377. *Experiments on the Synthesis of Substances related to the Sterols. Part XXIII. Formation of Oestrone from a Dicarboxylic Acid obtained by Degradation of Oestrone Methyl Ether.*

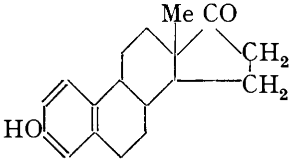
By F. LITVAN and ROBERT ROBINSON.

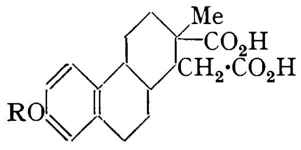
Some of the projected syntheses of oestrone (I) are by way of the dicarboxylic acid (II, R = Me) (cf. Robinson and Walker, this vol., p. 183) and we have therefore prepared this substance by degradation of oestrone methyl ether and have reconverted it into oestrone. The cycle of operations does not involve any stereochemical change. As a model for the conversion of (II, R = Me) into homologues by the method of Arndt and Eistert the conversions of phenylpropionic acid into phenylbutyric acid and of homocamphoric acid into hydrocamphorylacetic acid were studied.

BY fusion of oestriol with potassium hydroxide, Marrian and Haslewood (*J. Soc. Chem. Ind.*, 1932, **51**, 277T; cf. MacCorquodale, Thayer, and Doisy, *J. Biol. Chem.*, 1933, **99**, 327) obtained the acid (II, R = H), for which we now propose the name oestric acid. *O*-Methyloestric acid (II, R = Me) does not appear to have been previously prepared and instead of obtaining it by the methylation of oestric acid we adopted the method of degradation of iso*nitroso*-O-*methyloestrone* (III). After practising with small quantities of camphor we devised a process for the preparation of this derivative in excellent yield. The ketone was treated with potassium *tert.*-butoxide and amyl nitrite in *tert.*-butyl-alcoholic solution.

The action of phosphorus pentachloride on the *iso*nitroso-derivative in acetyl chloride solution, followed by prolonged hydrolysis of the product with alcoholic potassium hydroxide, afforded *O-methyloestric acid* in about 66% yield. The fact that the last stage required a fortnight for completion showed that we were dealing with a "hindered" acid

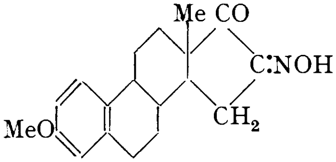
(I.)

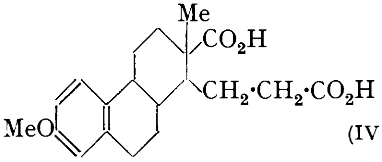




(II.)

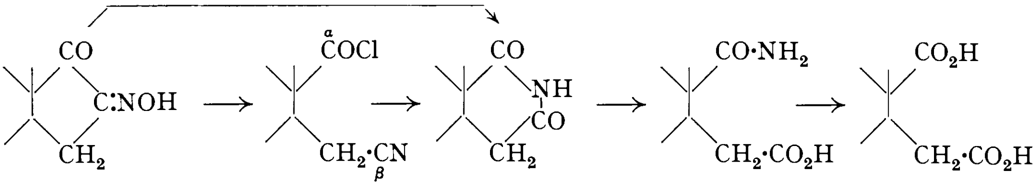
(III.)



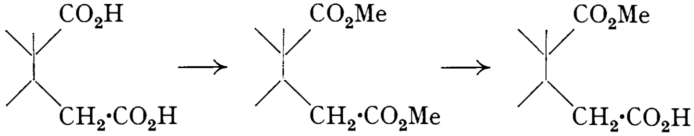


(IV.)

amide (α-carboxyamide) and hence methyloestrimide must be an intermediate product. This may be directly formed from the *iso*nitroso-compound or may be produced by the rearrangement of a β-nitrile acid as shown in the scheme :

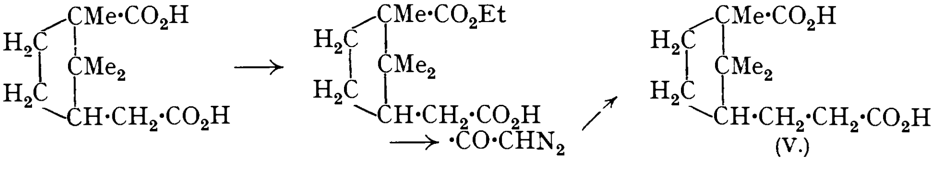


This hindrance phenomenon, which was to be anticipated for theoretical reasons, assured us that there could be no difficulty in preparing the α-monomethyl ester of *O*-methyloestric acid and as very little material was available we prepared the dimethyl ester by the action of diazomethane on the acid and hydrolysed this by means of methanolic potassium hydroxide (1·02 mols.). The viscous oil so obtained should undoubtedly be the desired monomethyl ester; it was not characterised but employed directly for the next stage.



O-Methylhomo-oestric acid (IV) has already been described by Bardhan (J., 1936, 1848), who applied a method first used for the preparation of homocamphoric acid from camphor (Bishop, Claisen, and Sinclair, *Annalen*, 1894, **281**, 331; Lapworth, J., 1900, **77**, 1062) to hydroxymethylene-*O*-methyloestrone. We desired to convert methyl hydrogen *O*-methyloestrate into this acid or a derivative thereof and for this purpose the elegant method of Arndt and Eistert (*Ber.*, 1935, **68**, 200; 1936, **69**, 1074) appeared the most promising. An acid, $R{\cdot}CO_2H$, is converted into its chloride and then into a diazo-ketone, $R{\cdot}CO{\cdot}CHN_2$, by the action of diazomethane. The homologous acid, $R{\cdot}CH_2{\cdot}CO_2H$, is produced as the result of a molecular rearrangement of the diazo-ketone under the influence of a solution of silver oxide in aqueous sodium thiosulphate.

As aromatic acids have for the most part been employed in this series of reactions we



(V.)

first satisfied ourselves that the conversion of phenylpropionic acid into phenylbutyric acid was practicable. We then proceeded to a closer analogy, namely, the conversion of homocamphoric acid by way of its monoethyl ester into hydrocamphorylacetic acid (V). This having been successfully accomplished, the methyl hydrogen *O*-methyloestrate was submitted to the Arndt–Eistert transformations. The acidic product was converted into the dimethyl ester and eventually *dimethyl* O-*methylhomo-oestrate*, identical with the dimethyl ester of Bardhan's acid, could be isolated although only in small yield. It is probable that some of the original acid was regenerated and the crystallisation of the mixture of esters was very difficult.

The dimethyl ester was hydrolysed by long boiling with aqueous methanolic barium hydroxide.

The formation of *O*-methyloestrone from *O*-methylhomo-oestric acid by means of Blanc's reaction has been described by Bardhan (*loc. cit.*), but the identity of the product was assumed from the m. p. 164—165°, and from analysis; apparently a mixed m. p. was not carried out. We have effected the cyclisation by heating the lead salt and have confirmed the identity of the resulting ketone with *O*-methyloestrone. The demethylation of *O*-methyloestrone was brought about by means of a mixture of acetic and hydriodic acids and oestrone was recovered.

EXPERIMENTAL.

γ-Phenylbutyric Acid.—The applications of the Arndt–Eistert reaction herein described were made exactly as prescribed (*loc. cit.*) by these authors (0·1 g.-mol. of acid chloride in 50 c.c. of ether is treated with 0·3 g.-mol. of ethereal diazomethane at 10°; a solution of the diazo-ketone so obtained is gradually added to a suspension of 13 g. of silver oxide in a solution of 19 g. of sodium thiosulphate in 650 c.c. of water at 70°) or with aliquot proportions. It is very important to ensure that the diazomethane solution is free from potassium hydroxide, either by careful filtration or, better, by distillation.

β-Phenylpropionyl chloride (3·0 g.) and diazomethane (2·2 g.) gave a yellow oily diazo-ketone, which was dissolved in dioxan (30 c.c.) and treated as above. The solution was acidified and filtered, the precipitate washed with alcohol, and the combined filtrate and washings rendered alkaline with sodium carbonate. The solution was extracted with ether, separated, and acidified, and the phenylbutyric acid isolated by means of ether. The product, crystallised from light petroleum (b. p. 40—60°), had m. p. 49—50° (yield, 60%) (Found: C, 73·1; H, 7·3. Calc. for $C_{10}H_{12}O_2$: C, 73·2; H, 7·3%).

Hydrocamphorylacetic Acid (V).—Ethyl hydrogen *d*-homocamphorate (m. p. 78°) was obtained by the method of Haller (*Compt. rend.*, 1889, **101**, 113). Esterification of *d*-homocamphoric acid with alcohol and sulphuric acid afforded the diethyl ester, b. p. 128—130°/1 mm., $n_D^{20°}$ 1·435 (Haller gives b. p. 205—210°/20 mm.) instead of the expected monoethyl ester (m. p. 47°). The hydrolysis of the diethyl ester with a 5% excess of potassium hydroxide gave ethyl hydrogen *d*-homocamphorate (m. p. 78°, b. p. 145—147°/0·44 mm.) in 90—95% yield (Found: C, 64·3; H, 9·2. Calc. for $C_{13}H_{22}O_4$: C, 64·5; H, 9·1%). The half ester (from 20 g. of diethyl ester) was converted into the chloride by means of thionyl chloride and submitted to the Arndt–Eistert procedure. The product was hydrolysed by heating with an excess of hydrobromic acid (*d* 1·5) on the steam-bath and hydrocamphorylacetic acid (9 g.), m. p. 137°, was then isolated and purified in the known manner (Found: C, 63·1; H, 8·7. Calc. for $C_{12}H_{20}O_4$: C, 63·2; H, 8·8%) (cf. Winzer, *Annalen*, 1890, **257**, 298).

The conversion of hydrocamphorylacetic acid into homocamphor by Blanc's acetic anhydride method has been described by Lapworth and Royle (J., 1920, **117**, 743), who also obtained the ketone by heating the lead salt of the dibasic acid; the yields obtained were not, however, stated. We found that 5 g. of the acid by Blanc's method gave 1·1 g. of homocamphor. After steam-distillation and vacuum sublimation the substance had m. p. 189·5—190·5° (Found: C, 79·4; H, 10·9. Calc. for $C_{11}H_{18}O$: C, 79·5; H, 10·9%).

A mixture of hydrocamphorylacetic acid (4 g.) and baryta (0·5 g.) was heated at 300—310° for 6 hours. There resulted only 0·2 g. of homocamphor and 3·2 g. of the unchanged acid was recovered. On a small scale the lead salt method appeared to give much better results. The 2 : 4-dinitrophenylhydrazone of homocamphor has m. p. 232°.

Ethyl d-l-*Carboxy*-1 : 2 : 2-*trimethyl*cyclo*pentane*-3-*acetate* (*Ethyl Hydrogen* d-*Homocamphorate*).—We are indebted to Dr. James Walker for the following improved preparation and for a specimen of the half ester. A mixture of *d*-homocamphoric acid (30·2 g.), ethyl alcohol (20 c.c.), benzene (100 c.c.), and concentrated sulphuric acid (5 c.c.) was refluxed for 4 hours and then washed with water and twice with sodium carbonate solution. The alkaline washings were acidified and the precipitated oil (32·6 g.), isolated by means of ether, rapidly solidified, m. p. 52—53°, b. p. 153—154°/0·44 mm.; the distillate cystallised in needles, m. p. 58·5—59·5°, $[\alpha]_D^{15^\circ}$ + 57·5° (*c*, 1·87 in alcohol) (Found: C, 64·5; H, 9·1. Calc. for $C_{13}H_{22}O_4$: C, 64·4; H, 9·1%). Haller (*Compt. rend.*, 1889, **109**, 113) gives m. p. 44—45°, and Palfray (*Ann. Chim.*, 1923, **20**, 329) records m. p. 56—56·5° and $[\alpha]_D^{17^\circ}$ + 55°47′ (*c*, 4·183 in alcohol). When twice as much alcohol was used in the above experiment, the diethyl ester was obtained.

When this ethyl hydrogen *d*-homocamphorate (m. p. 59°) was submitted to the Arndt–Eistert reaction, the product isolated after hydrolysis was pure *d*-homocamphoric acid, m. p. 232°, alone or mixed with an authentic specimen.

iso*Nitroso*-O-*methyloestrone* (III).—The methyl ether of oestrone was prepared by the method of Butenandt, Störmer, and Westphal (*Z. physiol. Chem.*, 1932, **208**, 167); yield, 5·2 g., m. p. 163°, from 5 g. of oestrone.

After a considerable number of experiments on the nitrosation of camphor and of *O*-methyloestrone the following conditions were found to give much the best results. Potassium (0·15 g.) was dissolved in *tert.*-butyl alcohol (10 c.c.), *O*-methyloestrone (0·1 g.) added, and the mixture stirred at room temperature for 5 hours. *iso*Amyl nitrite (0·1 g.) was then introduced, and the stirring continued for 4 hours, then at 50° for 2 hours, and again at room temperature for 12—15 hours; the whole operation was conducted under pure nitrogen. After the addition of ice and water the solution was thoroughly extracted with ether, and the aqueous layer separated and acidified with acetic acid. Separation of the product (0·08 g., m. p. 151—152°) was complete in about 2 hours. When potassium (0·5 g.), *tert.*-butyl alcohol (20 c.c.), *O*-methyloestrone (2 g.), and *iso*amyl nitrite (1·5 g.) were used, the yield was 1·95 g. (similarly 1·35 g. and 2·3 g. from 1·55 g. and 2·8 g. of *O*-methyloestrone respectively). The *substance* crystallised from light petroleum (b. p. 60—80°) in needles and irregular plates, m. p. 161—162° (decomp.) (Found: C, 72·1; H, 7·8; N, 4·5. $C_{19}H_{23}O_3N$ requires C, 72·9; H, 7·3; N, 4·5%), easily soluble in dilute aqueous sodium hydroxide to a faintly yellow solution.

O-*Methyloestric Acid* (II).—Experiments with *iso*nitrosocamphor showed that in acetyl chloride solution the reaction with phosphorus pentachloride gives chiefly the α-mononitrile of camphoric acid, m. p. 151—152°. With *iso*amyl ether as the solvent, the main product is the α-monoamide of camphoric acid, m. p. 174—175°.

In the case of *iso*nitroso-*O*-methyloestrone we have used ether as the solvent with fair results on a small scale; the following conditions are representative of those used in larger operations. Phosphorus pentachloride (1·8 g.) was gradually added to a mixture of *iso*nitroso-*O*-methyloestrone (2·3 g.) and acetyl chloride (200 c.c.); after 2 hours at room temperature, most of the excess of acetyl chloride was evaporated, the mixture decomposed with ice, and the solution thoroughly extracted with ether. The ethereal solution was washed with water, dried, and evaporated. The residue was refluxed with an excess of alcoholic potassium hydroxide (30%) for about 14 days or until the evolution of ammonia ceased. Towards the end of this period, zinc dust was added in order to eliminate nuclear-substituted chlorine. The solution was diluted and filtered, most of the alcohol removed by distillation, and the acid isolated by acidification and extraction with a large volume of ether. The *product* crystallised from 20% acetic acid (charcoal) in faintly yellowish plates, m. p. 189—190° (yield, 1·6 g. or 66%) (Found: C, 68·2, 68·3; H, 7·3, 7·4; equiv., 0·01N-sodium hydroxide, 168. $C_{19}H_{24}O_5$ requires C, 68·7; H, 7·2%; equiv., 161).

O-*Methylhomo-oestric Acid* (*Bardhan's Acid*) (IV).—The work of Bardhan (*loc. cit.*) has been confirmed in all respects. Hydroxymethylene-*O*-methyloestrone (2·35 g., m. p. 165°, from 2·2 g. of *O*-methyloestrone) gave Bardhan's acid (1·7 g. yielding 0·9 g., m. p. 253°) (Found: C, 69·0; H, 7·3. Calc. for $C_{20}H_{26}O_5$: C, 69·3; H, 7·5%) and an alkali-insoluble by-product (0·3 g.) which may be an *iso*oxazole derivative. The *dimethyl* ester, obtained by the action of diazomethane on the acid in ethereal solution (quantitative yield), crystallised from aqueous methyl alcohol in colourless plates, m. p. 85° (Found: C, 70·7; H, 8·1. $C_{22}H_{30}O_5$ requires C, 70·6; H, 8·1%). A specimen was hydrolysed by refluxing for 7 days with an excess of methyl-alcoholic barium hydroxide and, after the usual treatment, the original acid was recovered, m. p. 253° alone or mixed with the authentic specimen. Various attempts to obtain crystalline methylamides and a methylimide were unsuccessful.

O-Methyloestric acid was converted into its dimethyl ester (1·75 g.) by treatment with ethereal diazomethane and the crude product was refluxed for several hours with a solution of potassium hydroxide (0·29 g.) in methyl alcohol (10 c.c.) and water (5 c.c.). After addition of ether and water, the aqueous solution was acidified, and the ester-acid isolated by means of ether and thoroughly dried (1·2 g.). This material was dissolved in a little chloroform and treated with thionyl chloride (1 g.); when evolution of hydrogen chloride ceased, the solution was distilled under diminished pressure, benzene added to the residue, and the solvent removed as before; the addition of benzene and its removal were repeated five times. The residue was dissolved in anhydrous ether and added at 10° to ethereal diazomethane (from 1·0 g. of nitrosomethylurea). After removal of the ether, the diazo-ketone, a viscous yellow oil, was dissolved in dioxan (10 c.c.), and the solution gradually added to one of silver oxide (0·5 g.) and sodium thiosulphate (0·7 g.) in water (25 c.c.). The mixture was kept at 70° for an hour, then cooled, acidified, and extracted with ether. The dried and concentrated solution was treated with an excess of diazomethane and evaporated, and the residue taken up in methyl alcohol. No crystalline material could be obtained on long keeping and on slow concentration. The solution was mixed with dilute aqueous sodium hydroxide, the oil taken up in ether, and this solution shaken with a little activated alumina, dried, and evaporated. The residue did not crystallise. It was extracted with light petroleum (b. p. 80—110°) until almost all had passed into solution, the solvent removed and the process repeated with light petroleum (b. p. 60—80°). The residue from this extract showed signs of hardening on stirring; it was extracted with light petroleum (b. p. 40—60°), and the solution concentrated; an ill-defined solid slowly separated in the ice-box. Two more crystallisations from light petroleum (b. p. 40—60°) gave colourless flat needles, m. p. 85°, alone or mixed with the above-described specimen of dimethyl *O*-methylhomo-oestrate. The yield was about 20 mg., but doubtless the major part of the product remained in the mother-liquors, possibly mixed with dimethyl *O*-methyloestrate.

O-Methyloestrone from Bardhan's Acid.—An intimate mixture of *O*-methylhomo-oestric acid (0·27 g.) and lead carbonate (0·2 g.) was carefully heated over a free flame in a long, narrow hard-glass tube which was rotated so that gas could escape. The high vacuum pump was connected when the initial reaction had been completed and the mixture was gradually heated more strongly. Ketonisation proceeded remarkably smoothly and the product distilled as a colourless oil into a clean part of the tube; it crystallised at once on cooling. The substance crystallised from acetone in colourless prisms, m. p. 166—167° alone or mixed with *O*-methyloestrone (Found: C, 80·2; H, 8·4. Calc. for $C_{19}H_{24}O_2$: C, 80·3; H, 8·4%).

The demethylation of *O*-methyloestrone was carried out on a small scale. The methyl ether was dissolved in a little hot acetic acid, and hydriodic acid (*ca.* 2 vols.; *d* 1·9) gradually added to the boiling solution. After boiling for about 2 minutes, the solution was poured into an excess of aqueous sodium bisulphite, and the precipitate collected. This was extracted with boiling dilute aqueous sodium hydroxide, and the filtered solution acidified and extracted with a large volume of ether. The ethereal solution was dried and concentrated; the crystals that separated already consisted of nearly pure oestrone. The substance was recrystallised from acetic acid and obtained in flat, prismatic needles, m. p. 257—258° alone or mixed with a pure specimen.

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