ber.*, 1942, **75**, 326) after one recrystallization from ethanol.

2-*Methyl*cyclo*hex-2-enone*.—Methylation of dihydroresorcinol (cf. Desai, *J.*, 1932, 1079; Frank and Hall, *loc. cit.*; cf. Bastron, Davis, and Butz, *J. Org. Chem.*, 1943, **8**, 515, footnote 2) has not been described in detail before. A solution of dihydroresorcinol (90 g., 0·798 mole) in absolute ethanol (453 ml.) to which sodium (21·6 g., 0·93 mole) was added was cooled in ice. Methyl iodide (161·7 g., 1·14 mole) was added and the mixture refluxed for 3·5 hr. The solvent was removed *in vacuo*, water (1·6 l.) added to the remaining red solid, and the precipitate filtered off. Recrystallization from water (norite) afforded 2-methyl*cyclo*hexane-1 : 3-dione (43 g. 43%), m. p. 210° alone or mixed with a sample prepared according to Blaise and Maire (*Bull. Soc. chim.*, 1908, **3**, 421).

2-Methyl*cyclo*hexane-1 : 3-dione (12·5 g.) was converted into the enol methyl ether with ethereal diazomethane. Distillation and recrystallization from water gave 3-*methoxy*-2-*methyl*-cyclo*hex-2-enone* (13·5 g., 96%), m. p. 46°, b. p. 90°/0·8 mm. (Found: C, 68·2; H, 8·8. $C_8H_{12}O_2$ requires C, 68·6; H, 8·6%).

Hydrolysis of the enol ether with 0·5N-hydrochloric acid gave 2-methyldihydroresorcinol.

Reduction with lithium aluminum hydride afforded 2-methyl*cyclo*hex-2-enone, b. p. 74—75°/25 mm. (99%) ($\lambda_{max.}$ 234·5 mμ; *E* 9850) (cf. Butz, Davis, and Gaddis, *loc. cit.*) (Found: C, 76·4; H, 9·5. Calc. for $C_7H_{10}O$: C, 76·3; H, 9·2%). The dinitrophenylhydrazone melted at 207—208° (*idem, loc. cit.*) after one recrystallization from methanol.

Ethyl 6-*Cyano*-5-*keto*-6-*phenylhexanoate* (II*a*).—Benzyl cyanide (11·7 g., 0·1 mole) and ethyl glutarate (28·2 g., 0·15 mole) were added to a solution of sodium (3 g.) in absolute ethanol (35 ml.) with vigorous shaking, then heated on the steam-bath for 2 hr. with frequent shaking, and left at room temperature overnight. The sodium salt of (II*a*) usually crystallized at the end of this period and could be worked up in two ways: (*a*) The sodium salt was filtered off and washed as described in *Org. Synth.*, Coll. Vol. II, John Wiley, New York, 1943, p. 487. Acidification of its aqueous solution with acetic acid gave an oil which crystallized slowly when cooled and scratched. It was recrystallized from aqueous ethanol, m. p. 65° (sinters at 55°), and proved to be the *hydrate* of (II*a*) (Found: C, 64·9; H, 6·9. $C_{15}H_{17}O_3N,H_2O$ requires C, 65·0; H, 6·8%). The mother-liquor from the sodium salt, worked up as described (*op. cit.*), afforded an additional amount of crude sodium salt.

(*b*) When larger quantities were used the reaction mixture was acidified with a slight excess of acetic acid and then diluted with water. The whole was thoroughly extracted with ether, and the extracts were washed twice with water, dried ($MgSO_4$), and evaporated. Distillation afforded a fraction, b. p. 80—90°/1 mm. (starting materials), and (II*a*), b. p. 180—200°/1 mm. (66%; 80% based on the starting materials used). When (II*a*) was boiled for a short time with water the corresponding hydrate was obtained, m. p. 65°.

5-*Keto*-6-*phenylhexanoic Acid*.—A mixture of (II*a*) (50 g.), acetic acid (330 ml.), concentrated hydrochloric acid (110 ml.), and water (100 ml.) was refluxed for 15 hr. in an atmosphere of nitrogen. The solvents were evaporated *in vacuo* and the residue was taken up in ether, washed twice with water, and extracted with aqueous potassium carbonate solution (5%). The alkaline layer was separated, washed once with ether, and acidified with dilute hydrochloric acid. An oil was obtained which crystallized after a short time. Extraction with ether and concentration gave 5-*keto*-6-*phenylhexanoic acid* as an oil which crystallized. Recrystallization from di*iso*propyl ether gave long needles, m. p. 265° (Found : C, 69·8; H, 7·2. $C_{12}H_{14}O_3$ requires C, 69·9; H, 6·8%).

By azeotropic distillation with absolute ethanol (50 ml.), anhydrous benzene (100 ml.), and toluene-*p*-sulphonic acid (1 g.), the keto-acid (20 g.) gave the *ethyl* ester (20·4 g.), b. p. 140—160°/1 mm., m. p. 43—45°. Recrystallization (needles from hexane) (Found : C, 72·2; H, 8·0. $C_{14}H_{18}O_3$ requires C, 71·8; H, 7·7%).

2-*Phenyl*cyclo*hexane*-1 : 3-*dione* (IV*a*).—(*a*) Sodium ethoxide in absolute ethanol proved unsatisfactory for the cyclization of (III*a*). The ester (III*a*) was therefore refluxed under nitrogen with two equivs. of alcohol-free sodium ethoxide in ether. A gum was precipitated immediately which became crystalline after 30 min. The mixture was refluxed for 1 more hr., cooled, acidified with dilute hydrochloric acid, and diluted with ether, and the ethereal solution was washed once with a little water. Upon evaporation of the solvent, the *diketone* (IV*a*) was obtained crystalline. Recrystallization from benzene gave plates, m. p. 160—161° (Found : C, 76·8; H, 6·4. $C_{12}H_{12}O_2$ requires C, 76·6; H, 6·4%). The dione (IV*a*) gives a violet colour with aqueous, but not with alcoholic, ferric chloride. It is fairly soluble in water and decomposes within a short time on exposure to air.

(*b*) The ester (III*a*) (23·4 g.) was added to a suspension of sodium hydride (5 g.) in ether (200 ml.), with stirring. The reaction started after a short time and intermittent cooling was necessary. When the exothermic reaction had subsided the mixture was refluxed for 6 hr., then cooled, acidified, washed with water and dried. Treatment as in (*a*) gave 13·2 g. (70%) of (IV*a*).

3-*Methoxy*-2-*phenyl*cyclo*hex*-2-*enone* (V*a*).—The diketone (IV*a*) was dissolved in methanol and allowed to react with ethereal diazomethane. Evaporation gave a crystalline residue which by recrystallization from benzene afforded short prisms of the cyclo*hexenone* (V*a*) (90%), m. p. 96—98° ($\lambda_{max.}$ 270 mμ; *E* 14,500) (Found : C, 76·9; H, 6·9. $C_{13}H_{14}O_2$ requires C, 77·2; H, 6·9%).

3-*Ethoxy*-2-*phenyl*cyclo*hex*-2-*enone*.—The diketone (IV*a*) (1·88 g.), in absolute ethanol (20 ml.) containing ethyl orthoformate (10 ml.), was refluxed for 5 hr. under nitrogen. The blue colour which was present during the reaction disappeared on cooling. Solid sodium hydrogen carbonate (0·5 g.) was added and the solvents were removed *in vacuo*. The residue was taken up in ether, washed with aqueous sodium hydroxide solution (5%) and water, and dried (Na_2SO_4). On evaporation of the solvent *in vacuo* the residue crystallized. Recrystallization from methyl*cyclo*hexane afforded the 3-*ethoxy-ketone* (1 g., 50%) as prismatic needles, m. p. 102° (Found : C, 77·6; H, 7·5. $C_{14}H_{16}O_2$ requires C, 77·8; H, 7·4%). Acidification of the alkaline washings afforded unchanged material.

The methyl and ethyl enol ethers are stable in air. They readily revert in acidic and basic solution to the corresponding diketone (IV*a*).

2-*Phenyl*cyclo*hex*-2-*enone* (VI*a*).—A suspension of the ketone (V*a*) (1 g.) in absolute ether (50 ml.) was added to a solution of lithium aluminum hydride (0·2 g.) in absolute ether (40 ml.) with cooling. The mixture was refluxed for 1 hr., then cooled with ice and decomposed as usual with dilute hydrochloric acid. Thus an oily residue was obtained which crystallized from hexane as prismatic needles, m. p. 95—96° (43 g., 50%). Mixed m. p.s of this compound and the corresponding dinitrophenylhydrazone with authentic samples (Ginsburg and Pappo, *loc. cit.*) showed no depression.

αα-*Dimethylglutaric Acid*.—This was synthesized from 4-cyano-2 : 2-dimethylbutaldehyde (Walker, *Chem. Abs.*, 1947, **41**, 1235; U.S.P. 2,409,086) by simultaneous oxidation and hydrolysis with nitric acid (Franke and Bueren, *Z. Naturforsch.*, 1950, **5*b***, 122). Walker's procedure (*loc. cit.*) for the synthesis of the aldehyde gave erratic results, the yields varying from 10 to 40%; once the (exothermic) reaction went out of control. The following modification gave reproducible results with yields of 50—60%. 50% Sodium hydroxide solution (3 ml.) was added to acrylonitrile (100 ml.), and then *iso*butaldehyde (60 g.), and the mixture was heated cautiously. When the reaction started the heating was discontinued without removing the heating mantle. When the spontaneous reaction subsided (0·5—1 hr.) the mixture was refluxed for *ca.* 1·5 hr., then cooled and neutralized with concentrated hydrochloric acid. Some filter aid was added and the solution filtered from salt and polymeric material. The residue on the filter was washed thoroughly with ether and the combined filtrates were concentrated.

Ethyl αα-Dimethylglutarate (I*b*).—The foregoing crude acid (20 g.) was refluxed in absolute ethanol (100 ml.) and anhydrous benzene (100 ml.) containing 2 ml. of concentrated sulphuric acid until no more water collected at the top of the column. Isolation by the usual procedure and distillation gave 24·3 g. (95% yield) of the desired ester (Blaise, *Bull. Soc. chim.*, 1899, **21**, 626).

Ethyl 6-*Cyano*-5-*keto*-2 : 2-*dimethyl*-6-*phenylhexanoate* (II*b*).—The condensation was carried out as in the preparation of (II*a*) (procedure *b*), with a solution of sodium (3·5 g., 0·15 mole) in absolute ethanol (41 ml.), benzyl cyanide (17·6 g., 0·1 mole), and (I*b*) (21·6 g.; 0·1 mole). Distillation gave some starting material and 21·8 g. (76%) of the *ester* (II*b*), b. p. 180—210°/1 mm. (Found : C, 71·2; H, 7·0. $C_{17}H_{21}O_3N$ requires C, 71·0; H, 7·3%).

Hydrolysis and decarboxylation of (II*b*), carried out as with (II*a*), afforded crystalline 5-*keto*-2 : 2-*dimethyl*-6-*phenylhexanoic acid*. Recrystallization from di*iso*propyl ether gave fine needles, m. p. 83—84° (Found : C, 72·1; H, 8·0. $C_{14}H_{18}O_3$ requires C, 71·8; H, 7·7%). This gave a *semicarbazone*, m. p. 179° (decomp.) (from ethanol) (Found : C, 62·2; H, 7·6; N, 14·4. $C_{15}H_{21}O_3N_3$ requires C, 61·9; H, 7·2; N, 14·4%), and a 2 : 4-*dinitrophenylhydrazone*, m. p. 168—169° (from ethanol) (Found : C, 58·2; H, 5·7; N, 13·8. $C_{20}H_{22}O_6N_4$ requires C, 58·0; H, 5·3; N, 13·5%). Its *ethyl* ester (III*b*), prepared in the same manner as (III*a*), in 80% yield, had b. p. 145°/1 mm. (Found : C, 73·3; H, 8·4. $C_{16}H_{22}O_3$ requires C, 73·3; H, 8·4%).

4 : 4-*Dimethyl*-2-*phenyl*cyclo*hexane*-1 : 3-*dione* (IV*b*).—Best results were obtained when the ester (III*b*) was refluxed for 6 hr. with 2 equivs. of sodium hydride in anhydrous toluene. The mixture was carefully acidified with dilute hydrochloric acid, which gave the diketone (IV*b*) as a colourless crystalline precipitate. It was filtered off, washed with toluene and water, and dried. The combined toluene filtrate and washings were washed with water and 5% sodium hydroxide solution. The alkaline extracts were washed with ether and then acidified with 5% hydrochloric acid. The resultant oily precipitate was taken up in ether, washed with water, and dried ($MgSO_4$). Evaporation gave an oil which partly crystallized. Recrystallization from toluene afforded a further quantity of the diketone (IV*b*). The combined crops, recrystallized from toluene, had m. p. 210° (50% yield) (Found : C, 78·1; H, 7·8. $C_{14}H_{16}O_2$ requires C, 77·8; H, 7·4%). Evaporation of the neutral fraction gave only a negligible amount of starting material. The mother-liquor from the crystallization of the acidic fraction gave an oil which was not further investigated.

The dione (IV*b*) is soluble in dilute sodium carbonate solution and slightly soluble in aqueous sodium hydrogen carbonate It does not give a colour reaction with ferric chloride in alcohol or water.

3-*Methoxy*-6 : 6-*dimethyl*-2-*phenyl*cyclo*hex*-2-*enone* (V*b*) *and* 3-*Methoxy*-4 : 4-*dimethyl*-2-*phenyl*cyclo*hex*-2-*enone* (V*c*).—The diketone (IV*b*) was dissolved in methanol and allowed to react with ethereal diazomethane. The partly crystalline residue obtained on evaporation was recrystallized from hexane and then from methyl*cyclo*hexane. Thus, the *ketone* (V*b*) was obtained as stout prisms, m. p. 134—135° (60%) ($\lambda_{max.}$ 268 mμ; *E* 13,700) (Found : C, 78·3; H, 8·0. $C_{15}H_{18}O_2$ requires C, 78·3; H, 7·8%). The mother-liquor yielded, on evaporative distillation (120°/0·1 mm.), a mobile oil which crystallized at 0°. Recrystallization from hexane gave the *isomer* (V*c*), m. p. 37° ($\lambda_{max.}$ 263 mμ; *E* 12,000) (Found : C, 78·4; H, 8·0%).

The ketone (V*b*) is hydrolyzed more slowly than (V*c*) by boiling 5% aqueous sodium hydroxide.

4 : 4-*Dimethyl*-2-*phenyl*cyclo*hex*-2-*enone* (VI*b*).—Reduction of the ketone (V*b*), suspended in ether, with lithium aluminum hydride, as described above, gave an oil which afforded a 30% yield of the red 2 : 4-*dinitrophenylhydrazone*, m. p. 172—174° (from ethanol–ethyl acetate), of (VI*b*) (Found : C, 63·1; H, 5·3. $C_{20}H_{20}O_4N_4$ requires C, 63·2; H, 5·3%).

The low yields obtained in the reduction of (V*a*) and (V*b*) may well be due to the insolubility of those compounds in ether.

6 : 6-*Dimethyl*-2-*phenyl*cyclo*hex*-2-*enone* (VI*c*).—The ketone (V*c*) was more soluble in ether than either (V*a*) or (V*b*) and could, therefore, be reduced with lithium aluminum hydride *in solution*. The oily product was obtained in quantitative yield and afforded the orange 2 : 4-*dinitrophenylhydrazone*, m. p. 161—162° (from ethanol–ethyl acetate), of (VI*c*) in quantitative yield (Found : C, 63·3; H, 5·2%).

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