

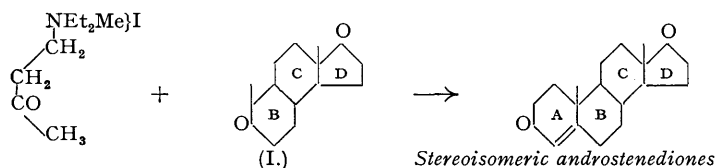
132. Experiments on the Synthesis of Substances related to the Sterols. Part XLI. Androstenedione. Part I.

By R. H. MARTIN and SIR ROBERT ROBINSON.

Theory predicts the existence of sixteen optically inactive (*dl*) stereoisomerides of androstenedione, but these are divided into two groups of eight when the relative configuration of two asymmetric centres is fixed. The present communication describes a method by means of which it is believed that such a mixture of a maximum of eight *dl*-stereoisomerides (probably fewer) has been obtained.

We are here concerned only with the elaboration of the androstenedione structure and the substance itself is most probably included in the second group of stereoisomerides, in which series the penultimate stage has been reached. If our interpretation of the final reaction in the synthesis (see below) proves to be incorrect, the method can nevertheless be used, with a small modification of procedure and one additional stage.

IN Part XXX (Robinson and Weygand, J., 1941, 386) a synthesis of testosterone was foreshadowed by the condensation of a keto-alcohol [the cyclopentanol corresponding to (I)] with 4-diethylaminobutan-2-one methiodide in the presence of basic catalysts. This followed the proof that a similar condensation with 1-methyl-2-decalone afforded a phenanthrene derivative including the testosterone structure of rings A and B. Earlier work (du Feu, McQuillin, and Robinson, J., 1937, 53; cf. Rapson and Robinson, J., 1935, 1285) had shown that this type of condensation always involved a group $-\text{CHMe}\cdot\text{CO}-$ in preference to $-\text{CH}_2\cdot\text{CO}-$. This conclusion, based on several proved cases, is not invalidated with the particular component mentioned by the observation that acetylcyclohexene in an analogous process attacks the keto-methylene group (Jones and Koch, J., 1942, 393 and private communication; cf. Rapson and Robinson, *loc. cit.*); the steric conditions are quite different in this example. For these reasons we decided, in the first instance, to attempt the synthesis of androstenedione by way of the diketone (I) in the hope that neither keto-methylene group would enter into reaction and that the process would take the course illustrated below.

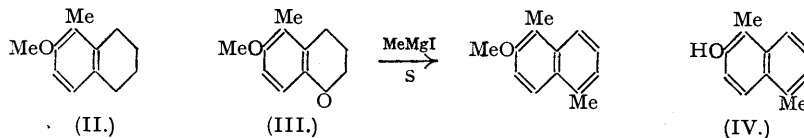


We have realised this scheme but have not yet proved the validity of the assumption made in regard to the constitution of the products.

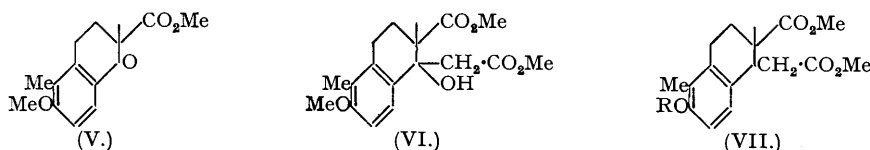
The synthesis of (I) has been carried out by adaptations of methods adumbrated in this series of papers (*e.g.*, Robinson and Schlittler, J., 1935, 1288; Robinson and Walker, J., 1936, 747; 1937, 1160; 1938, 183; Litvan and Robinson, J., 1938, 1997) and which with small, but useful, modifications of detail have been

employed by Bachmann and his collaborators in the synthesis of equilenin and some analogous substances (Bachmann, Cole, and Wilds, *J. Amer. Chem. Soc.*, 1939, **61**, 974; 1940, **62**, 824; and other papers).

The starting point in the present work was 1-methyl-2-naphthol, which was catalytically reduced and methylated to 6-methoxy-5-methyltetralin (II). On oxidation with chromic acid this substance afforded 6-methoxy-5-methyl-1-tetralone (III),* the constitution of which was proved by its conversion into 1:5-dimethyl-2-naphthol (IV) (Ruzicka and Sternbach, *Helv. Chim. Acta*, 1940, **23**, 355).



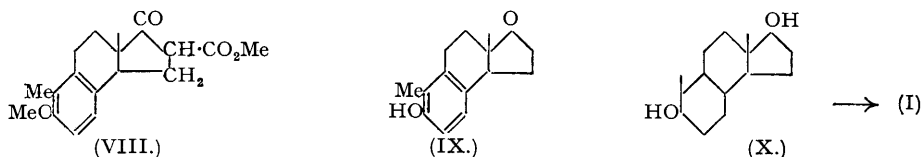
A further proof of the constitution of (III) is afforded by its conversion into 2:5-dimethoxy-1-methylnaphthalene (Cornforth, Cornforth, and Robinson, *J.*, 1942, 690). This substance can also be obtained from 1:6-dihydroxynaphthalene by a series of processes (the work forms part of a separate investigation and will be published later). A third link with known substances is mentioned in the experimental section. Condensation of (III) with methyl oxalate, heating of the product with loss of carbon monoxide, and C-methylation of the resulting β -keto ester afforded (V). The Reformatsky reaction with methyl bromoacetate then gave (VI).



This ester was dehydrated and reduced to stereoisomeric forms of (VII, R = Me), the details of the methods of Bachmann *et al.* (*loc. cit.*; also Bachmann and Thomas, *J. Amer. Chem. Soc.*, 1941, **63**, 598) being followed at these stages. We obtained an α -dimethyl ester, m. p. 112—113°, and a more readily soluble β -dimethyl ester, m. p. 53—54°. The corresponding α - and β -dicarboxylic acids give their respective anhydrides without configurational change. It appeared possible that a determination of spatial structure could be made by comparison of the first and the second dissociation constants of these acids (cf. Speakman, *J.*, 1941, 940), but Dr. Speakman, who very kindly made the necessary measurements, reports that the observed differences are not significant in this case. On grounds of analogy we are of the opinion that the more readily soluble β -series correspond in configuration to the natural hormones, and this was the experience of Bachmann and his colleagues in connexion with the intermediates from equilenin. This implies that CO₂Me and CH₂·CO₂Me are in the *cis*-position in the α -series and *trans*- in the β -series.

The α -derivatives were, however, obtained in the larger relative amount and accordingly the later stages were first examined in this series.

Conversion of (VII) (α) into (VIII) (α) was accomplished by the application of the Arndt-Eistert homologation process as developed by Litvan and Robinson (*loc. cit.*) for the transformation of *O*-methylæstric acid into œstrone. At the last stage the cyclopentanone ring was closed by the Dieckmann reaction (cf. Bachmann *et al.*, *loc. cit.*). The keto-ester was hydrolysed and demethylated in one operation to the phenolic ketone (IX).



Subsequently these reactions were carried out in the β -series also and the β -tricyclic phenolic ketone (IX) was isolated.

In order to proceed further it was necessary to reduce the aromatic nucleus at some stage and our first experiments in this direction were made with the phenolic α -di-ester (VII; R = H). This substance was either not reduced in useful yield or under more vigorous conditions of hydrogenation suffered loss of oxygen by hydrogenolysis. In these experiments we employed Raney nickel at 180—200°/150 atms. The failure led us to investigate other catalysts for high-pressure hydrogenation and the results are of general interest. Adkins ("Reactions of Hydrogen with Organic Compounds over Copper-Chromium Oxide and Nickel Catalysts," Wisconsin Univ. Press, 1937, p. 7) writes: "One would conclude that with platinum, for example, there is already a sufficient proportion of hydrogen upon the catalyst at one or two atmospheres pressure, since in general an increase of pressure of hydrogen does not increase the rate of hydrogenation."

There are few references to the use of platinum or palladium at higher temperatures and pressures. Spongy palladium has been used by Breteau (*Bull. Soc. chim.*, 1911, **9**, 729) for the vapour phase reduction of

* We find that this ketone, m. p. 114—115° (corr.), has previously been prepared by a nuclear synthetic method by Ruzicka and Hofmann (*Helv. Chim. Acta*, 1937, **20**, 1155).

phenanthrene at 150—160°. We have found, however, that 2% palladised strontium carbonate is an excellent catalyst for pressure hydrogenations at elevated temperatures. It does not appear to have been previously employed for this purpose. (a) Phenol was quantitatively hydrogenated to cyclohexanol in dioxan at 140—150°/123 atms. (b) Quinol dimethyl ether is reduced in dioxan to 1:4-dimethoxycyclohexane at 200°/100 atms. According to Adkins (*op. cit.*, p. 59) this substance is not reduced in presence of Raney nickel at 225°/100—200 atms. but can be hydrogenated at 200° with the help of reduced nickel on kieselguhr. (c) Ethyl *p*-hydroxybenzoate was quantitatively reduced to *trans*-4-carbethoxycyclohexanol in dioxan at 150—180°/150 atms. Here Raney nickel at 200°/160 atms. gave poor results and the present method of preparation of this important intermediate (and the related ketone) is greatly to be preferred to any of those already reported (Edson, *J. Soc. Chem. Ind.*, 1934, 53, 138; Balas and Srol, *Coll. Trav. chim. Tchechoslovaquie*, 1929, 1, 658; Mitsui, *Mem. Coll. Sci. Kyoto Imp. Univ.*, 1935, 18A, 329; cf. Perkin, J., 1904, 85, 416).

Although we were unsuccessful in applying this method to (VII; R = H), it was found that the tricyclic phenol (IX) could be reduced to the dihydric alcohol (X). In later work it was noted that the purity of the dioxan employed as solvent was of the utmost importance. The product was a glass and 32 inactive stereoisomerides are theoretically possible (32 more in the β -series). Oxidation with chromic acid gave the diketone (I), which should exist in eight inactive stereoisomeric forms (α -series). Owing, however, to possible isomerisation of the group $\cdot\text{CO}\cdot\text{CHMe}\cdot$ it is probable that four of these are labile forms and there are really four pairs of interconvertible diketones. A crystalline substance could be isolated in considerable relative amount from the mixture and there is little doubt that this particular isomeride preponderated.

The mixed diketones (I, α -series) were condensed with 4-diethylaminobutan-2-one methiodide after treatment with sodamide under the usual conditions, and mixed ketones, $\text{C}_{19}\text{H}_{26}\text{O}_2$, isolated. The absorption of an alcoholic solution confirmed the presence of an $\alpha\beta$ -unsaturated ketonic group.

Biological tests have been made so far only with the tricyclic compounds of the α -series. The results were negative and will be published along with other similar data.

The α -tricyclic phenolic ketone (IX) is not oestrogenic (up to 5 mg.).

EXPERIMENTAL.

Throughout this investigation it has been found essential to pay particular attention to the purity of the reagents employed. Except in the case of dioxan, no further reference to this matter is made.

6-Methoxy-5-methyltetralin (II).—(a) The preparation of 2-methoxy-1-naphthaldehyde by the Tiemann-Reimer reaction with β -naphthol, followed by methylation (Fosse, *Bull. Soc. chim.*, 1901, 25, 373), gave very unsatisfactory results.

The method of "Organic Syntheses" (XX, p. 11) for 2-ethoxy-1-naphthaldehyde gave a 67% yield when used for the methoxy-compound. Material of b. p. 153—154°/0.6 mm., m. p. 76—79° (81° pure), (200 g.) was hydrogenated in ethyl alcohol (600 c.c.) at 100°/100 atms. for 3 hours in the presence of Raney nickel (20 g.). The product was crystallised in contact with chilled methanol (yield, 105 g.); recrystallised several times from methanol and sublimed at 50°/0.01 mm., it formed colourless plates, m. p. 51.5—52° (Found: C, 81.4; H, 9.0. $\text{C}_{12}\text{H}_{16}\text{O}$ requires C, 81.8; H, 9.2%). On demethylation with hot hydriodic acid and acetic acid it afforded 6-hydroxy-5-methyltetralin, snow-white silky needles, m. p. 113.5—114.5°, from light petroleum (b. p. 60—80°) (Found: C, 81.5; H, 8.9. $\text{C}_{11}\text{H}_{14}\text{O}$ requires C, 81.5; H, 8.8%).

(b) In the preparation of 1-methyl-2-naphthol (Cornforth, Cornforth, and Robinson, J., 1942, 682) the quantity of sodium methoxide can be reduced. We used methylenediphenyl (150 g.), methanol (600 c.c.), and sodium (48 g.) and heated the mixture for 7 hours at 210°. The product was treated for $\frac{1}{2}$ hour with formalin (50 c.c. of 40%), isolated, and distilled, b. p. 180—184°/23 mm. (average yield, 100 g.; best yield, 108 g.). This material (280 g.) was reduced in alcohol (500 c.c.) for 2—3 hours at 110°/100 atms. in the presence of Raney nickel (25 g.). The residue after evaporation was dissolved in aqueous sodium hydroxide (1000 c.c. of 20%), the hot solution diluted with water (8—10 l.), treated with charcoal, and filtered, and the phenol set free and collected. After purification of a small sample it had m. p. 113.5—114.5°, undepressed by admixture with the above analysed specimen of 6-hydroxy-5-methyltetralin. It was at once methylated by shaking a solution in water (1500 c.c.) and sodium hydroxide (200 g.) with methyl sulphate (300 c.c.) at 80°, with final heating on the steam-bath for $1\frac{1}{2}$ hours. The neutral solid was collected, and phenolic material recovered from the alkaline solution and remethylated (30 c.c. of methyl sulphate). The combined product afforded 177 g. of distilled methoxymethyltetralone, as below, which is a 57% overall yield from methyl-naphthol.

6-Methoxy-5-methyl-1-tetralone (III).—A solution of chromic anhydride (100 g.) in acetic acid (600 c.c.) and water (80 c.c.) was added dropwise to one of methoxymethyltetralin (100 g.) in acetic acid (1000 c.c.) with stirring and cooling to below 20°. After being stirred for 3 hours (ice-bath), the mixture was kept for 18 hours at room temperature. Methanol (50 c.c.) was added and after $\frac{1}{2}$ hour the solvent was distilled under diminished pressure until frothing occurred. The residue was mixed with water (1.5 l.), and the solid collected and distilled, b. p. 185—195°/15 mm. (average yield, 70%). The crude, light yellow ketone, m. p. 103—105°, was crystallised from methanol, sublimed at 110°/0.1 mm., and recrystallised from methanol, being obtained in white plates, m. p. 112—113° (Found: C, 75.7; H, 7.3. Calc. for $\text{C}_{12}\text{H}_{14}\text{O}_2$: C, 75.8; H, 7.4%).

The 2:4-dinitrophenylhydrazone crystallised from xylene in dark red leaflets, m. p. 249—250° (Found: C, 58.6; H, 4.8; N, 15.2. $\text{C}_{18}\text{H}_{18}\text{O}_2\text{N}_4$ requires C, 58.4; H, 4.8; N, 15.2%). Conversion into the known 1:5-dimethyl-2-naphthol was effected as follows.

A solution of the ketone (2.5 g.) in ether (40 c.c.) and benzene (10 c.c.) was gradually added to one of methylmagnesium iodide (from 4.7 g. of magnesium) with ice-cooling. After 1 hour the product was isolated and found to be unsaturated to bromine and permanganate. It was dehydrogenated by means of sulphur (0.45 g.) at 215°, and the product distilled (1.8 g. of solid), crystallised from methanol, sublimed at 65°/0.1 mm., and recrystallised from methanol. 2-Methoxy-1:5-dimethylnaphthalene was obtained in white plates, m. p. 96—97° (Found: C, 84.1; H, 7.7. $\text{C}_{13}\text{H}_{14}\text{O}$ requires C, 83.8; H, 7.6%). On demethylation with hot hydriodic acid (*d* 1.7) and acetic acid the naphthol was produced; purified by sublimation at 150°/15 mm., it had m. p. 161—162° (Found: C, 84.0; H, 6.7. Calc. for $\text{C}_{12}\text{H}_{12}\text{O}$: C, 83.7; H, 6.9%) [Ruzicka and Sternbach, *loc. cit.*, give m. p. 162—163° (corr.)]. The benzoate, crystallised from methanol, had m. p. 149—150° [R. and S. give m. p. 151—151.5° (corr.)]. The m. p.'s cited in this communication are uncorrected.

Methyl 6-Methoxy-5-methyl-1-tetralone-2-glyoxylate.—A mixture of methyl oxalate (90.5 g.), dry powdered sodium

methoxide (from 17.7 g. of sodium), and benzene (570 c.c.) was refluxed under nitrogen for 20 minutes. It was then cooled and stirred during the addition (10 minutes) of methoxymethyltetralone (72 g.) in benzene (250 c.c.). The suspension was stirred for 1 hour at room temperature and for 4 hours on the steam-bath. After 12 hours, water was added, and the aqueous solution, together with further extracts by aqueous sodium hydroxide, acidified with hydrochloric acid. The precipitated product was collected, washed, and dried (yield, 93—94%). The *glyoxylate* crystallised from methanol in yellow needles, m. p. 136—137° (Found: C, 65.4; H, 5.8. $C_{15}H_{16}O_5$ requires C, 65.2; H, 5.8%). The ferric reaction in alcoholic solution was intense brown and the solution in sulphuric acid had a bright orange colour.

Methyl 6-Methoxy-5-methyl-1-tetralone-2-carboxylate.—A mixture of the above ester (76.7 g., crude) and powdered glass (30 g.) was heated at 170—180° until evolution of carbon monoxide ceased ($\frac{1}{2}$ — $\frac{3}{4}$ hour). The product was collected by means of benzene; it had b. p. 180—184°/0.4 mm., almost all at 182° (yield, 87%). The viscous oil slowly solidified; it was crystallised from methanol and from benzene—light petroleum, sublimed at 85°/0.0025 mm., and finally crystallised from benzene—light petroleum (b. p. 60—80°), forming thick, colourless prisms, m. p. 100—101° when immersed at 93° (Found: C, 68.0; H, 6.7. $C_{14}H_{16}O_4$ requires C, 67.7; H, 6.5%). The ferric reaction in alcoholic solution was dark green.

The 2:4-dinitrophenylhydrazones crystallised from benzene in feathery, brick-red needles, m. p. 223—224° after darkening at 195° (Found: C, 56.1; H, 4.8. $C_{20}H_{20}O_7N_4$ requires C, 56.1; H, 4.7%).

Methyl 6-Methoxy-2:5-dimethyl-1-tetralone-2-carboxylate (V).—A mixture of the above keto-ester (55 g.), benzene (250 c.c.), and methanol (250 c.c.) was added to a solution of sodium (25 g.) in methanol (500 c.c.) with stirring under nitrogen. After heating and cooling, methyl iodide (75 c.c.) was added and after 2 hours the mixture was refluxed for 8 hours and kept for 12 hours. The solution was just acidified with acetic acid, and most of the solvent distilled under diminished pressure. On addition of water and shaking, the precipitated oil solidified. It was collected, washed, dried, and distilled (b. p. 162—163°/0.4 mm.). It was found preferable to take the whole distillate and crystallise it from benzene—light petroleum (b. p. 60—80°) (80—85% yield, m. p. 84—86°, and about 89% on a smaller scale). The substance, recrystallised from the same solvent and sublimed at 90°/0.01 mm., formed transparent hexagonal prisms, m. p. 89—90.5° (Found: C, 68.5; H, 6.9. $C_{15}H_{16}O_4$ requires C, 68.7; H, 6.9%). The ferric reaction was negative.

Methyl 1-Hydroxy-6-methoxy-2-carbomethoxy-2:5-dimethyltetralin-1-acetate (VI).—A mixture of methyl methoxy-dimethyltetralonocarboxylate (20 g.), benzene (160 c.c.), ether (160 c.c.), zinc filings (40 g.), methyl bromoacetate (15 c.c.), and iodine (0.5 g.) was heated at 70°. Reaction usually commenced within 15 minutes but sometimes only after some hours' refluxing. When brisk reaction occurred, further additions were made as follows: 1 hour, zinc (15 g.) and a crystal of iodine; 2 hours, zinc (15 g.), methyl bromoacetate (10 c.c.) and a crystal of iodine; 3 hours, zinc (15 g.) and a crystal of iodine; 4 hours, the same; 5 hours, the same with methyl bromoacetate (5 c.c.); 6 hours, the same, no ester. Vigorous stirring was maintained during this process and during the following 5 hours (bath kept at 70°). After 12 hours the complex was decomposed with water and acetic acid, and the zinc washed with ether. The organic layer was washed with aqueous ammonia and dried, and the solvents removed. The residue crystallised in contact with light petroleum (b. p. 60—80°) and was a bright yellow solid (yield, 80—85%). For analysis the substance was crystallised from benzene—light petroleum, adsorbed on alumina, eluted by chloroform (ether—benzene, 1:1, or ether was an ineffective solvent for this purpose), and finally recrystallised from benzene—light petroleum. It formed colourless prisms, m. p. 106.5—108° (Found: C, 64.3; H, 7.1. $C_{18}H_{24}O_6$ requires C, 64.3; H, 7.2%). When pure benzene was employed as solvent in the reaction, the yield was much lower.

Derivatives of 1-Carboxymethylene-6-methoxy-2:5-dimethyltetralin-2-carboxylic Acid.—Anhydride. A solution of the Reformatzky product (12.5 g.) in benzene (35 c.c.) was gradually added to a mixture of thionyl chloride (11 c.c.), pyridine (5.5 c.c.), and benzene (50 c.c.) cooled in ice-salt. After $\frac{3}{4}$ hour at room temperature, with frequent shaking, ice-water was added and the benzene layer, mixed with potassium hydroxide (13 g.) and methanol (200 c.c.), was refluxed for $\frac{1}{2}$ hour. Aqueous potassium hydroxide (40 c.c. of 40%) was then added, and refluxing continued for $\frac{3}{4}$ hour. Water was introduced, and the solution distilled until it was homogeneous; it was then refluxed for 4 hours. Most of the alkali was neutralised, and insoluble material (1.1 g.) separated. The filtrate was acidified, and the precipitate collected (8.4 g.; on a larger scale 64 g. gave 49.5 g.). This material (A) is a mixture of *cis*-anhydride and *trans*-dicarboxylic acid. On crystallisation from acetic acid, the *anhydride* was obtained in transparent, colourless prisms, m. p. 204—205° (Found: C, 70.7; H, 6.1. $C_{16}H_{16}O_4$ requires C, 70.6; H, 5.9%). In one experiment 6-methoxy-2:5-dimethyl-1-tetralone was isolated as a non-saponifiable by-product. It crystallised from methanol in white prisms, m. p. 113—114° (Found: C, 76.8; H, 8.0. $C_{13}H_{14}O_2$ requires C, 76.5; H, 7.9%). The 2:4-dinitrophenylhydrazones crystallised from benzene—alcohol in dark red prisms, m. p. 229° (Found: N, 14.3. $C_{19}H_{20}O_5N_4$ requires N, 14.6%).

When the Reformatzky product was treated with sulphuric acid in benzene at room temperature and then at 50°, the above anhydride, m. p. 205—206°, was one of the products, but the process is not recommended as a method of preparation.

Dimethyl ester. A mixture of the above Reformatzky product (13.3 g.), calcium chloride (4 g.), and benzene (100 c.c.) was saturated with hydrogen chloride at room temperature and kept for 12 hours. It was then washed with aqueous sodium carbonate, dried, and passed through an alumina column, which removed colouring matters (a dark brown upper band and then a bright yellow band). The benzene solution was evaporated; the residue (B) partly crystallised in contact with methanol. The solid (6.3 g.), recrystallised from methanol, formed colourless needles, m. p. 105.5—106.5° (Found: C, 68.0; H, 6.8. $C_{18}H_{22}O_5$ requires C, 67.9; H, 7.0%). The pale yellow oil in the mother liquor was unsaturated; b. p. 150°/0.05 mm. (Found: C, 68.0; H, 6.9%). The disposition of the ω -carbomethoxyl group is evidently the cause of stereoisomerism in this case.

α - and β -Forms of 2-Carboxy-6-methoxy-2:5-dimethyltetralin-1-acetic Acid and Derivatives (as VII, R = Me).—(1) The crude anhydride (A, above) (5.6 g.) was hydrolysed with the minimum quantity of alcoholic potassium hydroxide and after evaporation of the solvent the resulting potassium salts were dissolved in water (120 c.c.) and reduced with sodium amalgam (150 g. of 2%). The dihydro-acids were isolated in the usual way and esterified in cold ethereal solution by means of diazomethane. The product was crystallised from a little methanol (refrigerator) and after 12 hours, 2.8 g., m. p. 108—110°, were collected. This α -dimethyl ester (VII, R = Me) crystallised from methanol in transparent, colourless plates, m. p. 112—113° (Found: C, 67.2; H, 7.5. $C_{18}H_{24}O_5$ requires C, 67.5; H, 7.6%). The β -dimethyl ester (VII, R = Me) in the mother-liquor would not crystallise, but on semi-hydrolysis it afforded a crystalline half-ester (see below). This was esterified with diazomethane and the product was again a somewhat intractable oil. It eventually crystallised from light petroleum (b. p. 60—80°) containing a little acetone. The derivative then crystallised from light petroleum in transparent, colourless prisms, m. p. 53—54° (Found: C, 67.5; H, 7.6%).

(2) The catalytic reduction of the unsaturated dimethyl ester (B, above) has been studied under different conditions and we give the yield of the solid α -dimethyl ester obtained. The oily material in the mother-liquors is doubtless largely the β -dimethyl ester, but it may still contain some α -ester and possibly other impurities. (a) With Adams's catalyst (25 mg.) in acetic acid (30 c.c.) at room temperature; 4 g. gave 3.4 g., m. p. 108—110°. (b) Similarly in ethyl acetate; reduction was slower and 2.5 g. gave 2.2 g. of α -ester. (c) Similarly in methanol or dioxan; reduction did not occur. (d) Palladium-black in acetone under similar conditions; rapid reduction, 2.5 g. gave 2.2 g. of the α -ester. (e) Similarly

with palladised charcoal; 10.5 g. gave 8.6 g. of α -ester. (f) Palladised strontium carbonate (2%); 2.6 g. gave 2.0 g. of α -ester. (g) Raney nickel at 60°/25 atms.; 4 g. gave 2.65 g. of α -ester [see (5)].

(3) The α - and β -dicarboxylic acids were obtained from the respective dimethyl esters. The α -ester (4 g.) was refluxed for 3 hours with aqueous potassium hydroxide (30 c.c. of 40%) and methanol (30 c.c.). The potassium salt that separated on cooling (long, silky, white needles) was collected, washed with methanol, dissolved in water, and acidified with hydrochloric acid. The gummy precipitate slowly crystallised and was converted, by refluxing for 2 hours with acetic anhydride, into the α -anhydride, which crystallised from acetic acid in microscopic snow-white needles, m. p. 173—174° (Found: C, 70.0; H, 6.7. $C_{16}H_{18}O_4$ requires C, 69.9; H, 6.6%). After hydrolysis with alkali and recovery the α -dicarboxylic acid crystallised from ethyl acetate in white prisms, m. p. 217—217.5° after slight sintering (Found in material dried over phosphoric oxide in a high vacuum: C, 65.8; H, 7.0. $C_{16}H_{20}O_6$ requires C, 65.7; H, 6.9%).

The β -anhydride, made in the same way, except that the potassium salt of the acid did not crystallise, separated from acetic acid in transparent prisms, m. p. 168—169° (Found: C, 70.1; H, 6.7%). The β -dicarboxylic acid crystallised from a little chilled ethyl acetate in prisms, m. p. 198—200° (Found: C, 65.9; H, 7.1%).

We are very grateful to Dr. J. C. Speakman of Sheffield University for the following report on the thermodynamic dissociation constants of the α - and the β -dicarboxylic acid.

Experiments in aqueous solution. The acids, though not very soluble, were sufficiently so to allow measurements to be made in aqueous solution. The β -acid was the more soluble of the two, and solutions about M/2000 could be obtained. On heating, the α -acid gave solutions almost as concentrated; these were supersaturated at room temperature, and deposited crystals overnight.

Experimental method. 0.010—0.015 G. of the acid (sometimes finely ground) was weighed, transferred to a Pyrex beaker and heated (if necessary to boiling) to bring about dissolution. The solution was then cooled and made up to 100 c.c. 40 C.c. portions were potentiometrically titrated with approximately N/30-sodium hydroxide (free from carbonate), a glass electrode being used. Experiments on the two isomers were carried out consecutively, each in turn being dealt with first. The pH-scale was standardised by interspersing amongst the above titrations similar ones using adipic acid, to the pK₁ value of which the value 4.40 was attributed (cf. J., 1940, 855, where other details are also given). The temperature was 20.0°.

Experiments in aqueous acetone. Experiments were also carried out in dilute aqueous acetone, though the glass electrode does not behave quite so conveniently in such mixed solvents. More concentrated solutions could be made rather more easily. The procedure was to weigh out the acid, transfer it to a 100 c.c. flask with 8 c.c. of acetone (which had been distilled from potassium carbonate), dissolve by shaking, and make up to the mark with water. The solutions (especially those of the α -acid) were apt to deposit crystals on standing. They were titrated in the way described.

Results (pK = $-\log_{10}K$; $\Delta pK = \log_{10}K_1/K_2$):

	pK ₁	pK ₂	ΔpK	No. of expts.
Aqueous solns. : α -Acid	4.37	5.63	1.26	8
β -Acid	4.42	5.70	1.28	8
Aqueous acetone solns. : α -Acid	4.51	5.75	1.24	5
β -Acid	4.52	5.78	1.26	3

The (average) pK values are probably accurate to ± 0.05 , the ΔpK 's to ± 0.03 .

Discussion. Although the results are unfortunately equivocal so far as the allocation of configurations is concerned, they quite certainly show that the ΔpK values are much closer together here than they are with the corresponding cyclopentane-1-carboxylic-2-acetic acids (*cis*, 1.39; *trans*, 1.28). They tend in fact towards the value for glutaric acid itself (1.11).

Two points may have some relevancy: (i) The cyclopentane ring is presumably (but not quite certainly) coplanar: the six-membered ring in these dibasic acids will be puckered. Hence in the *cis*-isomer the two carboxyl groups will probably be able to avoid the close approach that occurs between the carboxyl groups in the *cis*-cyclopentane diacid.

(ii) In the *trans*-acid the methyl group might conceivably exert what Hammett calls a "proximity effect" on the carboxyl group of the acetic acid residue. If this effect did obtain, it can easily be argued that it will tend to raise ΔpK for the *trans*-acid. A few preliminary measurements on *cis*-1-methylcyclohexane-1-carboxylic-2-acetic acid gave a ΔpK value of 1.34, which is perhaps significantly lower than that for the *cis*-cyclopentane-1-carboxylic-2-acetic acid mentioned earlier.

(4) The experiences of Litvan and Robinson (*loc. cit.*) and Bachmann *et al.* (*loc. cit.*) as well as other analogies make it certain that the monomethyl esters, obtained by semi-hydrolysis of di-esters, are correctly represented by the formula $C_{18}H_{16}O(CO_2Me) \cdot CH_2 \cdot CO_2H$. A mixture of the α -dimethyl ester (6.4 g.), methanol (100 c.c.), and 1.03N-sodium hydroxide (19.4 c.c.) was refluxed for 6 hours. Most of the methanol was distilled, and the solution filtered from a little unchanged material, acidified, and extracted with ether. The product slowly crystallised (C) from benzene-light petroleum (b. p. 40—60°) in the refrigerator; recrystallised in the same way, it formed colourless prisms, m. p. 137—139° (Found: C, 66.4; H, 7.2. $C_{17}H_{22}O_5$ requires C, 66.6; H, 7.3%).

The β -monomethyl ester, prepared in similar fashion, was crystallised from ethyl acetate, distilled at 0.01 mm. (bath at 160°), and recrystallised from ethyl acetate. It formed white prisms, m. p. 149—150° (Found: C, 66.7; H, 7.5%).

(5) The reduction in presence of Raney nickel as described under (2) (g) is unreliable and in one experiment a large part of the product was degraded. After hydrolysis with alcoholic potassium hydroxide, neutral, monobasic acidic and dibasic acidic fractions were separated. The acids were heated with acetic anhydride, after which the neutral anhydride of the unsaturated dicarboxylic acid, m. p. 204°, described above, was isolated.

The original neutral product was crystallised from methanol, sublimed at 70°/0.1 mm., and recrystallised from methanol. It formed white plates, m. p. 89—90° (Found: C, 83.8; H, 8.3. Calc. for $C_{14}H_{16}O$: C, 84.0; H, 8.1%). The unstable picrate crystallised from alcohol in dark brown needles, m. p. 127—128° (decomp.), and the brilliant red *s*-trinitrobenzene adduct crystallised from alcohol in needles, m. p. 146°. The substance is clearly 6-methoxy-1:2:5-trimethylnaphthalene, already synthesised by Ruzicka, Hofmann, and Schellenberg (*Helv. Chim. Acta*, 1936, **19**, 1391), who give m. p. 89—90° (corr.), trinitrobenzene compound, m. p. 146—147° (corr.). Incidentally this is a further proof of the correctness of the constitution assigned to the α -tetralone (III). The monobasic acidic fraction crystallised from methanol in long, white needles, m. p. 180—192° (Found: C, 73.3; H, 7.2. $C_{18}H_{18}O_3$ requires C, 73.2; H, 7.3%). The substance is soluble in aqueous sodium carbonate and unsaturated; the unsharp m. p. was not altered by several recrystallisations and may be due to lactonisation. It gives a red coloration with alcoholic picric acid and appeared to form a complex with *s*-trinitrobenzene. Hence this acid is probably a dihydronaphthalene derivative and if it is formed without migration of a group it should be 6-methoxy-2:5-dimethyl-3:4-dihydronaphthalene-1-acetic acid.

On hydrogenation of 0.9 g. in ethyl acetate-acetone (60 c.c., 1:1) in the presence of palladised strontium carbonate (2%) the theoretical volume of hydrogen was absorbed in 30 minutes at the ordinary temperature and pressure.

6-Methoxy-2 : 5-dimethyltetralin-1-acetic acid crystallised from alcohol in white prisms, m. p. 155.5—157° (Found : C, 72.6; H, 8.0. $C_{15}H_{20}O_2$ requires C, 72.5; H, 8.1%). It gave no coloration with alcoholic picric acid.

Derivatives of α - and β -2-carboxy-6-hydroxy-2 : 5-dimethyltetralin-1-acetic acid (as VII, R = H). The above α -dimethyl ester (2 g.) was demethylated and hydrolysed by refluxing for 3 hours with hydriodic acid (6 c.c. *d* 1.7) and acetic acid (15 c.c.). After addition of water (no precipitate) the solution was extracted ten times with ether, and the extract washed with aqueous sodium bisulphite, and saturated brine, and dried. After evaporation of the solvent, the residue (m. p. ca. 220°; probably hydroxy-dicarboxylic acid) was refluxed for 2 hours with methanol (50 c.c.) and sulphuric acid (1 c.c.). A little water was added, most of the methanol distilled, more water added, and the solution extracted seven times with ether. The extract was washed successively with brine, 10% aqueous sodium carbonate and 10% aqueous sodium hydroxide. The soda washings were acidified, thoroughly extracted with ether, the acid rendered to sodium bicarbonate solution and recovered as before. The product was crystallised from methanol; it melted at 100° and resolidified and was recrystallised from chloroform, being obtained in colourless, microscopic prisms, m. p. 169—170°, containing solvent of crystallisation (Found in material dried at 100° in a high vacuum : C, 65.9; H, 6.8. $C_{16}H_{20}O_5$ requires C, 65.7; H, 6.9%). This substance is formed by semi-esterification of the dicarboxylic acid and is therefore methyl α -2-carboxy-6-hydroxy-2 : 5-dimethyltetralin-1-acetate, $HO \cdot C_{12}H_{13}(CO_2H) \cdot CH_2 \cdot CO_2Me$. The washings with 10% aqueous sodium hydroxide doubtless contained initially the hydroxy-dimethyl ester but hydrolysis supervened. The product was recovered as above; it crystallised from aqueous methanol in clusters of colourless needles, m. p. 179.5—180.5° (large depression with the isomeride, m. p. 169—170°) (Found : C, 66.1; H, 7.1%). The substance is readily soluble in aqueous sodium carbonate and is regarded as α -2-carbomethoxy-6-hydroxy-2 : 5-dimethyltetralin-1-acetic acid, $HO \cdot C_{12}H_{13}(CO_2Me) \cdot CH_2 \cdot CO_2H$. When the crude product of the demethylation of the α -dimethyl ester (or the α -dicarboxylic acid) was refluxed for 4 hours with methanol (4 vols.) and sulphuric acid (1 vol.), the dimethyl ester (VII, R = H) of the phenolic dicarboxylic acid was produced. Its ethereal solution was washed with aqueous sodium bicarbonate and the residue, after evaporation, was crystallised from benzene-light petroleum, distilled at 160—180°/0.1 mm., and recrystallised from methanol, being obtained in colourless prisms, m. p. 122—123° (Found : C, 66.4; H, 7.4. $C_{17}H_{22}O_5$ requires C, 66.6; H, 7.3%).

The β -dicarboxylic acid of the preceding section was similarly demethylated, and the product esterified by means of methanolic hydrogen chloride for 1 hour under reflux. The isolated product, freed from acids, crystallised from aqueous methanol (charcoal) in white prisms, m. p. 125—126° (Found : C, 66.4; H, 7.2%). There was a large depression of m. p. on admixture with the isomeride, m. p. 122—123°. All the phenolic substances described in this section coupled readily with *p*-nitrobenzenediazonium salts to give red azo-compounds.

Methyl 2-Carbomethoxy-6-hydroxy-2 : 5-dimethyldecalin-2-acetate.—Experiments on the per-hydrogenation of substances described in the last two sections gave very unpromising results; only one example will be briefly described. The phenolic α -dimethyl ester, m. p. 122—123°, (3 g.) was hydrogenated in dry dioxan (100 c.c.) in the presence of Raney nickel (0.5 g.). Starting at 20°/119 atms., the conditions after 1 hour were 190°/155 atms., after 2 hours, 220°/172 atms. and after 4 hours, 214°/172 atms.; the autoclave was then allowed to cool. Extraction of the ethereal solution of the products with 10% sodium hydroxide solution afforded 0.9 g. of phenolic monomethyl ester, m. p. 178—180°, which was esterified to the dimethyl ester, m. p. 122—123°. The neutral moiety was a mobile oil, which was fractionated as follows : (a) bath at 175°/0.1 mm. (Found : C, 70.1; H, 9.9. $C_{17}H_{22}O_4$ requires C, 68.9; H, 9.5%); (b) bath at 180°/0.1 mm. (Found : C, 67.0; H, 9.2%); (c) bath at 180°/0.05 mm. (Found : C, 65.7; H, 8.8. $C_{17}H_{22}O_5$ requires C, 65.4; H, 9.0%). The fraction (a) is probably largely deoxygenated in position 6, and (c) appears to be the desired product. The yield was hopelessly inadequate and this was the best result obtained along these lines, which we were forced to abandon.

Methyl α -2-Carbomethoxy-6-methoxy-2 : 5-dimethyltetralin-1- β -propionate.—The α -monomethyl ester (C, above) (5.1 g.) was converted into the chloride by means of thionyl chloride in ethereal solution containing 2 drops of pyridine. After 1 hour at room temperature the mixture was evaporated at 40°, several small volumes of benzene added, and the evaporation repeated after each addition. A benzene solution (60 c.c.) of this derivative was added dropwise to an ethereal solution of diazomethane (from 15 g. of nitrosomethylurea). After $\frac{1}{2}$ hour at room temperature, the solution was evaporated (below 30°) under diminished pressure. The residual diazo-ketone was dissolved in methanol (65 c.c.) and treated at 70° with freshly prepared methanol-moist silver oxide (from 12 c.c. of 10% silver nitrate solution) added in three portions within $\frac{1}{2}$ hour. When the evolution of nitrogen ceased, the solution was passed through an alumina column and evaporated. The oily product was extracted with boiling light petroleum (150 c.c. of b. p. 40—60°) (charcoal), and the solution concentrated to 30—40 c.c. It deposited 3.6 g., m. p. 81—83°, on keeping at a low temperature. After two recrystallisations the colourless needles had m. p. 84—85° (Found : C, 68.4; H, 7.8. $C_{18}H_{26}O_5$ requires C, 68.2; H, 7.9%).

Methyl 3'-Keto-6-methoxy-2 : 5-dimethyl-1 : 2 : 3 : 4-tetrahydro-1 : 2-cyclopentenonaphthalene-2'-carboxylate (α - and β -Forms) (VIII).—A mixture of the above homologated α -ester (2.1 g.), dry sodium methoxide (0.3 g. of sodium), and benzene (20 c.c.) was refluxed under nitrogen for 2 hours. The neutral product, isolated in the known manner, was crystallised from light petroleum (b. p. 40—60°), passed in benzene solution through an alumina column, and recrystallised from light petroleum, forming colourless prisms, m. p. 107.5—108.5° (Found : C, 71.1; H, 7.4. $C_{18}H_{22}O_4$ requires C, 71.5; H, 7.4%). The ferric reaction in alcoholic solution was dark violet.

3'-Keto-6-hydroxy-2 : 5-dimethyl-1 : 2 : 3 : 4-tetrahydro-1 : 2-cyclopentenonaphthalene- α (IX).—A mixture of the above keto-ester- α (5 g.), hydriodic acid (18 c.c., *d* 1.7), and acetic acid (30 c.c.) was refluxed for 3 $\frac{1}{2}$ hours. The ethereal extract of the diluted solution was freed from iodine and acids and evaporated. The product was crystallised from benzene-light petroleum (b. p. 60—80°) (charcoal), sublimed at 160°/0.05 mm., and recrystallised from a little benzene. It was obtained in thick, white prisms, m. p. 189—191° (Found : C, 78.0; H, 7.9. $C_{15}H_{18}O_3$ requires C, 78.2; H, 7.9%). Starting with the monomethyl ester- α (from VII) (7 g.), the processes of homologation, ring-closure, and hydrolysis were also effected without isolation of intermediates and 3.6 g. (68.5% overall yield) of the hydroxy-ketone- α were obtained.

Similarly the related monomethyl ester- β (2.9 g.), by the same procedure, gave the hydroxy-ketone- β (0.5 g.). This substance was crystallised from methanol, sublimed at 200°/0.05 mm., and recrystallised from benzene. It formed thick, white prisms, m. p. 230—231° (Found : C, 78.2; H, 7.8%). Like equilenin, these hydroxy-ketones fuse to red liquids when heated in air. The m. p.'s were determined in evacuated sealed capillaries; colourless liquids then resulted. The β -form now melts at a higher temperature than the α , so the m. p. is no criterion of stereochemical configuration. Addition of *p*-nitrobenzenediazonium chloride to an alkaline solution of these phenolic ketones produces an intense violet-red coloration.

Use of Palladium-Strontium Carbonate as Catalyst in Pressure Hydrogenation.—(a) Phenol (30 g.) was reduced in dioxan (40 c.c.) in the presence of palladised strontium carbonate (5 g. of 2%). Starting at 20°/113 atms., after $\frac{1}{2}$ hour, 75°/125 atms., after 1 $\frac{1}{2}$ hours, 140°/125 atms., absorption ceased after 4 hours (150°). The yield of cyclohexanol was almost quantitative.

(b) Quinol dimethyl ether was similarly reduced but for too short a period (1 $\frac{1}{2}$ hours, finally at 210°/94 atms.) owing to mechanical trouble. The product was separated into 1 : 4-dimethoxycyclohexane, b. p. 169—170°/15 mm., n_D^{20} 1.450, and unchanged material.

(c) Ethyl *p*-hydroxybenzoate (20 g.) was reduced in dioxan (40 c.c.) in the presence of the catalyst (4 g.). Initial conditions were 15°/118 atms.; after 40 minutes, 155°/150 atms.; after 2 hours, 157°/90 atms. and reduction ceased. The product, obtained in almost quantitative yield, was *trans*-4-carbethoxycyclohexanol, b. p. 255—256°, n_D^{25} 1.463. The crude acid obtained on hydrolysis had m. p. 115—117°, raised to 120—121° by one crystallisation. The pure *trans*-acid has m. p. 121° and the *cis*-acid, m. p. 152° (Perkin, *loc. cit.*; Balas and Srol, *loc. cit.*). Oxidation of this *sec*-alcohol (10 g.) by means of chromic acid (10% excess) in acetic acid solution for $\frac{1}{2}$ hour at 0° and 18 hours at room temperature afforded 8.4 g. of 4-carbethoxycyclohexanone, b. p. 150—152°/40 mm.

The dioxan employed must be pure and in some cases reduction did not occur below 180—190°. Furthermore the catalyst loses activity when heated in the solvent under hydrogen without stirring. The reduction must therefore not be stopped and resumed later, and stirring must be continuous. Dr. E. Seijo (private communication) has recently found that ethyl acetate is a very satisfactory solvent for this reduction at about 140—150°/140 atms. Ethyl *p*-hydroxybenzoate may be used as a test substance to ensure that catalyst and solvent are in good condition. Using Raney nickel, reduction was very slow and far from completed after 6 hours at 200°/168—128 atms.

(d) The phenolic dimethyl ester-*a* (VII, R = H) was not reduced in dioxan after 4 hours at 180—200°/165 atms., or in methanol at 200°/160 atms. The substance was recovered unchanged.

3' : 6-Dihydroxy-2 : 5-dimethyldecahydrocyclopentenonaphthalene (Stereoisomerides of α -Series) (X).—The phenolic ketone (*a*) (2 g.) was hydrogenated in dioxan (70 c.c.) in the presence of palladised strontium carbonate (0.8 g.). Starting at 20°/93 atms., the conditions after 1 hour were 196°/134 atms.; after 2 hours, 227°/142 atms. for a few minutes; 202°/133 atms. was maintained for 3 $\frac{1}{2}$ hours. The solvent was removed, and an ethereal solution of the product washed with aqueous sodium hydroxide (10%); phenols were not found in these washings. The material was distilled: (a) bath at 140°/0.05 mm., one or two drops of a colourless mobile oil (Found: C, 78.8; H, 11.3. C₁₅H₂₆O requires C, 81.0; H, 11.8%); (b) bath at 140°/0.05 mm., a colourless glass (Found: C, 76.3; H, 10.9%); (c) bath at 145°/0.05 mm., a colourless glass (Found: C, 75.4; H, 10.9; active H in pyridine, 0.7%); (d) bath at 145—147°/0.05 mm., a colourless glass (Found: C, 75.7; H, 10.9. C₁₅H₂₆O₂ requires C, 75.6; H, 11.0; 2H, 0.8%). There was no residue, (b) and (c) constituted each about $\frac{2}{3}$ of the product and (d) about $\frac{1}{3}$. It is apparent from these results that the yield of the desired products was almost quantitative. In a later experiment it was found that the temperature needed was 220° but, in this case also, hydrogenolysis of the alcoholic groups did not occur.

3' : 6-Diketo-2 : 5-dimethyldecahydro-1 : 2-cyclopentenonaphthalene-*x-a* (I).—The above di-*sec*-alcohol of the α -series (1.5 g.) in acetic acid (40 c.c.) was treated at 10—15° with chromic anhydride (1.3 g.) in acetic acid (30 c.c.) and a few drops of water. After 24 hours at room temperature, a little methanol was added, and the solution concentrated under diminished pressure. Water was added, and an ethereal solution of the product washed with aqueous sodium carbonate and distilled. After the solvent the whole formed 3 fractions (2 : 2 : 1) of a colourless viscous oil: (a) bath at 130°/0.01 mm. (Found: C, 76.9; H, 9.7; active H, 0.08%); (b) bath at 135°/0.01 mm. (Found: C, 77.0; H, 9.6%); (c) bath at 140°/0.01 mm. (Found: C, 77.2; H, 9.6%). After a few days the substance partly crystallised in long prismatic needles; it could be recrystallised from light petroleum (b. p. 40—60°) (seeding) and separated in transparent, colourless prisms, m. p. 116—117° (Found: C, 76.9; H, 9.6. C₁₅H₂₂O₂ requires C, 76.9; H, 9.4%). The diketone has evidently been obtained largely in one stereoisomeric form (*x-a*). All the fractions afforded sparingly soluble, yellow dinitrophenylhydrazones, which have not yet been obtained in a pure condition and are mixtures of mono- and di-derivatives.

Unsaturated Ketones, C₁₉H₂₆O₂.—A mixture of the above diketone (1 g., not crystallised), powdered sodamide (1 g.), and ether (30 c.c.) was refluxed under nitrogen for 6 hours, then cooled in ice while a solution of 4-diethylaminobutan-2-one methiodide (from 1.2 g. of the base) in alcohol (8 c.c., and later 15 c.c.) was introduced. After $\frac{1}{2}$ hour the mixture was kept at room temperature for 1 $\frac{1}{2}$ hours and refluxed for 1 $\frac{1}{2}$ hours, always under nitrogen. The cooled mixture was decomposed with ice and hydrochloric acid, and the ethereal layer washed with aqueous sodium thiosulphate, water, aqueous sodium carbonate and water, and dried. The ether was evaporated, and the residue distilled (temperatures are those of the bath): (a) 125—135°/0.05 mm., (b) 135—150°/0.05 mm., (c) 150—220°/0.05 mm., (d) appreciable residue; (e) gave (e) 135°/0.05 mm., (f) 150—180°/0.05 mm., (g) 180—190°/0.05 mm.; (g) gave (h) —185°/0.1 mm., (i) 185°/0.1 mm., a light yellow, very viscous oil (Found: C, 78.9; H, 9.7%), (j) 190°/0.1 mm., a similar viscous oil (Found: C, 79.2; H, 9.3%); (f) gave (k) 130—140°/0.05 mm., (l) 160—180°/0.05 mm.; (l) gave (m) —150°/0.05 mm., (n) 160—180°/0.05 mm., a light yellow, very viscous oil (Found: C, 79.0; H, 9.6%); (d) gave (o) —240°/0.1 mm., (p) small residue; (o) gave (q) 180—190°/0.05 mm., a yellow viscous oil (Found: C, 79.4; H, 9.0. C₁₉H₂₆O₂ requires C, 79.7; H, 9.2%), (r) 190°/0.05 mm. This survey shows that a tetracyclic compound has been formed in accordance with anticipations. The tricyclic starting point requires C, 76.9% and the pentacyclic, doubly unsaturated ketone, C₂₂H₃₀O₂, requires C, 81.6; H, 8.9%. The absorption in alcoholic solution (c , 1.08 \times 10⁻⁴) was kindly examined by Dr. F. B. Strauss; fraction (j) was employed. The characteristic band of an $\alpha\beta$ -unsaturated ketone was observed; λ max., 2415 Å., ϵ max., 11,500 (cf. Woodward, *J. Amer. Chem. Soc.*, 1941, **63**, 1123). The absorption of androstenedione is recorded as follows: Butenandt and Kudzusz (*Z. physiol. Chem.*, 1935, **237**, 75), λ , 2350 for 0.01% solution in chloroform; Butenandt and Peters (*Ber.*, 1938, **71**, 2690), λ , 2400 for 0.02% solution in chloroform; Ruzicka and Wettstein (*Helv. Chim. Acta*, 1935, **18**, 986), λ 2350, solvent not specified; Hogness, Sidwell, and Zscheile (*J. Biol. Chem.*, 1937, **120**, 239), λ , 2408, in alcoholic solution. The investigation is being continued.

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