412. *Studies in the Sterol–Oestrone Group. Part I. A Synthesis of 3′-Keto-3 : 4-dihydro-1 : 2-cyclopentenophenanthrene.*

By J. C. BARDHAN.

WITH the introduction of the correct formula for the sterols and bile acids by Rosenheim and King (*Nature*, 1932, **130**, 315; *Chem. and Ind.*, 1932, **51**, 954; 1933, **52**, 299; also Wieland and Dane, *Z. physiol. Chem.*, 1932, **210**, 274) rapid advances have been made in our knowledge of this group of natural products and a correlation of the structures of the various sex hormones with sterols has been made possible through their artificial production from the latter (Ruzicka, Goldberg, Meyer, Brungger, and Eichenberger, *Helv. Chim. Acta*, 1934, **17**, 1375; 1935, **18**, 1264, 1478; Butenandt, Westphal, and Cobler, *Ber.*, 1934, **67**, 1611, 2085; Fernholz, *ibid.*, p. 2027; Marker, Kamm, Oakwood, and Laucius, *J. Amer. Chem. Soc.*, 1936, **58**, 1504 *).

Despite numerous attempts (Robinson, J., 1933, 607; Kon, *ibid.*, p. 1081; Cook, *ibid.*, p. 1098, and many other papers), however, these substances have not so far been synthesised in the laboratory owing not only to the lack of suitable methods for the elaboration of the cholane structure but also to the difficult stereochemical problems which have to be overcome (compare, however, Robinson, this vol., p. 1088). This series of investigations has been undertaken with the object of synthesising the sterol derivatives or their stereoisomers and physiologically active ketones related to the sex hormones.

The present communication, however, deals with the synthesis of the *ketone* (I), a preliminary account of which has already been published (*Nature*, 1934, **134**, 217). The

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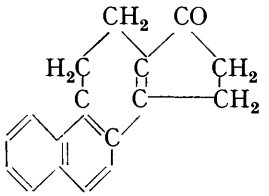


$CO_2Me{\cdot}CH_2{\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2Me$ (II.)

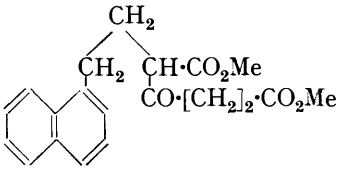
$CO_2Me{\cdot}CH(COMe){\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2Me$ (III.)

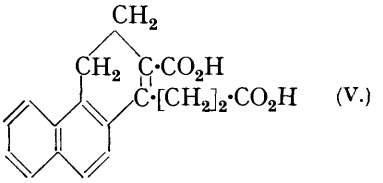
starting point was *methyl β-ketoadipate* (II), large quantities of which were prepared by an adaptation of Bouveault's method for the synthesis of β-ketonic esters (*Bull. Soc. chim.*, 1902, **27**, 1038), β-carbomethoxypropionyl chloride being brought into reaction with methyl sodioacetoacetate to give *methyl β-keto-α-acetyladipate* (III), which on treatment with ammonia in ethereal solution furnished the keto-ester (II) in an excellent yield. This substance showed all the properties of a β-ketonic ester and on boiling with dilute hydrochloric acid yielded lævulic acid. On treatment with concentrated hydrochloric acid at the ordinary temperature, however, it was quantitatively hydrolysed, giving β-ketoadipic acid, small quantities of which were also obtained by Kon and Nanji (J., 1932, 2560) by a different route. β-Ketoadipic acid is remarkably stable and in this respect resembles succinyldiacetic acid described by Willstätter and Pfannenstiel (*Annalen*, 1921, **422**, 14).

Methyl β-ketoadipate readily reacted with β-1-naphthylethyl bromide in presence of sodium methoxide, and the *product* (IV) on treatment with cold concentrated sulphuric acid underwent Bougault cyclisation (*Compt. rend.*, 1915, **159**, 745; Auwers and Moller,

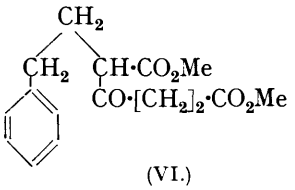
* It is remarkable that the reduction of dehydro*neo*ergosterol should have led only to the *trans*-locking of rings II and III to the exclusion of the other possible alternative.

J. pr. Chem., 1925, **109**, 124; Fieser and Hershberg, *J. Amer. Chem. Soc.*, 1935, **57**, 1851), giving 2-*carboxy*-3 : 4-*dihydrophenanthrene*-1-β-*propionic acid* (V), m. p. 237—238°, which on ketonisation with acetic anhydride afforded the ketone (I), m. p. 210°. As an additional control on its constitution it was reduced by Clemmensen's method and the resulting oil dehydrogenated with selenium, a good yield of 1 : 2-*cyclo*pentenophenanthrene being obtained. An extension of this work to β-7-methoxy-1-naphthylethyl bromide and its isomerides is in hand.

(IV.) 

 (V.)

β-Phenylethyl bromide also condensed with methyl β-ketoadipate in the expected manner, giving the *keto-ester* (VI), which was converted into the *methyl* derivative (VII). Preliminary attempts have been made to cyclise it to the keto-ester (VIII) with a view to investigate the action of dehydrating agents on the latter.



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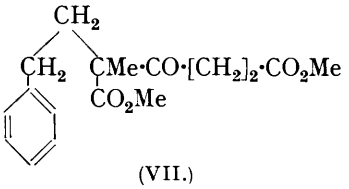

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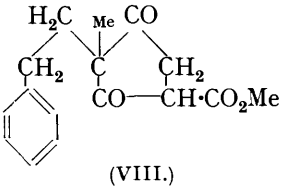
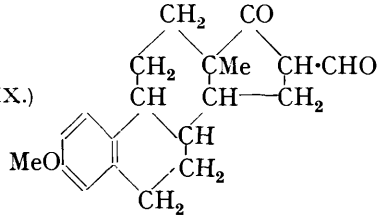
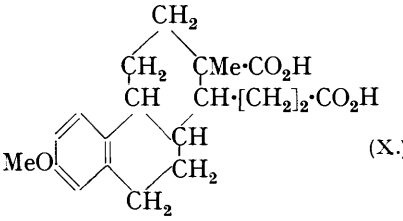


(VIII.)

(IX.) 

 (X.)

It should be mentioned in this connection that the m. p. of the ketone (I) differs from that of the dicarboxylic acid (V) from which it is derived by only a few degrees. This is rather unusual; and it seemed of interest to compare the behaviour of the methyl ether of oestrone with the related *dicarboxylic acid* (X), which does not appear to have been made before. Ethyl formate was condensed with the methyl ether of oestrone (Butenandt, Störmer, and Westphal, *Z. physiol. Chem.*, 1932, **208**, 167; Cohen, Cook, and Hewett, J., 1935, 449) in presence of sodium to give the *formyl* derivative (IX). This substance in marked contrast to that of hydroxymethylenecamphor shows none of the acidic properties of the latter. On treatment with hydroxylamine hydrochloride, however, followed by hydrolysis of the product with an excess of alkali, it gave a good yield of (X), m. p. 251—252° (compare, for instance, Lapworth, J., 1900, **77**, 1062). According to the accepted views on the stereochemical configuration of oestrone this new acid should belong to the *trans*-series, and as is to be expected, the acid on ketonisation with acetic anhydride furnished the methyl ether of oestrone as the sole product. The dehydrogenation of the acid (X) has yielded interesting results; these together with the corresponding products from equilenin will be dealt with in a subsequent communication.

Experimental.

Methyl β-*Keto*-α-*acetyladipate* (III).—A solution of methyl acetoacetate (116 g.) in dry ether (300 c.c.) was added to a suspension of finely divided sodium (23 g.) in ether (1000 c.c.), cooled in a freezing mixture. When the formation of the sodio-derivative was complete, 150 g. of succinic half-ester half-chloride (obtained from 140 g. of methyl hydrogen succinate by the

action of thionyl chloride and removal of excess of the reagent in a vacuum) in ether (400 c.c.) were gradually introduced with cooling, and after 12 hours the mixture was refluxed for 1 hour to complete the reaction. Ice and dilute hydrochloric acid were then added and the separated aqueous layer was extracted several times with ether; the combined ethereal solutions were washed with a little water, dried, and evaporated. The residual oil, consisting of a mixture of *C*-acyl and *O*-acyl esters, was treated with an ice-cold concentrated solution of sodium carbonate, and the undissolved oil collected in ether; the process was repeated several times until no more oil dissolved in sodium carbonate solution. The combined alkaline solutions were extracted once more with ether to remove any oily matter and cautiously acidified with ice-cold dilute hydrochloric acid, and the oil which separated collected in ether, dried, and distilled. *Methyl β-keto-α-acetyladipate* formed an almost colourless liquid, b. p. 137°/0·5 mm. (bath 160—165°) (Found : C, 51·8; H, 6·3. $C_{10}H_{14}O_6$ requires C, 52·1; H, 6·1%). Ferric chloride imparts a deep red coloration to its alcoholic solution.

The alkali-insoluble oil recovered in the above process still gave a ferric reaction and was not further examined.

Methyl β-Ketoadipate (II).—The diketo-ester (III) (120 g.), dissolved in dry ether (200 c.c.), was cooled in a freezing mixture and saturated with dry ammonia gas. After 12 hours the clear solution was washed with water and with cold dilute hydrochloric acid, dried (sodium sulphate), and distilled, *methyl β-ketoadipate* being obtained as a colourless oil, b. p. 122°/0·5 mm. (bath 145—150°) (Found : C, 50·8; H, 6·4. $C_8H_{12}O_5$ requires C, 51·1; H, 6·4%). It gives a reddish-brown coloration with ferric chloride.

Ethyl acetoacetate can be used instead of methyl acetoacetate in the above reaction without materially affecting the yields of the corresponding mixed esters, *methyl ethyl β-keto-α-acetyladipate*, b. p. 136°/0·6 mm. (Found : C, 54·1; H, 6·5. $C_{11}H_{16}O_6$ requires C, 54·1; H, 6·6%), and *methyl ethyl β-ketoadipate*, a colourless oil, b. p. 123°/0·5 mm. (Found : C, 53·4; H, 6·8. $C_9H_{14}O_5$ requires C, 53·5; H, 6·9%).

Methyl β-ketoadipate (1 c.c.) readily dissolved in concentrated hydrochloric acid (9 c.c.) at the ordinary temperature and the solution, on being evaporated over potassium hydroxide in a vacuum desiccator, deposited the corresponding acid in a crystalline state. On recrystallisation from ethyl acetate–light petroleum (b. p. 60—80°) β-ketoadipic acid formed colourless needles, m. p. 125—126° (decomp.) (Found : C, 45·2; H, 5·0. Calc. : C, 45·0; H, 5·0%). After long keeping, it was transformed into a liquid which, on treatment with semicarbazide acetate, furnished the semicarbazone of lævulic acid, m. p. and mixed m. p. 184—185°.

On boiling for a short time with dilute hydrochloric acid methyl β-ketoadipate gave lævulic acid as the chief product, which was identified by its b. p. 152—156°/15 mm. (Found : C, 51·4; H, 7·1. Calc. : C, 51·7; H, 6·9%), and semicarbazone, m. p. 184—185°.

Condensation of β-1-Naphthylethyl Bromide with Methyl β-Ketoadipate.—Methyl β-ketoadipate (18·8 g.) was slowly mixed with a solution of sodium (2·3 g.) in methyl alcohol (50 c.c.) cooled in ice, β-1-naphthylethyl bromide (24 g.) added, and the whole gently boiled for 18 hours under reflux. On cooling, the product was poured into a large volume of water and extracted with ether, and the extract washed with water, dried, and evaporated. *Methyl β-keto-α-(β′-1-naphthylethyl)adipate* (IV) distilled with slight decomposition as a colourless oil, b. p. *ca.* 195°/0·5 mm. (Found : C, 70·3; H, 6·6. $C_{20}H_{22}O_5$ requires C, 70·2; H, 6·4%). It gave a positive ferric reaction.

2-Carboxy-3 : 4-dihydrophenanthrene-1-β-propionic Acid (V).—The cyclisation of the keto-ester (IV) was carried out with the crude product and it was found convenient to work with small quantities at a time. Concentrated suphuric acid (*d* 1·84; 5 c.c.) was slowly dropped into the oil (2 c.c.), cooled in ice and salt, the mixture being vigorously shaken after each addition. After standing for a short time, the brown solution was diluted with a large volume of ice-water, and the flocculent precipitate collected. The crude product was hydrolysed with 10% methyl-alcoholic potash, excess of alcohol removed on the steam-bath, the solution filtered, cooled, and acidified, and the crystalline acid collected. On two crystallisations from acetic acid (charcoal) *2-carboxy-3 : 4-dihydrophenanthrene-1-β-propionic acid* formed magnificent colourless plates, m. p. 237—238° [Found : C, 72·9; H, 5·5; equiv., by titration, 148·5. $C_{18}H_{16}O_4$ (dibasic) requires C, 73·0; H, 5·4%; equiv., 148]. The *methyl* ester, prepared by refluxing the acid with alcohol and sulphuric acid, crystallised from aqueous methyl alcohol (charcoal) in colourless needles or plates, m. p. 75° (Found : C, 74·3; H, 6·1. $C_{20}H_{20}O_4$ requires C, 74·1; H, 6·2%).

3′-Keto-3 : 4-dihydro-1 : 2-cyclopentenophenanthrene (I).—The acid (V) (1 g.) was gradually heated with acetic anhydride (10 c.c.) in an air-bath to 155° until most of the acetic acid and

acetic anhydride distilled. The heating was then continued under reduced pressure (high vac.), the temperature being allowed to rise slowly above 210°. The yellow *product* which distilled was collected; after treatment with dilute sodium hydroxide solution and repeated crystallisation from dilute acetone (charcoal) it formed pale yellow scales, m. p. 210° (Found : C, 86·9; H, 6·0. $C_{17}H_{14}O$ requires C, 87·2; H, 6·0%). With semicarbazide acetate it formed a sparingly soluble semicarbazone, which did not melt at 285°.

1 : 2-cyclo*Pentenophenanthrene*.—A solution of the ketone (I) (0·2 g.) in acetic acid (10 c.c.) was heated with amalgamated zinc (5 g.) and concentrated hydrochloric acid (3 c.c.) at 120° in a slow current of hydrogen chloride for 7 hours. The mixture was diluted with water and extracted with ether, and the extract washed with sodium carbonate solution, and water, dried, and evaporated. The residual fluorescent oil was heated with selenium powder (1 g.) at 310—330° for 21 hours, an appreciable quantity of a crystalline solid collecting in the cooler part of the tube. After extraction with ether and removal of the solvent the solid residue was purified through its *s*-trinitrobenzene complex. It then separated from dilute alcohol in colourless plates, m. p. 135° (Found : C, 93·5; H, 6·4. Calc. : C, 93·6; H, 6·4%). This substance, its picrate (m. p. 133°), and its *s*-trinitrobenzene complex (m. p. 166°) did not depress the m. p.'s of the corresponding compounds prepared from authentic 1 : 2-*cyclo*pentenophenanthrene.

Methyl β-Keto-α-(β'-phenylethyl)adipate (VI).—β-Phenylethyl bromide was condensed with methyl β-ketoadipate exactly as described in the case of β-1-naphthylethyl bromide; the *product* on distillation formed a colourless liquid, b. p. 185°/1 mm. (Found : C, 65·7; H, 6·7. $C_{16}H_{20}O_5$ requires C, 65·8; H, 6·9%), giving a reddish-violet coloration with alcoholic ferric chloride.

Methyl β-Keto-α-methyl-α-(β'-phenylethyl)adipate (VII).—The keto-ester (VI) (29·2 g.) was introduced into a solution of sodium (2·3 g.) in methyl alcohol (50 c.c.) and to the mixture, cooled in ice, methyl iodide (10 c.c.) was added. The reaction mixture was kept in ice over-night and finally heated on the steam-bath until neutral. The *ester* formed a colourless oil, b. p. 189°/1 mm. (Found : C, 66·4; H, 7·0. $C_{17}H_{22}O_5$ requires C, 66·7; H, 7·2%). It did not develop any coloration with ferric chloride, and reacted vigorously with pulverised sodium in dry benzene, giving a product which is under examination.

Condensation of Oestrone Methyl Ether with Ethyl Formate.—The ether (1·5 g.), m. p. 168—169°, prepared by the methylation of oestrone with methyl sulphate and alkali (Butenandt, Störmer, and Westphal, *loc. cit.*, p. 167), ethyl formate (2 c.c.), and finely divided sodium (1 g.) were allowed to react in dry benzene (30 c.c.) for 15 hours. Excess of water was added, the aqueous layer isolated and acidified, and the colourless solid collected. On recrystallisation from dilute acetone the *formyl* derivative (IX) formed shining scales, m. p. 170—171° (Found : C, 77·0; H, 7·5. $C_{20}H_{24}O_3$ requires C, 76·9; H, 7·7%) (yield, almost quantitative). It was insoluble in sodium bicarbonate solution, but dissolved readily in dilute sodium hydroxide solution. Its alcoholic solution produced a characteristic violet coloration on the addition of ferric chloride.

7-Methoxy-2-methyl-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydrophenanthrene-2-carboxylic-1-β-propionic Acid (X).—The formyl derivative (IX) (1 g.) was gently warmed with sodium hydroxide (1 g. in water, 5 c.c.), the product cooled and rapidly mixed with hydroxylamine hydrochloride (1 g. in a small quantity of water), and the clear solution obtained on shaking, heated on the steam-bath for 15 minutes. The pasty mass was heated with an excess of 33% potassium hydroxide solution on the steam-bath until no more ammonia was evolved. The solution was diluted, filtered, and cautiously acidified. The *acid* on recrystallisation from dilute acetic acid (charcoal) formed minute colourless prisms, m. p. 251—252° [Found : C, 69·5; H, 7·6; equiv., by titration, 174·5. $C_{20}H_{26}O_5$ (dibasic) requires C, 69·4; H, 7·5%; equiv., 173]. On dehydrogenation with selenium it gave a crystalline hydrocarbon which is under investigation.

The foregoing acid on distillation with acetic anhydride in the usual way (p. 1850) furnished an oil which on treatment with acetone formed crystals, m. p. 150—152°. On repeated crystallisation, however, the m. p. was raised to 164—165° (Found : C, 80·3; H, 8·3. Calc. : C, 80·3; H, 8·5%), and the product evidently consisted of the methyl ether of oestrone.

In conclusion, I desire to thank Prof. J. F. Thorpe, C.B.E., F.R.S., for his interest in this research, and Dr. O. Rosenheim, F.R.S., for a gift of oestrone.

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