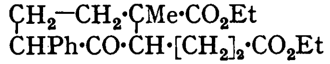
162. *Studies in the Sterol–Oestrone Group. Part II. Derivatives of 2-Phenyl*cyclo*hexanone.*

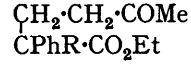
By J. C. BARDHAN.

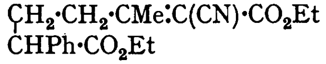
Ethyl 5-*carbethoxy*-2-*phenyl*-5-*methyl*cyclo*hexanone*-6-β-*propionate*, synthesised from γ-acetyl-α-phenylbutyric acid, might serve as an intermediate in the projected synthesis of oestrogenic ketones.

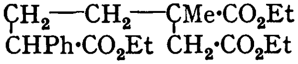
HYDROPHENANTHRENE derivatives related to *O*-methylhomo-oestric acid (Bardhan, J., 1936, 1949; Litvan and Robinson, J., 1938, 1919) are peculiarly difficult to prepare. Their formation from 2-phenyl*cyclo*hexanone has been envisaged by Cook and co-workers (J., 1936, 73; 1939, 168). It seemed probable, therefore, that *ethyl 5-carbethoxy-2-phenyl-5-methyl*cyclo*hexanone-6-β-propionate* (I) might be a valuable material for the synthesis of *O*-methylhomo-oestric acid and its relatives. It was prepared from γ-acetyl-α-phenylbutyric acid by an extension of the synthesis whereby closely related alicyclic compounds have been obtained from mesitonic acid (Bardhan and Ganguly, J., 1936, 1852) and γ-acetyl-ββ-dimethylbutyric acid (unpublished work by Mr. R. Chakravarti).

Ethyl α-carbethoxy-γ-acetyl-α-phenylbutyrate (II, R = CO_2Et), prepared by pairing ethyl sodiophenylmalonate with the methiodide of δ-diethylaminobutan-β-one (compare du Feu, McQuillin, and Robinson, J., 1937, 53), on hydrolysis and elimination of carbon dioxide yielded *γ-acetyl-α-phenylbutyric acid* (as II; R = H), the ethyl ester of which condensed with ethyl cyanoacetate in presence of piperidine and anhydrous sodium sulphate (Bardhan and Ganguly, *loc. cit.*, p. 1853) to give *ethyl α-cyano-ε-phenyl-β-methyl-Δ^{α}-pentene-αε-dicarboxylate* (III). This was allowed to react with potassium cyanide (compare Lapworth and McRea, J., 1922, **121**, 2752), the product hydrolysed, and the crude acid converted into *ethyl α-phenyl-δ-methylpentane-αδε-tricarboxylate* (IV). The triethyl ester was subjected to the Dieckmann reaction, and the product allowed to react with ethyl β-chloropropionate; hydrolysis and subsequent esterification gave ethyl 5-carbethoxy-2-phenyl-5-methyl*cyclo*hexanone-6-β-propionate (I).

(I.)

$$\begin{array}{l} CH_2{-}CH_2{\cdot}CMe{\cdot}CO_2Et \\ CHPh{\cdot}CO{\cdot}CH{\cdot}[CH_2]_2{\cdot}CO_2Et \end{array}$$

(II.)

$$\begin{array}{l} CH_2{\cdot}CH_2{\cdot}COMe \\ CPhR{\cdot}CO_2Et \end{array}$$

(III.)

$$\begin{array}{l} CH_2{\cdot}CH_2{\cdot}CMe{:}C(CN){\cdot}CO_2Et \\ CHPh{\cdot}CO_2Et \end{array}$$

(IV.)

$$\begin{array}{lll} CH_2 & {-}CH_2{-} & CMe{\cdot}CO_2Et \\ CHPh{\cdot}CO_2Et & & CH_2{\cdot}CO_2Et \end{array}$$

The preparation of the methoxy-derivatives required for the synthesis of *O*-methylhomo-oestric acid is well in hand and several methods are under consideration for the construction of the central nucleus of the hydrophenanthrene system.

EXPERIMENTAL.

Ethyl α-Carbethoxy-γ-acetyl-α-phenylbutyrate (II; R = CO_2Et).—A solution of ethyl sodiophenylmalonate prepared from sodium (3·1 g.), absolute alcohol (53 c.c.), and ethyl phenylmalonate (31·5 g.) was cooled in ice and gradually mixed with diethylaminobutanone methiodide (from 19·1 g. of δ-diethylaminobutan-β-one and 10 c.c. of methyl iodide) (du Feu, McQuillin, and Robinson, *loc. cit.*, p. 56) dissolved in a little absolute alcohol. The mixture was kept cold overnight and then refluxed on the steam-bath for 4 hours, cooled, faintly acidified with dilute hydrochloric acid, and extracted with ether. After removal of the solvent from the dried ethereal layer the residue was fractionated under reduced pressure. *Ethyl α-carbethoxy-γ-acetyl-α-phenylbutyrate* formed an almost colourless liquid, b. p. 182°/6 mm. (Found: C, 66·6; H, 7·3. $C_{17}H_{22}O_5$ requires C, 66·7; H, 7·2%). Yield 70%.

The yield of the condensation product is much improved when ethyl phenylmalonate is replaced by ethyl phenylcyanoacetate in the above experiment. *Ethyl α-cyano-γ-acetyl-α-phenylbutyrate* (II; R = CN) had b. p. 186°/6 mm. (Found: C, 69·6; H, 6·5. $C_{15}H_{17}O_3N$ requires C, 69·5; H, 6·5%).

*γ-Acetyl-α-phenylbutyric Acid** (as II; R = H).—The ester (II; R = CO_2Et) (75 g.) was boiled under reflux with a solution of potassium hydroxide (40 g.) in water (20 c.c.) and alcohol (180 c.c.) for 1 hour, the alcohol removed as completely as possible, and the residue diluted with water and extracted with ether to remove neutral impurities. The alkaline solution was acidified with dilute hydrochloric acid and again extracted with ether. After removal of the solvent the residue was heated at 130—140° until the evolution of carbon dioxide ceased (2—3 hours). *γ-Acetyl-α-phenylbutyric acid* thus obtained distilled almost wholly at 180°/4 mm. (185°/6 mm.) as a colourless oil (Found: C, 69·7; H, 6·7. $C_{12}H_{14}O_3$ requires C, 69·9; H, 6·8%). It was also obtained when the esters (II; R = CN and CO_2Et) were hydrolysed with an

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* Subsequent to the completion of these experiments some of the compounds mentioned in this paper were described by Banerjee (*Science and Culture*, 1940, **5**, 565).

excess of boiling concentrated hydrochloric acid. The *semicarbazone* had m. p. 161—162° (Found : C, 59·3 ; H, 6·6. $C_{13}H_{17}O_3N_3$ requires C, 59·3 ; H, 6·5%). The *methyl* ester, prepared from the acid by the alcohol–hydrogen chloride method, was a colourless liquid, b.p. 149°/5 mm., having a characteristic odour (Found : C, 70·8; H, 7·5. $C_{13}H_{16}O_3$ requires C, 70·9; H, 7·3%); its *semicarbazone*, prepared in cold aqueous alcoholic solution in the presence of sodium acetate, crystallised from alcohol in minute prisms, m. p. 151—152° (Found : C, 60·6; H, 6·8. $C_{14}H_{19}O_3N_3$ requires C, 60·6; H, 6·9%). The *ethyl* ester was an oil, b. p. 160°/9 mm. (Found : C, 71·7; H, 7·8. $C_{14}H_{18}O_3$ requires C, 71·8; H, 7·7%); its semicarbazone separated from aqueous alcohol in small prisms, m. p. 119—120°. The keto-acid, on oxidation with sodium hypobromite, gave an excellent yield of α-phenylglutaric acid, m. p. 82—83° (compare Fichter and Merckens, *Ber.*, 1901, **34**, 4175).

Ethyl α-Cyano-ε-phenyl-β-methyl-Δ^{α}*-pentene-αε-dicarboxylate* (III).—A mixture of ethyl γ-acetyl-α-phenylbutyrate (46·8 g.), ethyl cyanoacetate (22·6 g.), anhydrous sodium sulphate (25 g.), and piperidine (3 c.c.) was heated on the steam-bath for 18 hours, cooled, and poured into water. The heavy oil produced was isolated by means of ether and after the usual washing and drying was distilled. *Ethyl α-cyano-ε-phenyl-β-methyl-*Δ^{α}*-pentene-αε-dicarboxylate* (III) formed an almost colourless oil, b. p. 212°/7 mm. (Found : C, 69·5; H, 7·1. $C_{19}H_{23}O_4N$ requires C, 69·3; H, 7·0%). The yield was good.

Ethyl α-Phenyl-δ-methylpentane-αδε-tricarboxylate (IV).—The unsaturated cyano-ester (65·8 g.), dissolved in rectified spirit (300 c.c.), was treated with a solution of 26 g. of 98% potassium cyanide (2 mols.) in water (60 c.c.). After 48 hours the alcohol was distilled off, a large excess of concentrated hydrochloric acid added, and the liquid heated under reflux for 12 hours, cooled, diluted with water, saturated with salt, and extracted several times with ether. The crude acid recovered from the ethereal solution (40 g.) was mixed with absolute alcohol (150 c.c.) and concentrated sulphuric acid (10 c.c.) and heated for 6 hours at 110° in a current of alcohol vapour; purified in the usual way, *ethyl α-phenyl-δ-methylpentane-αδε-tricarboxylate* had b. p. 208°/7 mm. (Found : C, 66·7; H, 8·1. $C_{21}H_{30}O_6$ requires C, 66·7; H, 7·9%).

*Ethyl 5-Carbethoxy-2-phenyl-5-methyl*cyclo*hexanone-6-β-propionate* (I).—A mixture of the foregoing ester (37·8 g.) and granulated sodium (4·6 g.) in dry benzene (80 c.c.) was heated on a water-bath until the sodium disappeared (3—4 hours). The product was cooled in ice and gradually treated with ethyl β-chloropropionate (14 g.), the mixture being finally refluxed for 6 hours. After cooling, the product was poured into water, the benzene layer washed with dilute sodium hydroxide solution and dried, and the solvent removed under reduced pressure. The residue was refluxed with an excess of concentrated hydrochloric acid for 12 hours, and the liquid concentrated to small bulk under reduced pressure and repeatedly extracted with ether. The ethereal solution was dried and evaporated, and the residue esterified (alcohol–hydrogen chloride method). *Ethyl 5-carbethoxy-2-phenyl-5-methyl*cyclo*hexanone-6-β-propionate* formed a colourless, somewhat viscous liquid, b. p. 200°/5 mm. (Found : C, 70·2; H, 8·1. $C_{21}H_{28}O_5$ requires C, 70·0; H, 7·8%).

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