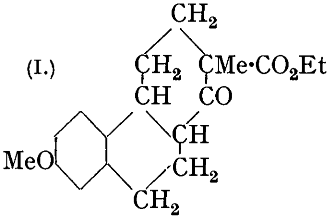
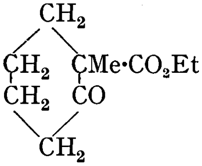
14. *Experiments on the Synthesis of Substances related to the Sterols. Part XV (Part IX continued).*

By Robert Robinson and James Walker.

Ethyl 1-keto-7-methoxy-2-methyl-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydrophenanthrene-2-carboxylate (I), obtained by the method of Part IX (J., 1936, 752) as an oil, proves to be largely convertible into a homogeneous *semicarbazone* and thus could be safely employed as an intermediate in the projected synthesis of oestrone or a stereoisomeride. Before proceeding to further stages with such valuable material, however, we have instituted a comparison of the various methods anticipated to be available for the construction of the fourth ring.

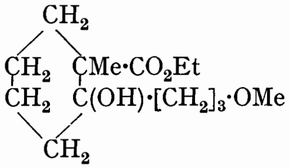

(I.)

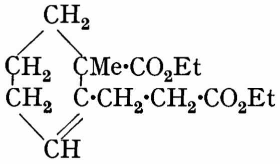

(II.)

For this purpose we have examined the reactions of the keto-ester (II) in directions not previously investigated; the Reformatzky reaction with ethyl bromoacetate has already been studied (Chuang, Tien, and Huang, *Ber.*, 1935, **68**, 864; Linstead and Millidge, J., 1936, 480), and the condensation of (II) with ethyl cyanoacetate has been mentioned by Linstead and Millidge (*loc. cit.*; unpublished work by Linstead, Newitt, and Sapiro). (II) was readily reduced by means of aluminium *iso*propoxide (with partial transposition of alkoxy-groups), but the *sec.*-alcohol obtained could not be smoothly converted into a corresponding chloride or bromide. The subject was studied in considerable detail and a selection of typical experiments is described in the experimental section.

Reaction of (II) with ethylmagnesium iodide gave a mixture of esters undoubtedly containing the *sec.*-alcohol obtained by reduction of the ketone. The products obtained by using γ-methoxypropylmagnesium iodide could be separated except for contamination with a trace of an unsaturated compound. The main product was *ethyl 2-methyl-1-γ-methoxypropyl*cyclo*hexan-1-ol-2-carboxylate* (III), and this substance was dehydrated, and the resulting unsaturated compound catalytically hydrogenated. In the last two stages the products had the expected boiling points and other properties, but analysis disclosed the presence of impurities and further investigation of the subject is in progress. We have obtained indications of the condensation of (II) with acetylene in the presence of potassium and with ethyl β-chloropropionate and magnesium; the product of the latter reaction is probably (IV) or an isomeride with the double bond in a different position.

(III.)



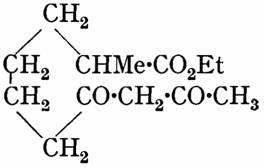


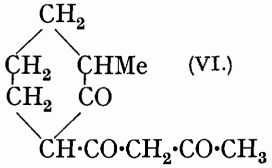
(IV.)

Under the influence of sodamide, (II) condensed readily with acetone with formation of a β-*diketone*, but the additive process was unaccompanied by loss of the elements of water or of alcohol.

Evidently the acetonyl group unites with the keto-carbonyl of the keto-ester and ring-scission occurs with formation of (V). The hydrolysis of this diketone, even by means of aqueous alkalis, gives rise to the formation of 2-methyl*cyclo*hexanone. The mechanism may be in part a reversal of the original ring-fission, accompanied by loss of acetone, but it is also probable that the intermediate (VI) is produced under the appropriate conditions. When (V) was treated with boiling alcoholic sodium ethoxide, methyl*cyclo*hexanone was obtained in high yield, accompanied by a little ethyl acetoacetate.

(V.)





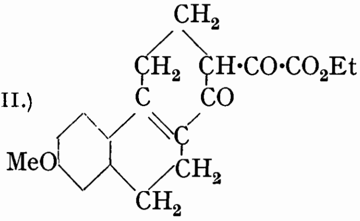
(VI.)

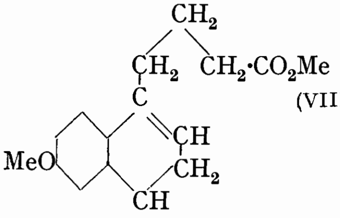
We have also been engaged, and are continuously engaged, in the study of alternatives to, or improvements of, the method of preparation of the ester (I).

The least satisfactory stage is the oxidation of 7-methoxy-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydrophenanthrol to the corresponding ketone by means of chromic acid; somewhat better results are obtained by heating the *sec.*-alcohol with cupric oxide.

Two methods designed to avoid this stage have been tried, but neither succeeded. In the first place we found that carbethoxyl cannot be introduced into the unsaturated ketone (XII) by way of the *oxalyl* derivative (VII); the latter is readily obtained, but suffers extensive decomposition on heating.

(VII.)

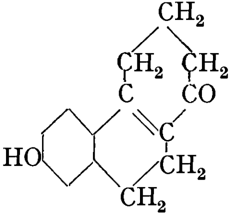


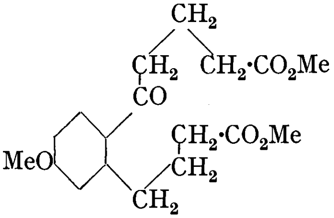


(VIII.)

Secondly, we thought that the acid chloride corresponding to the ester (VIII) might be ring-closed and simultaneously reduced on treatment with aluminium chloride in *cyclo*hexane solution. A general method along these lines has been disclosed by Nenitzescu and Ciorănescu (*Ber.*, **1936**, **69**, 1820). The *ester* (VIII) was readily obtained by the action of sulphuric acid at −10° on methyl 5-keto-8-*m*-methoxyphenyloctoate and on hydrolysis furnished *γ-6-methoxy-3 : 4-dihydro-1-naphthylbutyric acid*, but the method of the above-mentioned authors applied to the chloride of this acid furnished no saturated ketones and instead 1-*keto*-7-*hydroxy*-1 : 2 : 3 : 4 : 9 : 10-*hexahydrophenanthrene* (IX) and its known methyl ether (XII).

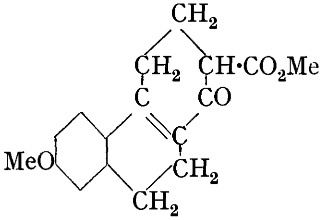
(IX.)

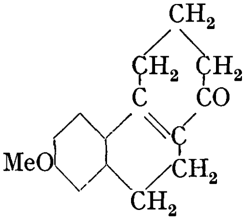




(X.)

(XI.)





(XII.)

A promising new synthetic device, which is further developed in the succeeding communication, consists in applying the Friedel–Crafts reaction to derivatives of γ-*m*-methoxyphenylbutyric acid in such a way as to introduce appropriate chains in the *p*-position to the methoxyl group. Thus methyl *m*-methoxyphenylbutyrate and γ-carbomethoxybutyryl chloride afford the *ester* (X) among the products of their interaction in the presence of aluminium chloride. Double ring-closure with the aid of potassium methoxide gives (XI), recognised as such by its ferric reaction and by hydrolysis with formation of (XII). The constitution of (XII) follows from a number of indications, the only point under consideration being the orientation of substituents in the aromatic benzene ring. The present authors (Part IX) have obtained the dehydro-derivative of the ketone as a by-product of the oxidation of its tetrahydro-compound. This ketomethoxytetrahydrophenanthrene is of known constitution (Butenandt and Schramm, *Ber.*, 1935, **68**, 2090). Furthermore, Haberland (*Ber.*, 1936, **69**, 1380), starting from β-naphthol, has synthesised a substance to which the constitution (XII) was assigned. The properties tally with those previously described by Robinson and Schlittler (J., 1935, 1288), to whose paper Haberland makes a general reference without specifically stating that the substance in question was already known.

EXPERIMENTAL.

Ethyl 1-*Keto*-7-*methoxy*-2-*methyl*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydrophenanthrene*-2-*carboxylate Semicarbazone.*—When ethyl 1-keto-7-methoxy-2-methyl-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydrophenanthrene-2-carboxylate (J., 1936, 752) (80 mg.) was treated with semicarbazide hydrochloride (40 mg.) and crystallised sodium acetate (60 mg.) in aqueous alcoholic solution at room temperature for a few days, the *semicarbazone* (65 mg.) separated as a cream-coloured solid. Crystallisation from methyl alcohol afforded colourless, elongated, diamond-shaped prisms, m. p. 197—199° (Found : C, 64·5; H, 7·2. $C_{20}H_{27}O_4N_3$ requires C, 64·4; H, 7·2%).

Condensation of 1-*Keto*-7-*methoxy*-1 : 2 : 3 : 4 : 9 : 10-*hexahydrophenanthrene with Ethyl Oxalate.*—Freshly prepared, alcohol-free sodium ethoxide (2·3 g.) was added to a solution of 1-keto-7-methoxy-1 : 2 : 3 : 4 : 9 : 10-hexahydrophenanthrene (6·0 g.) and ethyl oxalate (4·5 g.) in dry ether (100 c.c.) and the lumps were disintegrated with a glass rod. The sodium ethoxide rapidly dissolved and an orange sodio-derivative soon separated. After the mixture had been kept for 40 hours at room temperature, ice and dilute sulphuric acid were added, orange needles then separating. These were taken up in a large volume of ether; the dried extract on evaporation gave an orange solid in practically quantitative yield. Recrystallisation from methyl alcohol afforded deep orange prisms, m. p. 90—91° (Found : C, 70·1, 69·9; H, 6·2, 6·3. $C_{19}H_{20}O_5$ requires C, 69·5; H, 6·0%). With ferric chloride in aqueous-alcoholic solution a greenish-brown coloration was produced.

The *ester* (VII) was heated at 185—195° for 4 hours and the evolution of gas which started at *ca.* 180° was still in progress at the end of that time; the appearance of the material suggested that further decomposition was taking place. The cooled product was dissolved in ether, the solution filtered, and after removal of the solvent the residue was distilled, b. p. 170—200°/0·2 mm.; the distillate (4·9 g.) gave a ferric reaction indistinguishable from that of the starting material. The product (280 mg.) was heated with phenylhydrazine (170 mg.) on a steam-bath for 5 hours. The resulting viscous brown syrup crystallised on trituration with a little ether and the solid was collected, washed with ether, and dried. From its ready solubility it was obviously not the expected phenylpyrazolone derivative; crystallisation from ethyl alcohol gave a voluminous mass of small prisms, m. p. 162° after sintering and darkening from 159° (Found : C, 79·1; H, 6·9; N, 9·0. $C_{21}H_{22}ON_2$ requires C, 79·2; H, 6·9; N, 8·8%). Evidently the oxalyl residue had been split off completely during heating and the substance last described is the *phenylhydrazone* of 1-*keto*-7-*methoxy*-1 : 2 : 3 : 4 : 9 : 10-*hexahydrophenanthrene.*

Methyl γ-6-*Methoxy*-3 : 4-*dihydro*-1-*naphthylbutyrate* (VIII).—A solution of methyl 5-keto-8-*m*-methoxyphenyloctoate (J., 1936, 750) (16·3 g.) in concentrated sulphuric acid (70 c.c.) at −10° was kept for 4 hours and then poured on ice. The colourless oil that separated (13·2 g.) was isolated by means of ether and distilled as a faintly yellow, limpid oil (12·5 g.) at 175—178°/0·2 mm., $n_D^{17.5°}$ 1·5550 (Found : C, 73·8; H, 7·7. $C_{16}H_{20}O_3$ requires C, 73·8; H, 7·7%).

γ-6-*Methoxy*-3 : 4-*dihydro*-1-*naphthylbutyric Acid.*—The above ester (1 mol.) was refluxed for 6½ hours with 3% methyl-alcoholic potassium hydroxide (2 mols.) and the resulting crystalline acid was isolated by means of ether. Repeated crystallisation from 75% acetic acid failed to give a product with a sharp melting point, since the microcrystalline powder softened from 123°, collapsed at 129—130°, and only cleared on further heating at *ca.* 146° (Found : C, 73·3; H, 7·0. $C_{15}H_{18}O_3$ requires C, 73·2; H, 7·3%). The *substance* was freely soluble in dilute aqueous sodium carbonate and hence was not mixed with the isomeric lactone.

1-*Keto*-7-*hydroxy*-1 : 2 : 3 : 4 : 9 : 10-*hexahydrophenanthrene.*—Dry methoxydihydronaphthylbutyric acid (11·6 g.) was converted into the acid chloride in ethereal solution (100 c.c.) by the method of Carré and Libermann (*Compt. rend.*, 1934, **199**, 1422) by means of thionyl chloride (3·8 c.c.; 1 mol.) in the presence of pyridine (3·8 c.c.; 1 mol.). The chloride, after standing in a vacuum desiccator over potassium hydroxide, was dissolved in a mixture of purified *cyclo*hexane (70 c.c.) and carbon disulphide (50 c.c.), the latter being necessary owing to the insolubility of the chloride in the former solvent, and the solution was treated in the manner described by Nenitzescu and Ciorănescu (*loc. cit.*) with finely powdered aluminium chloride (13 g.). The reaction mixture was finally treated with ice and concentrated hydrochloric acid; addition of ether facilitated separation of the resulting emulsion. It was not practicable to wash the ether–carbon disulphide solution with sodium carbonate solution owing to persistent emulsions, and therefore the crude product was isolated by evaporation of the solvent, redissolved in sufficient ether to effect complete solution, and shaken with sodium carbonate solution to remove any acidic material. On evaporation of the dried ethereal solution the crude product (5·8 g.) largely crystallised. Trituration with ether removed oily material and the cream-coloured solid (0·8 g.) then crystallised from aqueous alcohol (norit) in pale yellow plates, m. p. 220—221° (Found : C, 78·6; H, 6·5. $C_{14}H_{14}O_2$ requires C, 78·5; H, 6·5%). The *substance* dissolved in caustic alkalis to yellow solutions with an intense apple-green fluorescence and its yellow solution in concentrated sulphuric acid had a bluish-green fluorescence which was not diminished on dilution with acetic acid. When the yellow, fluorescent, aqueous alcoholic caustic alkali solution of the substance was neutralised, both colour and fluorescence disappeared and returned on continuing the addition of hydrochloric acid. The substance gave no ferric reaction.

The ethereal filtrate (above) was evaporated and the product was treated with an excess of semicarbazide hydrochloride and sodium acetate crystals in aqueous alcoholic solution. The *semicarbazone* of 1-*keto*-7-*methoxy*-1 : 2 : 3 : 4 : 9 : 10-*hexahydrophenanthrene* which separated rapidly was collected and washed with a little alcohol. It was sparingly soluble in the usual solvents and separated from *n*-propyl alcohol as a microcrystalline, cream-coloured powder which showed marked phototropy, becoming bright yellow on exposed surfaces, m. p. 238—239° (decomp.) after sintering and darkening from 232° (Found : C, 67·4; H, 6·5. $C_{16}H_{19}O_2N_3$ requires C, 67·4; H, 6·7%).

Oxidation of 7-*Methoxy*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydrophenanthrol with Copper Oxide.*—Methoxyoctahydrophenanthrol (J., 1936, 750) (12·8 g.) was heated with copper oxide (4·4 g.), added at intervals, during 20 minutes at 280—300° (metal bath) and the cooled mixture was extracted with ether. The distillate (10·9 g.) obtained on evaporation of the ether and distillation (0·2 mm.) of the crude product was treated with semicarbazide hydrochloride (6·5 g.) and sodium acetate (8·0 g.) in the usual way; the semicarbazone (cf. *loc. cit.*) (4·9 g.) rapidly separated, m. p. 225°. Unoxidised material (7·4 g.) was recovered on dilution of the mother-liquors and extraction with ether.

Ethyl 2-*Methyl*cyclo*hexan*-1-*ol*-2-*carboxylate*.—Ethyl 2-methyl*cyclo*hexanone-2-carboxylate was reduced by Ponndorf's method (*Z. angew. Chem.*, 1926, **39**, 138). Aluminium *iso*propoxide (7 g.) was added to a solution of ethyl 2-methyl*cyclo*hexanone-2-carboxylate (12 g.) in dry *iso*propyl alcohol (60 c.c.), and the mixture was slowly distilled through an 18-inch column, fresh *iso*propyl alcohol being added at intervals to compensate for the distillate. When acetone could no longer be detected by means of sodium nitroprusside in the distilling liquid (*ca.* 2 hours), the remainder of the *iso*propyl alcohol was distilled and the residue was steam-distilled until no more oily drops came over. The crude colourless oil isolated by means of ether distilled as a colourless mobile oil (11·6 g.), b. p. 118—122°/15 mm., $n_D^{14°}$ 1·4600 [Found in two different preparations: C, 64·7, 65·4, 65·1; H, 9·6, 9·6, 9·9. $C_{11}H_{20}O_3$ (*iso*propyl ester) requires C, 66·0; H, 10·0%. $C_{10}H_{18}O_3$ (ethyl ester) requires C, 64·5; H, 9·7%]. The analysis indicates that partial replacement of ethyl by *iso*propyl has taken place and this is borne out by the composition of the 3 : 5-dinitrobenzoate.

The 3 : 5-*dinitrobenzoate* of the iso*propyl ester* was obtained by the action of 3 : 5-dinitrobenzoyl chloride in slight excess on the hydroxy-ester (490 mg.) in dry pyridine (5 c.c.). The amber syrup (1047 mg.) isolated in the known manner crystallised in contact with methyl alcohol and recrystallisation from the same solvent afforded colourless plates, m.p. 92—93° [Found: C, 54·7; H, 5·7. $C_{18}H_{22}O_8N_2$ (*iso*propyl ester) requires C, 54·8; H, 5·6%. $C_{17}H_{20}O_8N_2$ (ethyl ester) requires C, 53·7; H, 5·2%].

Attempted Replacement of the Hydroxyl Group in the Foregoing Ester by Halogen.—(a) The hydroxy-ester (9·9 g.) in pyridine (7 c.c.) was added slowly to a mixture of phosphorus tribromide (1·9 c.c.) and pyridine (1 c.c.) cooled to 0°. The ester was washed in with pyridine (3 c.c.) and the mixture was left in the ice-bath for some time. Ice-water and ether were then added and the separated ethereal solution was washed several times with dilute sulphuric acid, once with sodium carbonate solution, dried, and evaporated. The crude product gave only a feeble Beilstein test for halogen and on distillation in a vacuum a colourless, halogen-free oil (4·8 g.), $n_D^{18°}$ 1·4570, distilled over a wide range, leaving a very viscous still-residue.

(b) The hydroxy-ester (9·5 g.) in pyridine (5 c.c.) was added dropwise during 15 minutes to thionyl chloride (4 c.c.; 10% excess) in chloroform (25 c.c.) with cooling in ice-water and thorough shaking. After remaining for 2 hours at 0°, the solution was warmed on the water-bath for ½ hour, sulphur dioxide and some hydrogen chloride being evolved. The mixture was then worked up in the usual way and on distillation of the crude product in a vacuum there were obtained: (i) a colourless mobile oil (3·5 g.), b. p. 90—100°/16 mm., $n_D^{17°}$ 1·4525, with pleasant "unsaturated" odour, decolorising aqueous potassium permanganate solution and bromine in chloroform; (ii) a colourless mobile oil (1·3 g.), b. p. 100—133°/16 mm., $n_D^{17°}$ 1·4562, containing a trace of halogen; (iii) a faintly yellow oil (2·0 g.), b. p. mainly above 200°/16 mm., $n_D^{17°}$ 1·465, containing halogen.

(c) The hydroxy-ester (10 g.) in light petroleum (20 c.c.) was added slowly to phosphorus pentachloride (12 g.; slight excess) under light petroleum (20 c.c.) cooled to −10°. The mixture was allowed to rise slowly to room temperature and after 30 hours ice-water was added, and the washed solution dried and evaporated. On fractional distillation of the crude product in a vacuum there were obtained: (i) a colourless pleasant-smelling mobile oil (4·8 g.), b. p. 88—95°/15 mm., $n_D^{20°}$ 1·4513 (Found: C, 70·7; H, 9·6. $C_{10}H_{16}O_2$ requires C, 71·4; H, 9·5%); the *substance* contained a trace of chlorine and from the analysis and the decolorisation of potassium permanganate and bromine in chloroform it was obviously a derived unsaturated ester; (ii) a colourless halogen-containing oil (2·6 g.), b. p. to 130°/17 mm., leaving a small decomposed still-residue.

(d) The hydroxy-ester (5 g.) in ethyl acetate (20 c.c.) was saturated with dry hydrogen bromide at 0°, and the mixture kept below room temperature for 3 days. On examination of the product there was obtained a colourless mobile oil (2·7 g.), b. p. 133—140°/20 mm., $n_D^{24°}$ 1·4470 (Found: C, 63·4; H, 9·1; Br, 0·1. $C_{12}H_{20}O_4$ requires C, 63·2; H, 8·8%); there was a considerable still-residue.

Attempted Condensation of Ethyl 2-*Methyl*cyclo*hexanone*-2-*carboxylate with Acetylene*.—Ethyl 2-methyl*cyclo*hexanone-2-carboxylate (23·5 g.) was added to a suspension of powdered potassium (5 g.) in benzene (*ca.* 100 c.c.). When the potassio-derivative had been formed, a brisk stream of purified acetylene was passed for 5 hours through the amber solution, which assumed a deep reddish-brown colour. On shaking with water and ether the colour was discharged to pale yellow. The separated upper layer was dried and evaporated. On a preliminary distillation of the crude product in a vacuum there was some decomposition and on further fractionation of the distillate there were obtained: (i) a slightly yellow, mobile oil (2·9 g.), b. p. to 126°/18 mm., $n_D^{20°}$ 1·4636; (ii) a colourless mobile oil (11·7 g.), b. p. 127—138°/18 mm., $n_D^{20°}$ 1·4642; a middle fraction of

(ii) was analysed (Found : C, 65·1 ; H, 8·3%) ; (iii) a faintly yellow oil (2·6 g.), b. p. to 149°/19 mm., $n_D^{20°}$ 1·451. Fraction (ii) was unsaturated to dilute potassium permanganate solution and gave a white turbidity with ammoniacal silver nitrate solution.

*Action of Ethylmagnesium Iodide on Ethyl 2-Methyl*cyclo*hexanone-2-carboxylate.*—A solution of ethylmagnesium iodide (2·5 g. of magnesium; 17·2 g. of ethyl iodide; 80 c.c. of ether) was added to a solution of ethyl 2-methyl*cyclo*hexanone-2-carboxylate (18·4 g.) in ether (150 c.c.) with shaking and cooling in ice-water. Next day the mixture was warmed on the water-bath for ½ hour, cooled, and treated with ice and dilute sulphuric acid. The separated ethereal solution was washed with sodium thiosulphate solution, dried, and evaporated. The crude product was further distilled in a vacuum, giving a colourless mobile oil (17·6 g.), $n_D^{17°}$ 1·4640, without fore-running at 130—140°/19 mm., mainly at 135—138°/19 mm. (Found in two different preparations : C, 65·6, 65·7; H, 9·7, 9·6%).

The above product (17 g.) was refluxed for 18 hours with 20% methyl-alcoholic potassium hydroxide solution (4 mols.). The mixture, added to water, was extracted thrice with ether and the acid (11·4 g.) recovered from the alkaline solution was esterified with diazomethane (from 21 g. of nitrosomethylurea). The resulting ester was fractionally distilled into four approximately equal fractions : (i) b.p. 131—135°/21 mm., $n_D^{18°}$ 1·4578 (Found: C, 65·0; H, 9·8%) ; (ii) b. p. 131—136°/21 mm., $n_D^{18°}$ 1·4560; (iii) b. p. 134—140°/21 mm., $n_D^{18°}$ 1·4512; (iv) b. p. 139—145°/21 mm., $n_D^{18°}$ 1·4432 (Found: C, 65·5; H, 9·9. $C_{11}H_{20}O_3$ requires C, 66·0; H, 10·0%. $C_9H_{16}O_3$ requires C, 62·8 ; H, 9·3%). The analyses suggest contamination of the desired product with a small amount of the secondary alcohol produced by the reduction of the carbonyl group of the keto-ester by the Grignard reagent (cf. Kharasch and Weinhouse, *J. Org. Chem.*, 1936, **1**, 210, for further examples of the reduction of *cyclo*hexanones by Grignard reagents).

*Ethyl 2-Methyl-1-γ-methoxypropyl*cyclo*hexan-1-ol-2-carboxylate* (III).—The Grignard reagent was prepared from γ-methoxypropyl iodide (31 g.) (Haworth and Perkin, J., 1894, **65**, 597; Hamonet, *Bull. Soc. chim.*, 1905, **33**, 525), magnesium (3·6 g.) activated by heating with iodine (0·9 g.), and ether (75 c.c.) and added to a stirred solution (mercury seal) of ethyl 2-methyl*cyclo*hexanone-2-carboxylate (27 g.) in ether (140 c.c.) cooled in ice-water. A vigorous reaction ensued and after being stirred for ½ hour and kept at room temperature for 15 hours, the mixture was refluxed for ½ hour, and then decomposed by the addition of dilute sulphuric acid; the separated ethereal solution was washed with sodium thiosulphate solution, dried, and evaporated. On distillation of the crude product in a vacuum there were obtained : (i) a colourless mobile oil (11·8 g.), b. p. to 129°/14 mm., $n_D^{18°}$ 1·4528; (ii) a colourless, rather limpid oil (17 g.; approx. 45%), b. p. 158—168°/13 mm., $n_D^{18°}$ 1·4660 (Found: C, 65·9; H, 9·9. $C_{14}H_{26}O_4$ requires C, 65·1; H, 10·1%). There was no significant distillate in the range 130—158°/13 mm. Fraction (i) showed unsaturation towards tetranitromethane and bromine in chloroform.

Dehydration of the Foregoing Ester with Potassium Hydrogen Sulphate.—The above ester (17 g.) was heated with potassium hydrogen sulphate at 175° for 1·25 hours and then the product was isolated by means of ether. On distillation of the crude product a colourless mobile oil (15 g.) was collected at 140—145°/15 mm., $n_D^{18°}$ 1·4691 (Found : C, 68·1; H, 9·8%). The foregoing treatment with potassium hydrogen sulphate was repeated and the product isolated as before was a colourless mobile oil, b. p. 140—147°/17 mm., $n_D^{16°}$ 1·4684 (Found : C, 69·0, 69·2; H, 9·7, 9·9. $C_{14}H_{24}O_3$ requires C, 70·0; H, 10·0%. $C_{13}H_{22}O_3$ requires C, 69·0; H, 9·7%). The *compound* instantly decolorised bromine in chloroform and developed an intense orange-yellow colour with tetranitromethane.

Catalytic Hydrogenation of the above Unsaturated Ester.—The unsaturated ester (11·3 g.) in methyl alcohol (140 c.c.) was shaken with 2% palladised strontium carbonate (11 g.) in hydrogen under an excess pressure of 3 atms. Absorption ceased when 76% of the theoretical amount of hydrogen for the saturation of one double bond had been taken up in 40 minutes. The crude product, after removal of the solvent from the filtered solution, was heated on the water-bath with 1% ethyl-alcoholic potassium hydroxide (1·1 g.; 50% aqueous alcohol) for 2·5 hours. The mixture, diluted with water, was then extracted with ether and the extract was dried and evaporated. A small first fraction was collected up to 139°/13 mm. and then a colourless mobile oil (8·1 g.), saturated to bromine in chloroform and tetranitromethane, distilled steadily at 140—144°/13 mm., $n_D^{15°}$ 1·4587 (Found : C, 68·3; H, 10·7; OEt + OMe, 28·4, 26·6, 28·8. $C_{14}H_{26}O_3$ requires C, 69·4; H, 10·7; OEt + OMe, 31·4%. $C_{13}H_{24}O_3$ requires C, 68·4; H, 10·5; OEt + OMe, 33·3%).

The divergence in the analytical figures from the anticipated C_{14} formula is being further investigated; the possibility of persistent contamination with some carbinol which had survived the treatment with potassium hydrogen sulphate appears to be precluded on consideration of the relevant boiling points.

*Condensation of Ethyl 2-Methyl*cyclo*hexanone-2-carboxylate with Ethyl β-Chloropropionate.*—Magnesium (2 g.) activated by Baeyer's method was placed under a mixture (1 : 1) of anisole–benzene (15 c.c.). From a dropping-funnel charged with ethyl β-chloropropionate (9 g.; slight excess) a small quantity (*ca.* 1 g.) was added to the magnesium along with a little methyl iodide (1 c.c.). Ethyl 2-methyl*cyclo*hexanone-2-carboxylate (9 g.) was then mixed with the chloro-ester in the dropping-funnel, and the mixture was added slowly to the magnesium. There was marked evidence of reaction on warming the mixture gently over a bare flame and after all the mixture of esters had been added with intermittent heating to maintain reaction, the mixture was warmed on the water-bath for ½ hour after washing in the last traces of ester mixture with mixed solvent (16 c.c.). After keeping at room temperature for 15 hours, ether and saturated aqueous ammonium chloride solution were added and the upper layer was separated, dried, and evaporated. After elimination of fore-runnings distilling up to 130°/18 mm., distillation under a pressure of 1·5 mm. indicated the presence of two fractions having b. p.'s 150—175° and *ca.* 200°. The total distillate (6·4 g.) was refluxed for 8 hours with methyl-alcoholic potassium hydroxide (3 g.; 250 c.c.), methyl alcohol was then removed by distillation, and the neutral material recovered in the usual way by means of ether. On distillation of the crude product a rather viscous yellow oil (3·2 g.) passed over at 142—152°/0·3 mm., $n_D^{10°}$ 1·4906 (Found : C, 66·8; H, 9·3. $C_{15}H_{24}O_4$ requires C, 67·1; H, 8·9%). The *substance* immediately decolorised bromine in chloroform, which fact along with the analytical figures indicated it to be the anticipated unsaturated ester.

Ethyl 7 : 9-*Diketo*-2-*methyldecoate* (V).—A mixture of ethyl 2-methyl*cyclo*hexanone-2-carboxylate (20 g.) and acetone (8 g.) was added to powdered sodamide (5 g.) stirred under dry ether (100 c.c.). Ammonia was at once evolved and heat was generated. When the initial reaction subsided, the yellow solution was refluxed for 3 hours and kept for 12 hours at room temperature. Ice and water were added and the bright yellow aqueous solution was separated and acidified. The oil was taken up in ether, and the extract dried over sodium sulphate and distilled. After removal of the solvent there were obtained 9·8 g., b. p. 140—145°/0·33 mm. (Found : C, 63·1; H, 9·3; EtO, 18·3%), and 3·3 g. of higher b. p. (Found : C, 60·5; H, 8·8; EtO, 13·2%). The latter material was far from homogeneous and was not further examined. A portion of the lower-boiling material was twice redistilled, b. p. 138—142°/0·3 mm. (Found : C, 64·2; H, 9·2; EtO, 18·3. $C_{13}H_{22}O_4$ requires C, 64·4; H, 9·1; EtO, 18·6%). This β-diketone gives a deep blood-red ferric reaction in alcoholic solution and when ferric chloride is added to an aqueous suspension the oily drops are coloured orange-red. It condenses with diaminoveratrone in acetic acid solution to a yellow copyrine derivative exhibiting green fluorescence, and with hydroxylamine it yields an *iso*oxazole derivative as a colourless oil insoluble in aqueous alkalis. It is insoluble in aqueous sodium carbonate, but dissolves readily in sodium hydroxide solution. On boiling the alkaline solution the odour of methyl*cyclo*hexanone becomes intense. The diketone (5 g.) was refluxed with anhydrous alcoholic sodium ethoxide (0·2 g. of sodium in 50 c.c.) for 2 hours, and two-thirds of the alcohol distilled. The solution was then acidified with acetic acid, diluted with water, and shaken with ether. The extract was washed with brine, concentrated, and washed several times with aqueous sodium hydroxide. The combined alkaline aqueous solutions were acidified and extracted with ether; after removal of the solvent the small oily residue had the odour and ferric reaction of ethyl acetoacetate. This identification was confirmed by the preparation of the copper derivative, green needles from benzene, m. p. 191—192°. The dried ethereal solution was distilled, giving eventually 1·7 g. of 2-methyl*cyclo*hexanone, b. p. 155—160°; semicarbazone, m. p. 194°.

*Condensation of Methyl γ-*m*-Methoxyphenylbutyrate with γ-Carbomethoxybutyryl Chloride.*—Aluminium chloride (13·4 g.; 2 mols.) was finely powdered and placed under carbon disulphide (50 c.c.) in a three-necked flask fitted with a stirrer (mercury seal), reflux condenser and dropping-funnel. A mixture of methyl γ-*m*-methoxyphenylbutyrate (10·4 g.; 1 mol.) and γ-carbomethoxybutyryl chloride (12·5 g.; 1·5 mols.) (Clutterbuck and Raper, *Biochem. J.*, 1925, **19**, 385) in carbon disulphide (30 c.c.) was added dropwise with thorough stirring. The light brown viscous complex was stirred thoroughly and a gentle evolution of hydrogen chloride took place; no external cooling was used. After 2—3 days at room temperature the carbon disulphide was decanted, and the residue treated with ice and concentrated hydrochloric acid. The resulting heavy, light yellow oil (17·4 g.), isolated by means of ether, was immediately refluxed for 3·5 hours with 10% methyl-alcoholic potassium hydroxide solution (120 c.c.). After dilution with water, acidification with hydrochloric acid, and extraction with ether, the extract was well washed with water, dried, and evaporated, leaving a viscous, light brown syrup (9·0 g.). The crude product was dissolved in 10% potassium hydroxide solution (*ca.* 3 mols.) and shaken for

6 hours with methyl sulphate (15 c.c.), and the mixture after the addition of an excess of potassium hydroxide was heated for 3 hours on the steam-bath to hydrolyse esters. The acidic material was collected in ether in the usual way and re-esterified with methyl alcohol (40 c.c.) containing concentrated sulphuric acid (1·5 c.c.) by refluxing for 7·5 hours. The crude ester (9 g.), isolated by dilution with water and extraction with ether, distilled as a viscous, light amber oil (7·6 g.), b. p. 205—210°/0·6 mm., $n_D^{15^\circ}$ 1·5228 (Found : C, 64·5; H, 7·1. $C_{18}H_{24}O_6$ requires C, 64·3; H, 7·1%). The following experiments show that this ester is *methyl* γ-[5-*methoxy*-2-(γ-*carbomethoxybutyryl*)*phenyl*]*butyrate* (X).

Ring-closure.—The above product (4·15 g.) in benzene (40 c.c.) was refluxed with freshly-prepared alcohol-free potassium methoxide (from 1 g. of potassium) for 4 hours. After a further 12 hours at room temperature the benzene layer had become much lighter in colour and a separation of a yellowish solid had occurred; ether and dilute sulphuric acid were added and neutral and acidic material were separated in the usual way. The acidic material (1·36 g.) was set aside (see below) and the neutral material (2 g.), which gave a reddish-brown colour with ferric chloride in alcoholic solution, was refluxed with 12% hydrochloric acid (30 c.c.) for 7 hours and the product was again separated into acidic (see below) and neutral (0·5 g.) portions; the latter still gave a coloration with ferric chloride and it was therefore refluxed for 7 hours with 20% methyl-alcoholic potassium hydroxide (large excess) and, as previously, some acidic material (see below) was isolated along with a neutral brown oil (0·3 g.), which was devoid of ferric reaction and gave a copious precipitate of the 2 : 4-dinitrophenylhydrazone of 7-methoxy-1 : 2 : 3 : 4 : 9 : 10-hexahydrophenanthrone on treatment with Brady's reagent; the very dark maroon product after recrystallisation from toluene had m. p. 256°, alone or in admixture with an authentic specimen (J., 1935, 1288).

The combined acidic material referred to above was collected and refluxed with methyl alcohol (45 c.c.) containing concentrated sulphuric acid (1 c.c.) for 10 hours. The mixture was then diluted with much water and extracted with ether. The ethereal solution was washed twice with dilute sodium carbonate solution and on acidification of the alkaline washings a small amount of acidic material was precipitated; this was collected, washed and dried (68 mg.) and after two crystallisations from aqueous acetic acid the cream-coloured prisms had m. p. 228—230° (Found in a specimen dried at 100°/15 mm. : C, 71·3; H, 5·5. $C_{14}H_{12}O_2,C_2H_4O_2$ requires C, 70·6; H, 5·9%). For 7-hydroxy-1-keto-1 : 2 : 3 : 4-tetrahydrophenanthrene Butenandt and Schramm (*loc. cit.*) quote m. p. 232° and it is considered that this may be the constitution of the present by-product (for analogous demethylation with sodium ethoxide, cf. Cohen, Cook, and Hewett, J., 1935, 454).

The crude ester (2·63 g.) was distilled in a vacuum, a viscous syrup (1·7 g.) distilling largely at 180—190°/0·1 mm. with a small amount at *ca.* 200°/0·1 mm. On standing, most of the syrup crystallised, but recrystallisation was impracticable, although fine rectangular plates separated from the oil left behind on evaporation of the solvent from a solution in light petroleum. The product in dry benzene (20 c.c.) was left with molecular potassium (0·3 g.) at room temperature for 14 hours and then boiled for 1·5 hours. Alcohol was then added to the dark brown solution, which contained gelatinous material, and the benzene solution separated after addition of water was dried and evaporated, leaving a brown glass (1·5 g.) which gave a brownish-red colour with ferric chloride in alcoholic solution. An attempt to prepare a phenylpyrazolone only gave a non-crystallisable resin.

The product was refluxed with a 20% solution of sulphuric acid in acetic acid (30 c.c.); the neutral material (0·74 g.) recovered gave a fine blood-red colour in alcoholic solution with ferric chloride. After hydrolysis of the neutral material at the boiling point with 15% methyl-alcoholic potassium hydroxide (25 c.c.) for 7 hours, the recovered neutral material (0·57 g.), a viscous red syrup, still had a faint ferric reaction and gave a copious precipitate (0·78 g.) on treatment with Brady's reagent. The dark maroon crystals which separated from toluene had m. p. 256° alone or in admixture with the 2 : 4-dinitrophenylhydrazone of 1-keto-7-methoxy-1 : 2 : 3 : 4 : 9 : 10-hexahydrophenanthrene.

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