354. *Synthesis of Polycyclic Compounds. Part V.* The Cyclodehydration of 3-Benzylcyclohexanol.*

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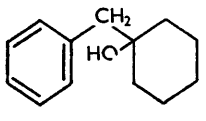
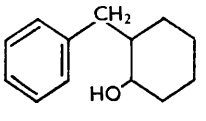
3-Benzyl*cyclo*hexanol, the preparation of which is described, on dehydration with phosphoric anhydride furnishes 4 : 8-*endo*methylenebenzo*cyclo*octene (III), yielding on oxidation with chromic acid the 3-ketone (IV). This has been synthesised by the cyclisation of 3-phenyl*cyclo*hexanecarboxylic acid, which has been prepared by two methods. The ketone, on Clemmensen reduction, gives the tricyclic hydrocarbon (III), and, consequently, the structure assigned to it by Cook and Hewett [1] is confirmed.

COOK and HEWETT [1] have shown that the dehydration of the alcohols (I) and (II) gives a tricyclic hydrocarbon which they represented as (III). This structure is in harmony with the resistance of the hydrocarbon to dehydrogenation, its conversion into phthalic acid, and its oxidation by chromic acid to the ketone (IV; R = H), which was further degraded to *cis*-hexahydro*iso*phthalic acid through the related phenol (IV; R = OH). However, the structures assigned to the hydrocarbon (III) and the ketone (IV; R = H) have not been confirmed by an alternative synthesis.



(I)



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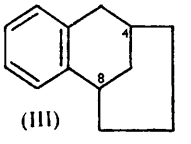
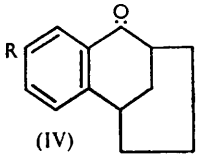
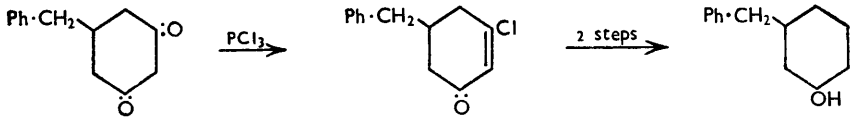


(III)



(IV)

To extend this cyclisation, we have prepared 3-benzyl*cyclo*hexanol, by reactions shown in the annexed scheme. Curiously, on treatment with phosphoric anhydride this alcohol



gave the hydrocarbon (III); the yield was low but oxidation with chromic acid afforded the ketone (IV; R = H) which was readily characterised.

We have established the structure of the ketone (IV; R = H) by the following unequivocal synthesis. α-Phenylglutaric anhydride [2] was converted into the derived ethyl ester, and the latter condensed with ethyl oxalate in the presence of potassium ethoxide;

(V) $CO_2Et{\cdot}CHPh{\cdot}CH_2{\cdot}CH(CO_2Et)_2$ $CO_2Et{\cdot}CHPh{\cdot}CH_2{\cdot}C(CO_2Et)_2{\cdot}[CH_2]_2{\cdot}CO_2Et$ (VI)

(VII) $CO_2Et{\cdot}CHPh{\cdot}CH_2{\cdot}CH(CO_2Et){\cdot}[CH_2]_2{\cdot}CO_2Et$

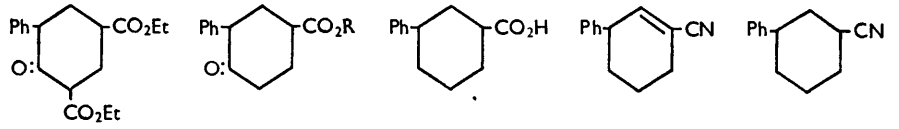
the resultant product on distillation gave a good yield of ethyl α-ethoxycarbonyl-α′-phenylglutarate (V). The sodio-derivative of this with ethyl β-chloropropionate gave ethyl

* Part IV, *J.*, 1956, 1346.

[1] Cook and Hewett, *J.*, 1936, 67.

[2] *Org. Synth.*, 1950, **30**, 817; Hornig and Finelli, *J. Amer. Chem. Soc.*, 1949, **71**, 3204.

γγ-diethoxycarbonyl-α-phenylpimelate (VI), which on hydrolysis, elimination of carbon dioxide, and re-esterification afforded ethyl γ-ethoxycarbonyl-α-phenylpimelate (VII). Cyclisation with finely divided potassium then gave diethyl 4-oxo-5-phenyl*cyclo*hexane-1 : 3-dicarboxylate (VIII), hydrolysed by hydrochloric–acetic acid to the oily keto-acid (IX; R = H) which gave a crystalline semicarbazone. The corresponding ethyl ester on Clemmensen–Martin[3] reduction furnished 3-phenyl*cyclo*hexanecarboxylic acid (X) as a viscous liquid, apparently a mixture of *cis*- and *trans*-isomerides. However, a crystalline acid (X) was obtained by treatment of 3-phenyl*cyclo*hexanone with anhydrous hydrogen



(VIII) (IX) (X) (XI) (XII)

cyanide[4] followed by dehydration of the product with phosphoryl chloride and pyridine to the unsaturated nitrile (XI, and an isomeride); this was hydrogenated over palladised charcoal[5] to the saturated nitrile (XII) which on hydrolysis gave 3-phenyl*cyclo*hexanecarboxylic acid (X), m. p. 81°. From its method of formation the acid is tentatively regarded as having the *cis*-form.

Cyclisation of the crystalline acid (X) with polyphosphoric acid,[6] or by a Friedel–Crafts reaction, gave smoothly an excellent yield of the tricyclic ketone (IV; R = H) which had properties and derivatives in close agreement with those previously recorded.[1] Under similar conditions the impure liquid 3-phenyl*cyclo*hexanecarboxylic acid also afforded the ketone (IV; R = H) in about the same yield. Finally, the synthetic ketone was reduced by the Clemmensen procedure to the hydrocarbon (III), the structure of which is, therefore, fully established.

Experimental

4-Phenylbut-3-enoic acid[7] (m. p. 87°) was prepared by Döbner condensation of phenylacetaldehyde (b. p. 88°/18 mm.) with malonic acid. Its ethyl ester had b. p. 137—138°/5 mm.

*5-Benzyl*cyclo*hexane-1 : 3-dione.*[7b]—For large quantities the following modified procedure was convenient. To a solution of ethyl sodioacetoacetate [from sodium (6·5 g.), ethanol (107 ml.), and ethyl acetoacetate (40 ml.)], ethyl 4-phenylbut-3-enoate (55 g.) was added and the mixture heated on the water-bath for 10 hr. The sodio-derivative of the condensation product, which crystallised, was mixed with water (125 ml.), treated with potassium hydroxide (35 g.) in water (35 ml.), made up to 450 ml. with the addition of more water, and boiled for 15 min. On cooling, the solution was acidified with hydrochloric acid, and heated as before for 30 min. 5-Benzyl*cyclo*hexane-1 : 3-dione which separated on cooling is best purified from ethyl acetate–light petroleum (b. p. 60—80°) and forms colourless needles, m. p. 117° (lit.,[7b] 118°) (Found: C, 77·1; H, 7·1. Calc. for $C_{13}H_{14}O_2$: C, 77·2; H, 7·0%).

*5-Benzyl-3-chloro*cyclo*hex-2-enone.*—The above diketone (33·2 g.) was refluxed with phosphorus trichloride (7·3 ml.) and chloroform (82 ml.) for 4 hr. After removal of the chloroform, the residue was decomposed with cold water and extracted with ether. After being washed and dried in the usual way the ethereal solution was distilled. *5-Benzyl-3-chloro*cyclo*hex-2-enone* formed a colourless liquid (19·5 g.), b. p. 176—178°/5 mm. (Found: Cl, 16·4. $C_{13}H_{13}OCl$ requires Cl, 16·1%).

*3-Benzyl*cyclo*hexanone.*—The preceding compound (18·0 g) was hydrogenated in ethanol (30 ml.) in the presence of gum arabic (0·1 g.), water (5 ml.), and palladium chloride (0·1 g.). Absorption of hydrogen was complete in 1 hr. The *ketone* (14·5 g.), b. p. 142—144°/5 mm. (Found: C, 82·9; H, 8·6. $C_{13}H_{16}O$ requires C, 83·0; H, 8·5%), gave a *semicarbazone*,

[3] Martin, *J. Amer. Chem. Soc.*, 1936, **58**, 1438.
[4] Wade and Panting, *J.*, 1898, **73**, 256.
[5] Hartung, *J. Amer. Chem. Soc.*, 1928, **50**, 3372.
[6] Birch, Jaeger, and Robinson, *J.*, 1945, 582; Snyder and Werber, *J. Amer. Chem. Soc.*, 1950, **72**, 2962, 2965; Birch and Smith, *J.*, 1951, 1885.
[7] (*a*) Vorlander, *Annalen*, 1906, **345**, 244; (*b*) Linstead and Williams, *J.*, 1926, 2741.

prisms (from ethanol), m. p. 168° (Found: C, 68·5; H, 7·9. $C_{14}H_{19}ON_3$ requires C, 68·6; H, 7·8%).

3-*Benzyl*cyclo*hexanol*.—The foregoing ketone (5 g.) in absolute ethanol (50 ml.) was treated on a water-bath with sodium (5 g.) as rapidly as possible, the mixture being heated until no more sodium remained. The excess of ethanol was removed in steam and, after cooling, the residual liquid was extracted with ether, and the extract washed, dried (K_2CO_3), and distilled. 3-*Benzyl*cyclo*hexanol* formed a viscous oil (3·5 g.), b. p. 148—149°/ 5 mm. (Found: C, 82·3; H, 9·5. $C_{13}H_{18}O$ requires C, 82·1; H, 9·4%).

4 : 8-endo*Methylenebenzo*cyclo*octene* (III).—The foregoing alcohol (3·8 g.) was heated with phosphoric anhydride (7·6 g.) at 145—150° for 1 hr. and then slowly distilled in a vacuum, giving an almost colourless oil (1·5 g.). This was dissolved in ether, washed with a little concentrated sulphuric acid, then with water, dried, and recovered by evaporation. On repeated distillation over sodium the hydrocarbon formed a colourless mobile liquid (1·1 g.), b. p. 100°/5 mm., $n_D^{20\cdot5}$ 1·5430 (lit.,[1] $n_D^{12\cdot8}$ 1·5523) (Found: C, 90·1; H, 9·1. Calc. for $C_{13}H_{16}$: C, 90·6; H, 9·4%). It was saturated towards the usual reagents. On oxidation with chromic acid in purified acetic acid it gave the ketone (IV), b. p. 129—132°/5 mm., whose semicarbazone had m. p. and mixed m. p. 222—223° (lit.,[1] 222—224°) (Found: N, 17·2. Calc. for $C_{14}H_{17}ON_3$: N, 17·3%).

Ethyl α-*Phenylglutarate*.—Ethyl α-cyano-α-phenylacetate (b. p. 135—138°/5 mm.), prepared by the action of sodium on a solution of benzyl cyanide and ethyl carbonate in dry ether, was converted into the anhydride (b. p. 192—195°/5 mm., m. p. 94—95°) by known methods.[2] The anhydride (21 g.) was refluxed with absolute ethanol (40 ml.), concentrated sulphuric acid (3 ml.), and benzene (42 ml.) for 5 hr. The *ethyl ester* was an oil (24 g.), b. p. 152—153°/5 mm. (Found: C, 68·4; H, 7·7. $C_{15}H_{20}O_4$ requires C, 68·2; H, 7·6%).

Ethyl α-*Ethoxycarbonyl*-α′-*phenylglutarate* (V).—Ethyl oxalate (9·4 g.) was added to a suspension of potassium ethoxide in ether [prepared from powdered potassium (2·5 g.), calcium-dried ethanol (2·96 g.), and ether (70 ml.)]. The clear solution was cooled in ice and treated drop-wise with ethyl α-phenylglutarate (17·2 g.) in a little ether. The dark brown solution was kept at room temperature for 2 days, then diluted with ice water, the aqueous solution was separated and acidified with dilute sulphuric acid, and the oil was extracted with ether. The ethereal solution was washed with a little water, dried, and evaporated. The residual oil was heated at 180—190° for 10 hr. and then distilled, giving the *triethyl ester* (V) (15 g.), b. p. 183—185°/4 mm. (Found: C, 64·1; H, 7·3. $C_{18}H_{24}O_6$ requires C, 64·3; H, 7·1%). It gave no colour with ferric chloride.

Ethyl γγ-*Diethoxycarbonyl*-α-*phenylpimelate* (VI).—To a cooled solution of sodium (2 g.) in ethanol (36 ml.), ethyl α-ethoxycarbonyl-α′-phenylglutarate (30 g.) was added, followed, after cooling, by ethyl β-chloropropionate (12·3 g.). Next morning the mixture was heated on the water-bath for 6 hr. The excess of ethanol was removed, water was added to the residue, and the oil extracted with ether and fractionated. The *ester* (VI) formed a pale yellow liquid (12·2 g.), b. p. 210—212°/4 mm. (Found: C, 63·1; H, 7·2. $C_{23}H_{32}O_8$ requires C, 63·3; H, 7·3%).

Ethyl γ-*Ethoxycarbonyl*-α-*phenylpimelate* (VIII).—The preceding ester (72 g.) was refluxed for 1·5 hr. with potassium hydroxide (50 g.) in water (50 ml.) and ethanol (200 ml.). The crude acid, isolated in the usual way, was heated at 170—180° until no more carbon dioxide was evolved (3 hr.). The product (45 g.) was esterified by absolute ethanol (70 ml.) and concentrated sulphuric acid (7 ml.), in a current of ethanol vapour, at 110—115° for 6 hr. The *triethyl ester* (VII) formed an almost colourless liquid (42 g.), b. p. 192—194°/ 5 mm. (Found: C, 65·8; H, 7·6. $C_{20}H_{28}O_6$ requires C, 66·0; H, 7·7%).

Diethyl 4-*Oxo*-5-*phenyl*cyclo*hexane*-1 : 3-*dicarboxylate* (VIII).—The above tricarboxylic ester (18·2 g.) was added to a suspension of finely divided potassium (2·4 g.) in benzene (40 ml.), cooled in ice. As soon as the vigorous reaction was over, the mixture was heated on the water-bath until the last traces of potassium were dissolved. The product was worked up as usual, giving the *keto-ester* (9·5 g.), b. p. 205—206°/5 mm. (Found: C, 67·6; H, 6·9. $C_{18}H_{22}O_5$ requires C, 67·9; H, 6·9%). An ethanolic solution of the ester gave a violet colour with ferric chloride.

Ethyl 4-*Oxo*-5-*phenyl*cyclo*hexanecarboxylate* (IX; R = Et).—The preceding keto-ester (5·2 g.) was refluxed for 10 hr. with concentrated hydrochloric acid (10 ml.) and glacial acetic acid (20 ml.). The keto-acid (IX; R = H) (3 g.), isolated in the usual way, was an oil. Its *semicarbazone* formed colourless prisms (from ethanol; charcoal), m. p. 225° (decomp.) (Found: C, 61·4; H, 6·2. $C_{14}H_{17}O_3N_3$ requires C, 61·1; H, 6·1%). The *ethyl ester* (IX; R = Et), prepared from the acid (14·4 g.) and ethanolic hydrogen chloride (48 ml.; 3%), was a

liquid (12·2 g.), b. p. 183—184°/ 5 mm. (Found : C, 73·1; H, 7·4. $C_{15}H_{18}O_3$ requires C, 73·2; H, 7·3%). A semicarbazone could not be obtained under the usual conditions.

Ethyl 3-*Phenyl*cyclo*hexanecarboxylate*.—The keto-ester (IX; R = Et) (10 g) was refluxed for 30 hr. with amalgamated zinc (20 g.), concentrated hydrochloric acid (70 ml.), water (30 ml.), acetic acid (2 ml.), and toluene (40 ml.). The product (6 g.) obtained on evaporation of the combined toluene layer and ether-extracts of the aqueous layer was hydrolysed with 10% ethanolic potassium hydroxide in the usual way. The oily acid isolated as usual was converted into the *ethyl ester* (4·5 g.), b. p. 145—146°/ 5 mm. (Found : C, 77·3; H, 8·5. $C_{15}H_{20}O_2$ requires C, 77·6; H, 8·6%). This on hydrolysis with alkali yielded the acid as an oil.

1-*Cyano*-3-*phenyl*cyclo*hexene* (XI). 3-Phenyl*cyclo*hexanone [8] (b. p. 138—139°/5 mm.) (5 g.) was added to hydrogen cyanide [4] (from potassium cyanide, 10 g.), and cooled to 0°. After the addition of a drop of potassium cyanide solution the mixture was kept at this temperature overnight; a drop of sulphuric acid was then added, and the excess of hydrogen cyanide removed at the water-pump. The crude product was heated with phosphoryl chloride (23 ml.), and dry pyridine (85 ml.) at 140—150° for 1 hr., then cooled, treated with ice, and poured into dilute hydrochloric acid, and the unsaturated nitrile was extracted with ether. The ethereal extract was washed with dilute sulphuric acid, then aqueous sodium hydroxide, and dried, and the solvent was removed. The residue gave the unsaturated *nitrile* (3·5 g.), b. p. 150—152°/5 mm., having a characteristic smell (Found : C, 85·5; H, 7·3. $C_{13}H_{13}N$ requires C, 85·2; H, 7·1%).

1-*Cyano*-3-*phenyl*cyclo*hexane* (XII).—The above-mentioned unsaturated nitrile (6 g.), ethanol (5 ml.), and palladised charcoal [5] (1 g.; 10%) were shaken in hydrogen until the calculated amount of hydrogen (830 ml.; 30°/760 mm.) was absorbed (1 hr.). The catalyst was filtered off, excess of ethanol removed, and the residual liquid distilled. The *nitrile* (5·7 g.) had b. p. 145—146°/5 mm. (Found : C, 84·1; H, 8·3. $C_{13}H_{15}N$ requires C, 84·3; H, 8·1%).

3-*Phenyl*cyclo*hexanecarboxylic Acid* (X).—The foregoing nitrile (5 g.) was refluxed with potassium hydroxide (4 g.), water (4 ml.), and ethanol (15 ml.), until no more ammonia was evolved (40 hr.). The *acid* which separated on acidification was collected and formed needles, m. p. 81°, from dilute acetic acid (charcoal) (Found : C, 76·5; H, 7·9. $C_{13}H_{16}O_2$ requires C, 76·5; H, 7·8%).

4 : 8-endo*Methylenebenzo*cyclo*octen*-3-*one* (IV; R = H).—(*a*) The preceding acid (1 g.) was heated on the water-bath with phosphoric anhydride (6 g.) and phosphoric acid [6] (6 ml.; 85%) for 1·5 hr. After cooling, ice and water were added, the product was extracted with ether, the ethereal solution washed with a dilute solution of ammonia and with water and dried, and the solvent removed. The residual oil (0·7 g.) readily formed a semicarbazone, which separated in needles, m. p. 222—223° (lit.,[1] 222—224°) from ethanol (Found : C, 69·3; H, 7·3. Calc. for $C_{14}H_{17}ON_3$: C, 69·1; H, 7·0%). The pure ketone regenerated from the semicarbazone (4 g.), on distillation in an all-glass apparatus, formed a colourless oil (2·5 g.), b. p. 130°/5 mm., $d_4^{30\cdot5}$ 1·10659, $n_D^{30\cdot5}$ 1·5726, $[R_L]_D$ 55·35 (Calc., 54·24) (lit.,[1] $d_4^{19\cdot5}$ 1·11385, $n_D^{19\cdot9}$ 1·5770, $[R_L]_D$ 55·38) (Found : C, 83·6; H, 7·6. Calc. for $C_{13}H_{14}O$: C, 83·8; H, 7·6%). The oxime, by which the ketone can be readily characterised, crystallised from ethanol in needles, m. p. 122—123° (lit.,[1] 123—124°) (Found : C, 77·7; H, 7·4. Calc. for $C_{13}H_{15}ON$: C, 77·6; H, 7·5%). (*b*) The acid (X) (4·5 g.) was gently heated with thionyl chloride (3 ml.), excess of the reagent removed under reduced pressure, and the residue dissolved in carbon disulphide (20 ml.). The solution was cooled in ice, powdered anhydrous aluminium chloride (4 g.) was added all at once, and the mixture left overnight at room temperature. The product was decomposed with ice and dilute hydrochloric acid; the carbon disulphide solution yielded the ketone (2·5 g.), b. p. 129—130°/5 mm. which formed a semicarbazone, m. p. 222—223°, and an oxime, m. p. 122—123°, identical with those described above.

4 : 8-endo*Methylenebenzo*cyclo*octene* (III).—The foregoing ketone (2·3 g.) was reduced with amalgamated zinc (10 g.), and hydrochloric acid (20 ml.) during 10 hr. The pure hydrocarbon, on distillation over sodium, formed a colourless liquid (1·2 g.), b. p. 99°/5 mm., $d_4^{30\cdot5}$ 1·0075, $n_D^{30\cdot5}$ 1·5535, $[R_L]_D$ 54·65 (Calc., 54·23) (lit.,[1] d_4^{14} 1·020, n_D^{14} 1·5580, $[R_L]_D$ 54·47) (Found : C, 90·5; H, 9·3%).

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[8] Crossley and Renouf, *J.*, 1915, **107**, 608; Boyd, Clifford, and Probert, *ibid.*, 1920, **117**, 1382; France, Heilbron, and Hey, *ibid.*, 1939, **155**, 1288.