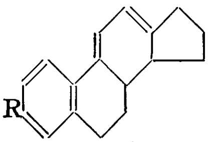
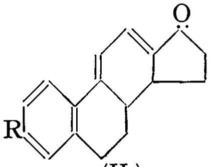
72. *Experiments on the Synthesis of Substances related to the Sterols. Part XXIX.*

By Sir Robert Robinson and S. N. Slater.

The work described below comprises four parts and arose from attempts to develop more convenient syntheses of hydrogenated *cyclo*pentenophenanthrenes. Attention may be directed to Section D, in which it is shown that the application of the Reformatzky reaction to certain keto*cyclo*pentenophenanthrenes affords products that may be reduced to an octahydro-stage in the aromatic nuclei. This observation gives promise for future developments.

(A) This section is concerned with the synthesis of dienes of the type (I, R = H or OMe) with the object of effecting subsequent oxidation to (II). In the case where R = OMe it should then be possible to remove the double bonds by hydrogenation and obtain the ketone (III), which is closely related to oestrone methyl ether (IV).


(I.)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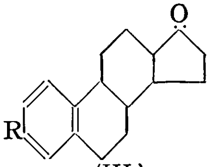
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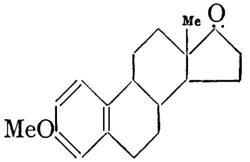
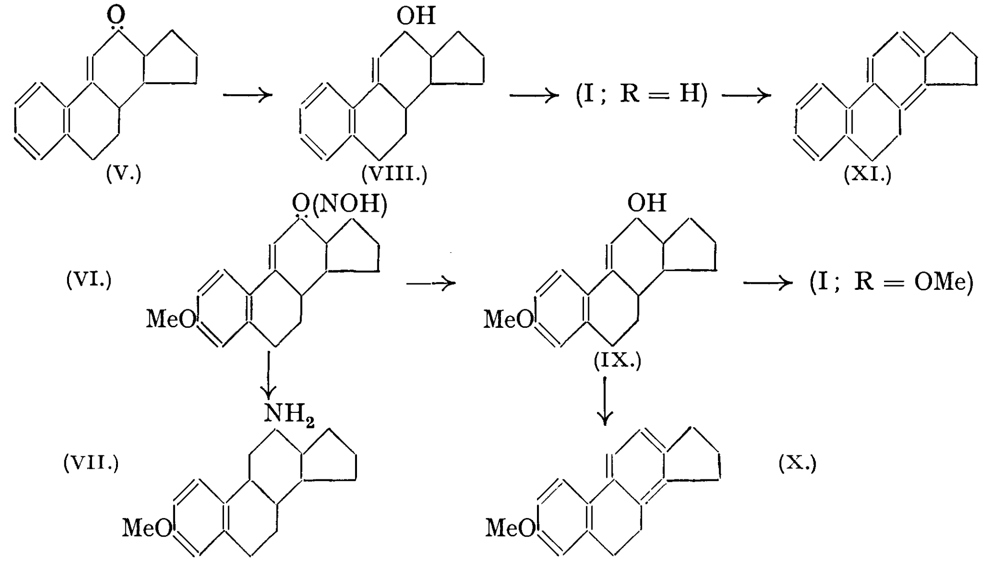

(IV.)

The required dienes were prepared, but readily passed into aromatic compounds either during the course of their preparation or when oxidation by selenium dioxide was attempted. As starting points for the preparation of (I; R=H, OMe) the ketones (V) (Hawthorne and Robinson, J., 1936, 763) and (VI) (Rapson and Robinson, J., 1935, 1285) were employed.



The oxime of 3-keto-7-methoxy-1 : 2 : 3 : 9 : 10 : 11-hexahydro-1 : 2-*cyclo*pentenophenanthrene-A (VI) (Peak and Robinson, J., 1937, 1581) was reduced with sodium and butyl alcohol, but yielded 3-amino-7-methoxy-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-1 : 2-*cyclo*pentenophenanthrene (VII) and not the hexahydrophenanthrene derivative required for degradation to (I; R = OMe). The crude reduction product proved difficult to crystallise and the amine was therefore isolated as the *hydrochloride* in two isomeric forms, which were separated by fractional crystallisation.

Attention was next turned to the corresponding carbinols. 3-Keto-1 : 2 : 3 : 9 : 10 : 11-

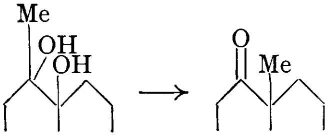
hexahydro-1 : 2-*cyclo*pentenophenanthrene (V), the preparation of which has been improved, was reduced in good yield to 3-*hydroxy*-1 : 2 : 3 : 9 : 10 : 11-*hexahydro*-1 : 2-cyclo*pentenophenanthrene* (VIII) by the Pondorff method. Dehydration with anhydrous potassium hydrogen sulphate gave a small yield of the required 1 : 9 : 10 : 11-*tetrahydro*-1 : 2-cyclo*pentenophenanthrene* (I, R=H).

The Pondorff reduction of (VI) yielded 3-*hydroxy*-7-*methoxy*-1 : 2 : 3 : 9 : 10 : 11-*hexahydro*-1 : 2-cyclo*pentenophenanthrene* (IX), although even after 24 hours the reduction was not complete. Treatment with anhydrous potassium hydrogen sulphate caused dehydrogenation as well as dehydration and the resulting substance was a saturated compound, $C_{18}H_{18}O$, which is regarded as 7-*methoxy*-9 : 10-*dihydro*-1 : 2-cyclo*pentenophenanthrene* (X). The action of heat on the methylxanthate of the carbinol (IX) gave the required 7-*methoxy*-1 : 9 : 10 : 11-*tetrahydro*-1 : 2-cyclo*pentenophenanthrene* (I, R = OMe) in small yield.

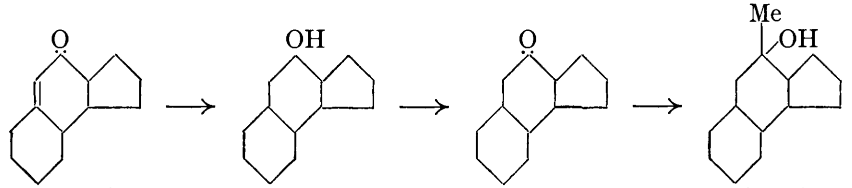
The main product of the oxidation of (I, R = H) with selenium dioxide was a hydrocarbon $C_{17}H_{16}$, which is considered to be 9 : 10-*dihydro*-1 : 2-cyclo*pentenophenanthrene* (XI). There appeared to be small quantities of some ketonic substance present in the oxidation products, but the amount of (I) available was not sufficient to enable the isolation of by-products to be attempted.

(B) One of the difficulties encountered in the synthesis of substances closely related to the sex hormones is the introduction of the angle-methyl groups and a possible method of surmounting this obstacle depends on applying the pinacol-pinacolin rearrangement to glycols of the type (XII).

(XII.)

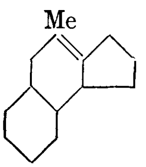


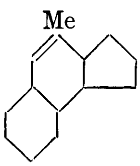
With this object in view the following experiments were carried out. *cyclo*Hexanone was condensed with acetyl*cyclo*pentene under the conditions described by Huber (*Ber.*, 1938, **71**, 725), which represent a slight modification of the procedure of Rapson and Robinson (*loc. cit.*). 3-*Keto*-1 : 2 : 3 : 5 : 6 : 7 : 8 : 9-*octahydro*-1 : 2-cyclo*pentenonaphthalene* (XIII) was isolated in two isomeric forms, *a* and *b*, although there is the possibility that one form is an isomer of (XIII) with the double bond in a different position. The lower-boiling isomeride-*a*, obtained in the greater amount, gave a low-melting amorphous dinitrophenylhydrazone. The higher-boiling isomeride-*b* afforded a crystalline *dinitrophenylhydrazone*. Isomeride-*a* was reduced with sodium and alcohol to 3-*hydroxydecahydro*-1 : 2-cyclo*pentenonaphthalene* (XIV), which was then oxidised by the Oppenauer method (*Rec. Trav. chim.*, 1937, **56**, 137) to 3-*ketodecahydro*-1 : 2-cyclo*pentenonaphthalene* (XV). This reacted vigorously with methylmagnesium iodide and the resulting 3-*hydroxy*-3-*methyldecahydro*-1 : 2-cyclo*pentenonaphthalene* (XVI) was dehydrated with anhydrous potassium hydrogen sulphate to an unsaturated hydrocarbon, $C_{14}H_{22}$, which is regarded as having the structure (XVII) or (XVIII).



(XIII.) (XIV.) (XV.) (XVI.)

(XVII.)



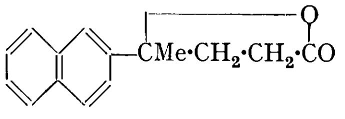


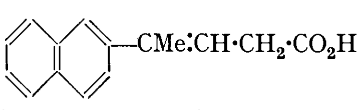
(XVIII.)

This hydrocarbon was treated with perbenzoic acid, and the product hydrolysed with water in a sealed tube at 110°. The analysis of the product indicated that it did not consist of the pure glycol, but an attempt was made to effect a rearrangement by dissolving it in ice-cold concentrated sulphuric acid. A ketonic product was obtained, but the amount available was insufficient to allow of closer investigation.

(C) Interaction of β-naphthylmagnesium bromide and ethyl lævulate yielded *γ-hydroxy-γ-2-naphthylvalerolactone* (XIX) together with a small amount of 2 : 2′-dinaphthyl and a substance, m. p. 139°, which is probably the isomeric unsaturated acid mentioned below. In an attempt to improve the yield, the ethyl ester of β-2-naphthoylpropionic acid (Haworth, J., 1932, 1129) was allowed to react with methylmagnesium iodide in cold ethereal solution. The main product was the lactone (XIX), but a certain amount of the isomeric *γ-2-naphthyl-Δ^{β}-pentenoic acid* (XX), m. p. 141—142°, was also obtained. Treatment with dilute sulphuric acid at 100° converted the unsaturated acid into the lactone. By carrying out the second condensation in benzene and refluxing the mixture for some time (cf. Haworth, J., 1932, 1784), the acid (XX) was produced in good yield.

(XIX.)

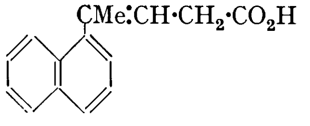


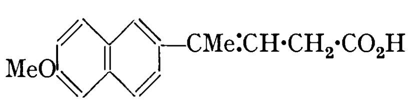


(XX.)

Under similar conditions ethyl β-1-naphthoylpropionate reacted with methylmagnesium iodide to yield *γ-1-naphthyl-Δ^{β}-pentenoic acid* (XXI), and from 6-methoxy-β-naphthylmagnesium bromide and ethyl lævulate the unsaturated acid (XXII) was obtained.

(XXI.)



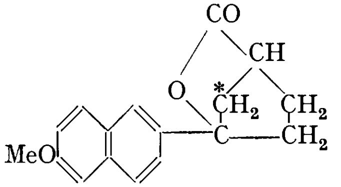


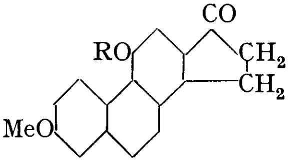
(XXII.)

These substances are readily converted into naphtholsulphonic acids (azo-dye tests), but up to the present we have not made a successful cyclisation without sulphonation.

The *lactone* of *3-hydroxy-3-(6′-methoxy-2′-naphthyl)*cyclo*pentane-1-carboxylic acid* (XXIII) was similarly prepared from 6-methoxy-β-naphthylmagnesium bromide and ethyl *cyclo*pentanone-3-carboxylate.

(XXIII.)





(XXIV.)

It was found advantageous to prepare the Grignard reagent alongside an equimolecular proportion of methylmagnesium iodide; there was naturally no difficulty in separating the products and a better use of the bromomethoxynaphthalene was secured by this device.

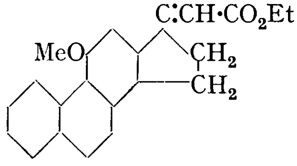
It was hoped to apply the method so as to obtain the compound with $CH_2{\cdot}CO_2H$ at the asterisked position, but we have not yet succeeded in acquiring a specimen of the necessary intermediate. This work is being continued.

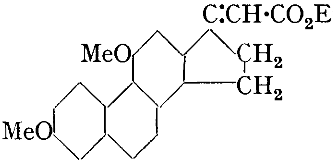
(D) Much attention has been paid to methods of attaching a reactive but non-reducible group to the *cyclo*pentane nucleus in derivatives of ketones of the type (XXIV), which are now readily accessible (Robinson, J., 1938, 1390). Robinson and Rydon (J., 1939, 1394) found one solution of the problem in the opening of the *cyclo*pentenone ring to a dicarboxylic acid. This could be reduced in the aromatic nuclei and subsequently the acid could be recyclised. The method involves a number of steps with consequent loss of material and we have explored other possibilities. The use of Grignard reagents such as allylmagnesium bromide and of acetylene in the presence of potassium did not hold out good prospects and cyanohydrin formation has been studied in detail with little result by other workers in the laboratory.

However, the Reformatzky reaction could be successfully used and this development will be followed up in other cases.

The unsaturated *esters* (XXV and XXVI) were obtained from the appropriate components in satisfactory yields, but the conditions must be carefully observed.

(XXV.)



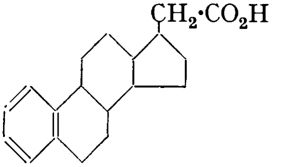


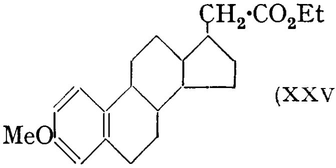
(XXVI.)

The double bond may be in the βγ-position to the carbethoxyl group.

Hydrogenation by means of palladised norit and hydrogen affords the dihydro-derivatives and further hydrogenation in the presence of Raney nickel at 200—220°/65 atms. causes elimination of the methoxyl group in position 4 and reduction to (XXVII) (after hydrolysis) and (XXVIII) respectively. We assume that the methoxyl group common to (XXV) and (XXVI) is the one removed in the reduction and the experience of Robinson and Rydon (*loc. cit.*) may be cited in support.

(XXVII.)





(XXVIII.)

These substances are important intermediates offering a variety of possibilities for further investigation.

EXPERIMENTAL.

(A) 3-*Amino*-7-*methoxy*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydro*-1 : 2 : cyclo*pentenophenanthrene* (VII).—Sodium (20 g.) was added to the oxime (10 g.) of 3-keto-7-methoxy-1 : 2 : 3 : 9 : 10 : 11-hexahydro-1 : 2-*cyclo*pentenophenanthrene-A (Peak and Robinson, J., 1937, 1581) in butyl alcohol (300 c.c.). The reaction was completed by heating (oil-bath) and, when all the sodium had disappeared, excess of dilute hydrochloric acid was added, and the hot liquids separated. The amine hydrochloride was dissolved in the butyl-alcoholic layer, which was concentrated and filtered from a small precipitate of sodium chloride. The filtrate on keeping set to a thick, dirty yellow paste, from which the hydrochloride was collected, dried, and dissolved in boiling dilute hydrochloric acid. On cooling, the *hydrochloride* separated in white flocculent masses of extremely slender, microscopic needles; a further quantity separated after several days. The main crop was recrystallised several times from dilute hydrochloric acid (charcoal); it sintered at 258° and melted to a very viscous liquid at 272° which became quite mobile at 278° (Found: N, 4·4. $C_{18}H_{25}ON,HCl$ requires N, 4·4%). The second crop was recrystallised several times from dilute hydrochloric acid (charcoal), m. p. 302° (Found: N, 4·4%); mixed m. p. with the main product, 266—270°.

3-*Keto*-1 : 2 : 3 : 9 : 10 : 11-*hexahydro*-1 : 2-cyclo*pentenophenanthrene* (V).—The following slight modification of the method described by Hawthorne and Robinson (J., 1936, 763) gives an improved yield. Freshly distilled α-tetralone (10 g.) and sodamide (3 g.) in dry ether (140 c.c.) were refluxed in a current of dry, oxygen-free nitrogen until the evolution of ammonia had ceased. Acetyl*cyclo*pentene (8 g.) was added to the boiling mixture, and refluxing continued for about 12 hours. The product was cooled, acidified with dilute sulphuric acid, and filtered. The solid was washed with ether and crystallised from ethyl alcohol (yield, 5·4 g. of m. p. 171°).

3-*Hydroxy*-1 : 2 : 3 : 9 : 10 : 11-*hexahydro*-1 : 2-cyclo*pentenophenanthrene* (VIII).—The ketone (5 g.), aluminium *iso*propoxide (5 g.), and dry *iso*propyl alcohol (150 c.c.) were placed in a flask fitted with a fractionating column and heated in an oil-bath so that a slow distillation took place. Fresh *iso*propyl alcohol was added from time to time, and the distillation continued until the presence of acetone in the distillate could no longer be detected (10 hours). Most of the *iso*propyl alcohol was then distilled, and excess of dilute hydrochloric acid added to the residue. The product was extracted four times with ether, and the extract washed with water and sodium hydrogen carbonate solution and dried. Removal of the solvent gave 4 g. of a pungent-smelling liquid which crystallised on keeping. It separated slowly from dilute benzene solutions in white masses of microscopic needles, m. p. 131—132° after softening at 128°. On drying in a vacuum at 100° it became discoloured and the analytical figures were not quite satisfactory (Found : C, 84·3; H, 8·0. $C_{17}H_{20}O$ requires C, 85·0; H, 8·3%).

Dehydration of the Carbinol $C_{17}H_{20}O$.—The above carbinol (2 g.) was mixed with freshly fused potassium hydrogen sulphate (4 g.) and distilled under diminished pressure (oil-bath at 160—180°). The crystalline distillate was recrystallised from ethyl alcohol, separating in needles, m. p. 79° (Found : C, 92·3, 91·5; H, 7·7, 8·4. $C_{17}H_{18}$ requires C, 91·9; H, 8·1%). The *hydrocarbon* decolourised alkaline permanganate immediately.

Oxidation of the Hydrocarbon $C_{17}H_{18}$ (I, R = H).—The hydrocarbon (0·2 g.), selenium dioxide (0·07 g.), and ethyl alcohol (10 c.c.) were refluxed for 2 hours on the steam-bath. The precipitated selenium was separated, and the filtrate concentrated and cooled in a freezing mixture. The solid (0·1 g.) which separated was recrystallised from ethyl alcohol, forming small plates, m. p. 61—62° (Found : C, 92·4; H, 7·6. $C_{17}H_{16}$ requires C, 92·7; H, 7·3%). The *hydrocarbon* (XI) was stable to alkaline permanganate. The mother-liquor from the first crystallisation gave indication (dinitrophenylhydrazone) of the presence of a ketonic substance.

3-*Hydroxy*-7-*methoxy*-1 : 2 : 3 : 9 : 10 : 11-*hexahydro*-1 : 2-cyclo*pentenophenanthrene* (IX).—3-Keto-7-methoxy-1 : 2 : 3 : 9 : 10 : 11-hexahydro-1 : 2-*cyclo*pentenophenanthrene-A was treated with an equal weight of aluminium *iso*propoxide in dry *iso*propyl alcohol exactly as described in the case of compound (VIII). On concentration of the dried ethereal extract a considerable amount of unchanged ketone, m. p. 192°, was deposited. After filtration the ether was evaporated, and the carbinol usually dehydrated as below without further purification. The *substance* separated from methyl alcohol as a nearly colourless, crystalline powder, m. p. 157—161° (Found : C, 80·0; H, 8·1. $C_{18}H_{22}O_2$ requires C, 80·0; H, 8·2%).

Dehydration of the Carbinol $C_{18}H_{22}O_2$.—(*a*) The crude carbinol was mixed with approximately twice its weight of freshly fused potassium hydrogen sulphate and distilled under diminished pressure (oil-bath at 220°). The mixture frothed badly and the first portions of the distillate were considerably contaminated. The last portion was much cleaner and crystallised on standing. It was recrystallised from ethyl alcohol, being so obtained in needles, m. p. 101—102° (Found : C, 86·4; H, 7·3. $C_{18}H_{18}O$ requires C, 86·4; H, 7·2%). The carbinol had evidently undergone dehydrogenation as well as dehydration and the product is probably (X).

(*b*) A mixture of the carbinol (4 g.) and sodium (1 g.) in dry toluene (20 c.c.) was refluxed for 5 hours; almost the theoretical amount of sodium had then disappeared. The excess of sodium was removed, and dry ether (20 c.c.) added. Carbon disulphide (1 g.) was added in the cold, followed by methyl iodide (2·5 g.), and the mixture was refluxed for an hour on the steam-bath. Water was added, and the upper layer separated and dried. The solvents were removed, and the residue heated under reduced pressure at 180° until the evolution of low-boiling material was complete. The residue was distilled in a high vacuum, the distillate crystallising; it was recrystallised from ethyl alcohol, forming small plates, m. p. 82—85° (Found : C, 85·8; H, 7·9. $C_{18}H_{20}O$ requires C, 85·7; H, 7·9%). This unsaturated *substance* is considered to be (I, R = OMe).

(B) 3-*Keto*-1 : 2 : 3 : 5 : 6 : 7 : 8 : 9-*octahydro*-1 : 2-cyclo*pentenonaphthalene* (XIII) (cf. Huber, *loc. cit.*).—Dry *iso*propyl alcohol (83 c.c.) was added dropwise to finely divided potassium (14 g.) in dry ether. A mixture of *cyclo*hexanone (13 g.), acetyl*cyclo*pentene (15 g.), and dry pyridine (70 c.c.) was added dropwise, and the mixture refluxed on the water-bath for 6 hours. The product was poured into water, acidified, and extracted four times with ether. The extract was dried and distilled. After the solvent and unchanged materials had been removed, the distillate up to 175°/0·14 mm. (13 g.) was collected. In a further preparation from 40 g. of *cyclo*hexanone a yield of 40 g. of a product boiling up to 230°/0·93 mm. was obtained. This was combined with the distillate from the first preparation and separated into the following fractions, possessing a rather sweet odour :

(i) B. p. 110—130°/0·88 mm. (20 g.). This was redistilled, and the distillate up to 120°/0·057 mm. (mainly 110—115°; 18 g.) collected. This was again distilled, and a portion of the middle distillate collected, b. p. 110—115°/0·28 mm. (Found : C, 82·5; H, 9·9. $C_{13}H_{18}O$ requires C, 82·1; H, 9·5%). The dinitrophenylhydrazone was formed in alcoholic solution, but was not obtained crystalline.

(ii) B. p. 130—160°/0·88 mm. (7 g.). This was added to the residues from (i) and redistilled, b. p. 118—140°/0·042 mm. (6 g.). This was again distilled, and a middle fraction collected, b. p. 125—140°/0·28 mm. (Found : C, 82·9; H, 10·0%). The *dinitrophenylhydrazone* was formed in alcoholic solution and recrystallised from alcohol, m. p. 164—165° (Found: N, 15·4. $C_{19}H_{22}O_4N_4$ requires N, 15·1%). A considerable residue remained in the flask.

3-*Keto*-1 : 2 : 3 : 4 : 5 : 6 : 7 : 8 : 9 : 10-*decahydro*-1 : 2-cyclo*pentenonaphthalene* (XV).—(*a*) 3-Keto-octahydro*cyclo*pentenonaphthalene (11·3 g., b. p. up to 120°/0·057 mm.) in methyl alcohol (100 c.c.) was shaken with a 2% palladium–strontium carbonate catalyst under hydrogen at 2 atms., but the original material was recovered unchanged.

(*b*) 3-Keto-octahydro*cyclo*pentenonaphthalene (11 g.) was reduced with sodium (50 g.) in ethyl-alcoholic solution. The solvent was removed by steam distillation, and the residue extracted with ether, dried, and distilled. The product (8 g., b. p. 110—130° under high vacuum) was a viscous, pale yellow liquid with a characteristic pleasant odour similar to that of the essential oil from the *Hypericum sp.* prevalent in the South Island of New Zealand.

A mixture of the carbinol (8 g.), dry acetone (200 g.), dry benzene (300 c.c.), aluminium *iso*propoxide (10 g.), and *tert.*-butyl alcohol (11 g.) was refluxed for 20 hours. The product was cooled and washed with dilute sulphuric acid, and the benzene layer separated and dried. Distillation yielded 7 g. of a pale yellow oil with a characteristic penetrating and unpleasant odour, b. p. 120—130°/0·74 mm. This was redistilled, and a middle distillate collected (Found: C, 84·1; H, 10·2%). The carbon content is too high for any anticipated product.

3-*Hydroxy*-3-*methyl*-1 : 2 : 3 : 4 : 5 : 6 : 7 : 8 : 9 : 10-*decahydro*-1 : 2-cyclo*pentenonaphthalene* (XVI).—A Grignard reagent was prepared from magnesium (1·42 g.) and methyl iodide (8 g.) in dry ether (20 c.c.). 3-Ketodecahydro-1 : 2-*cyclo*pentenonaphthalene (4·5 g.) in ether (20 c.c.) was added slowly, each drop reacting vigorously. When all the ketone had been added, the mixture was refluxed for 2 hours. The product was decomposed with ice and hydrochloric acid and exhaustively extracted with ether. Distillation of the combined extracts yielded the *carbinol* (4 g.) as a viscous, pale yellow oil with a terpenoid odour, b. p. 108—128°/0·22 mm. A portion of the distillate, b. p. 114—118°, was collected for analysis (Found: C, 81·5; H, 11·2. $C_{14}H_{24}O$ requires C, 80·8; H, 11·5%).

Dehydration of the Carbinol $C_{14}H_{24}O$.—The carbinol (4 g.) was heated at 180—190° for 10 minutes with freshly fused potassium hydrogen sulphate (2 g.). The product was extracted with ether, and the ether distilled, yielding a pale yellow oil with an odour somewhat similar to that of the saturated ketone, b. p. 90—115°/0·17 mm. A middle distillate, b. p. 90—93°, was collected for analysis (Found: C, 86·7; H, 11·5. $C_{14}H_{22}$ requires C, 88·4; H, 11·6%). The impurity of low carbon content could not be removed. An attempt to form the glycol by oxidation with the theoretical amount of perbenzoic acid in ether, followed by hydrolysis of the oxide, did not succeed.

(C) β-2-*Naphthoyl- and* β-1-*Naphthoyl-propionic Acids.*—The method is that of Haworth (J., 1932, 1129), but the method of separation of the products is perhaps an improvement.

A mixture of naphthalene (160 g.) and succinic anhydride (80 g.) was added with stirring to a cold solution of anhydrous aluminium chloride (220 g.) in nitrobenzene (600 g.). After standing overnight, the product was decomposed with ice and hydrochloric acid, and the liquid filtered. The precipitate was freed from a small amount of adhering nitrobenzene by steam-distillation and remained in the flask as a crystalline deposit consisting of nearly pure β-2-naphthoylpropionic acid. The colour was removed by boiling the solution in sodium carbonate with norit, and the acid precipitated and crystallised from methyl alcohol. Yield, 40 g., m. p. 172° after previous softening.

The nitrobenzene filtrate was steam-distilled; the oil remaining in the flask solidified on cooling. It was dissolved in boiling aqueous sodium carbonate, boiled with norit, filtered, acidified, and the precipitated acid crystallised first from glacial acetic acid and then from methyl alcohol. The yield of β-1-naphthoylpropionic acid was 48 g., m. p. 131° after previous softening.

The Lactone of γ-*Hydroxy*-γ-2-*naphthylvalerolactone* (XIX).—2-Bromonaphthalene (20·7 g.) in dry ether (80 c.c.) was added slowly to magnesium (2·4 g.) activated with a little ethyl iodide. The mixture was refluxed until most of the magnesium had disappeared. The Grignard reagent was added with shaking to ethyl lævulate (14·4 g.) in ether. The vigorous reaction was completed by refluxing for 30 minutes. After 12 hours the product was decomposed with ice and hydrochloric acid, isolated by means of ether, and distilled. After naphthalene and unchanged bromonaphthalene had been removed, a fraction, b. p. 190—205°/1·6 mm. (8·5 g.), was collected. A considerable residue was a viscous liquid which slowly solidified on standing. It was dissolved in hot ethyl alcohol; on cooling, shining white plates of dinaphthyl separated, m. p. 185°. The mother-liquors were diluted with water, and the precipitated solid collected, dried, and exhaustively extracted with hot light petroleum (b. p. 60—80°). On cooling, γ-*hydroxy*-γ-2-

naphthylvalerolactone crystallised in rosettes of white needles, m. p. 77° (Found : C, 79·6; H, 6·3. $C_{15}H_{14}O_2$ requires C, 79·6; H, 6·2%).

The residue of viscous liquid insoluble in light petroleum crystallised on standing overnight. It was dissolved in chloroform, diluted with light petroleum (b. p. 40—60°) until cloudy, warmed, and kept. An oil was first deposited and then crystals. A little chloroform was added to dissolve the oil and the solution was then concentrated by slow evaporation. The material melted at 135°, and finally, after two further crystallisations, at 139°. It is presumably the isomeric unsaturated acid described below.

γ-2-*Naphthyl*-Δ^{β}-*pentenoic Acid* (XX).—(*a*) Methylmagnesium iodide (from magnesium, 3 g., and methyl iodide, 18 g.) in ether was added dropwise to a cold solution of ethyl β-2-naphthoylpropionate (31 g.) in ether. After standing overnight, the product was decomposed with ice and hydrochloric acid, isolated by means of ether, and distilled (yield, 24 g., b. p. mainly 188—195°/0·35 mm.). This distillate was dissolved in chloroform, and the hot solution diluted with light petroleum (b. p. 40—60°). Shining white plates of γ-2-*naphthyl*-Δ^{β}-*pentenoic acid* were deposited, m. p. 139° after previous softening. Two further crystallisations raised the m. p. to 141—142° (Found : C, 79·6; H, 6·3. $C_{15}H_{14}O_2$ requires C, 79·6; H, 6·2%). The mother-liquors were evaporated, and the residue extracted with boiling light petroleum (b. p. 60—80°). On cooling, crystals of the above lactone were deposited, m. p. 75°.

(*b*) Methylmagnesium iodide (from magnesium, 3·6 g., and methyl iodide, 21 g.) in ether was added dropwise to methyl β-2-naphthoylpropionate (26 g.) in dry benzene (100 c.c.), and the mixture refluxed for 2 hours on the steam-bath. The product was decomposed with dilute sulphuric acid, and the ether–benzene layer separated and extracted with potassium carbonate solution. The alkaline extract was boiled with norit, filtered, and acidified. The precipitated acid (yield of dried acid, 14 g.), after crystallisation from chloroform, had m. p. 140° with previous softening. The unsaturated acid was heated with dilute sulphuric acid on the steam-bath for 12 hours. On cooling, the oil which had formed solidified. After crystallising from light petroleum (b. p. 60—80°), it melted at 75° alone or mixed with the analysed specimen of the above lactone.

γ-(6-*Methoxy*-2-*naphthyl*)-Δ^{β}-*pentenoic Acid*.—The formation of the Grignard reagent from 2-bromo-6-methoxynaphthalene (Fries and Schimmelschmidt, *Ber.*, 1925, **58**, 2840) was sluggish, so an equimolecular proportion of methyl iodide was employed. 2-Bromo-6-methoxynaphthalene (18 g.; 1 mol.) in ether was added to magnesium (3·6 g.; 2 mols.) and a solution of methyl iodide (11 g.; 1 mol.) in ether was then run in. A vigorous reaction took place and ultimately almost all the magnesium disappeared. The Grignard reagent was added to ethyl lævulate (14·4 g.; 2 mols.) in dry benzene, and the mixture refluxed for 2 hours. After standing overnight, the product was decomposed with dilute hydrochloric acid, and the ether–benzene layer extracted with potassium carbonate solution. The alkaline extract was acidified; the precipitated acid crystallised (after drying) from chloroform–light petroleum (b. p. 40—60°) in hexagonal plates, m. p. 177° after previous softening (Found : C, 75·0; H, 6·2. Calc. for $C_{16}H_{16}O_3$: C, 75·0; H, 6·3%) (yield of crude acid, 5 g.). Short, Stromberg, and Wiles (J., 1936, 319) give m. p. 171—171·5°.

Cyclisation was attempted under various conditions with acetic anhydride, sulphuric acid, phosphoric anhydride, potassium hydrogen sulphate, benzoic anhydride, and by pyrolysis. In several cases phenolic substances were produced (azo-compounds), but the minute yields precluded further examination.

Ethyl cyclo*Pentanone*-2 : 3-*dicarboxylate*.—This ester was prepared as described by Kay and Perkin (J., 1906, **89**, 1640) from ethyl butane-$\alpha\beta\delta$-tricarboxylate. The esterification of butane-$\alpha\beta\delta$-tricarboxylic acid with alcohol and sulphuric acid as described is difficult and incomplete, but by employing a continuous esterification process (in which the water is removed by means of carbon tetrachloride) the esterification proceeds readily and an excellent yield is obtained.

The Lactone of 3-*Hydroxy*-3-(6′-*methoxy*-2′-*naphthyl*)cyclo*pentane*-1-*carboxylic Acid* (XXIII).—2-Bromo-6-methoxynaphthalene (18 g.; 1 mol.) in ether (250 c.c.) was warmed with magnesium (3·6 g.; 2 mols.), and methyl iodide (11 g.; 1 mol.) in ether added. After gentle heating on the steam-bath the reaction commenced and continued briskly until most of the magnesium had disappeared. The Grignard reagent was added slowly in the cold to a solution of ethyl *cyclo*pentanone-3-carboxylate (15·6 g.; 2 mols.) (Haworth and Perkin, J., 1908, **93**, 591) in ether. After standing overnight, the product was refluxed for an hour and then decomposed with dilute hydrochloric acid. The ethereal layer was separated and washed with sodium carbonate solution; no acid was obtained on acidifying these washings. The ethereal extract was dried and distilled, and the following fractions collected :

(i) Up to 130°/25 mm. (*cyclo*pentane derivatives).

(ii) B. p. 130—200°/27 mm. (mainly 180—200°) (6 g. of bromomethoxynaphthalene).

(iii) Up to 220°/0·8 mm. (9 g.). This fraction consisted of a pale yellow liquid which slowly set to a pasty mass on standing. It was crystallised with difficulty from methanol, the *lactone* separating in clumps of microscopic needles, m. p. 97—98° (Found : C, 75·6; H, 6·7. $C_{17}H_{16}O_3$ requires C, 76·1; H, 6·0%).

(D) 4-*Methoxy*-3′-*ethyl*-Δ$^{3'}$-1:2-cyclo*pentenophenanthrene*.—3′-Keto-4-methoxy-1 : 2-*cyclo*pentenophenanthrene (1 g.) was added in one portion to ethylmagnesium bromide (from magnesium, 0·5 g., and ethyl bromide, 3 g.) in ethereal solution, and reacted completely in a few seconds. The mixture was refluxed for 2 hours, cooled; and decomposed with ice and dilute hydrochloric acid. The ethereal layer was separated, washed with potassium carbonate solution, and dried, and the solvent distilled. The residue, crystallised from ethyl alcohol (yield, 0·6 g.), had m. p. 105° after previous softening (Found : C, 87·3; H, 6·4. $C_{20}H_{18}O$ requires C, 87·6; H, 6·6%).

Ethyl 4-*Methoxy*-1 : 2-cyclo*pentenophenanthrylidene*-3′-*acetate* (XXV).—A mixture of 3′-keto-4-methoxy-1 : 2-*cyclo*pentenophenanthrene (2 g.), ethyl bromoacetate (1·6 g.), zinc wool (0·5 g.), benzene (20 c.c.), and toluene (10 c.c.) was refluxed for 4 hours. The product was decomposed with dilute sulphuric acid and after filtration the benzene–toluene layer was evaporated. The residue was taken up in boiling ethyl alcohol, cooled, and decanted several times from the sticky material which separated first on cooling. The solution was then kept and gradually deposited the crude ester as a yellow solid (1 g.). After recrystallising four times from ethyl alcohol (norit), the pure *ester* was obtained in pale yellow, microcrystalline needles, m. p. 144° (Found : C, 79·6; H, 6·0. $C_{22}H_{20}O_3$ requires C, 79·5; H, 6·0%).

The ester decolorised permanganate immediately and was readily saponified by heating with methyl-alcoholic potassium hydroxide. The colour of the purest specimens (repeatedly boiled with norit in alcohol) was a pale cream; the solution in alcohol possessed a strong blue fluorescence.

The yield is variable (the purity of the bromoacetic ester is one factor), and the isolation and complete purification of the ester a matter of some inconvenience, but it is to be preferred to saponifying the reaction product and working up the acid, because the latter is very sparingly soluble and difficult to purify. When working with larger quantities or successive preparations, mother-liquors may be used for fresh extractions.

In the course of the purification the ester sometimes separates in large plates, but further crystallisation always gives micro-needles.

4-*Methoxy*-1 : 2-cyclo*pentenophenanthrene*-3′-*acetic Acid*.—The unsaturated ester was shaken in warm alcoholic solution with palladised norit under hydrogen. When absorption had ceased, the solution of the dihydro-ester (colourless but exhibiting a lilac fluorescence) was evaporated, and the residue saponified with methyl-alcoholic potassium hydroxide. After removal of most of the alcohol the residue was acidified; the precipitated *acid*, crystallised from aqueous acetic acid, had m. p. 169° (Found : C, 78·4; H, 5·8. $C_{20}H_{18}O_3$ requires C, 78·4; H, 5·9%).

The saturated ester and acid are much more readily soluble than the corresponding unsaturated compounds.

Ethyl 4 : 7-*Dimethoxy*-1 : 2-cyclo*pentenophenanthrylidene*-3′-*acetate* (XXVI).—A mixture of 3′-keto-4 : 7-dimethoxy-1 : 2-*cyclo*pentenophenanthrene (12 g.), pure ethyl bromoacetate (8 g.), zinc wool (2·7 g.), and a little iodine was refluxed in a large volume of solvent (2 parts of benzene to 1 part of toluene) for 6—8 hours. The product was decomposed by refluxing for several hours with dilute sulphuric acid, the liquid filtered, and the toluene–benzene layer separated, washed, and concentrated to a small bulk. The hot liquid was poured into water, and the rapidly precipitated solid collected, washed with alcohol, and dried at 100° (yield, 11·5 g.). This material was employed for further experiments without purification. The *ester* crystallised from toluene in interlaced needles, m. p. 192° (Found : C, 76·1; H, 6·2. $C_{23}H_{22}O_4$ requires C, 76·2; H, 6·1%). It was practically unchanged by boiling for several hours with methyl-alcoholic potassium hydroxide.

1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*Octahydro*-1 : 2-cyclo*pentenophenanthrene*-3′-*acetic Acid* (XXVII).—Ethyl 4-methoxy-1 : 2-*cyclo*pentenophenanthrylidene-3′-acetate (4·4 g.) in ethyl alcohol (30 c.c.) together with a Raney nickel catalyst was placed in a pressure hydrogenator, and hydrogen admitted at *ca.* 45 atms. Heating was commenced and at 160° shaking was also commenced; the temperature was raised to 200—220°, and the pressure kept at *ca.* 65 atms. by removing hydrogen as required during the period at which the temperature was rising. Shaking

and heating were continued for 8 hours. After cooling, the catalyst was separated and washed several times with hot alcohol, giving a colourless non-fluorescent solution. Removal of the solvent yielded a viscous, pleasant smelling liquid which could not be crystallised. It was therefore saponified by refluxing for 20 minutes with excess of methyl-alcoholic potassium hydroxide. Most of the methyl alcohol was then evaporated (water being added to keep the volume constant); acidification with dilute hydrochloric acid precipitated a sticky dough-like mass. This was dissolved in potassium carbonate solution, and the hot solution extracted with benzene. The alkaline layer was boiled to remove benzene, cooled, and acidified, and the precipitated acid dissolved in hot ethyl alcohol (norit) and filtered, yielding a clear water-white solution. Water was added to produce a slight cloudiness and most of the alcohol was then evaporated, and the residue poured into water. The precipitated acid (fraction 1) was a rather sticky solid and a further amount of material of a harder, more nodular character was quickly deposited from the filtrate (fraction 2). Both fractions were dried in a vacuum desiccator, fraction 1 becoming harder and more nodular on keeping.

Fraction 1 was dissolved in boiling glacial acetic acid; on standing, a white crystalline mass was slowly deposited. This was collected, and the filtrate diluted with water and kept for several days, whereby the precipitated oil slowly solidified. This material was collected and recrystallised from a small quantity of glacial acetic acid (fraction 1A). The bulk of fraction 1 was dissolved in glacial acetic acid and the material which crystallised on standing was collected and dried first in a vacuum desiccator over caustic potash and then in a drying pistol at 100° in a vacuum (fraction 1B). The mother-liquors on standing deposited further crystals, which were collected and dried as above (fraction 1C). The mother-liquors on standing in the ice-chest for some days deposited a small amount of crystalline material, which was collected and dried as above (fraction 1D).

Fraction 2 was dissolved in boiling glacial acetic acid; on standing, crystalline material was slowly deposited. This was collected and dried (fraction 2A). The mother-liquors on standing for several days deposited a further small crop of crystals, which were collected and dried (fraction 2B). The mother-liquors were kept in the ice-chest, but no further significant amount of material was deposited.

The melting points and analytical figures for these fractions are given below:

Fraction 1A: This melted over a wide range and was obviously a mixture. It was not further examined. Fraction 1B: m. p. 196° after previous softening (Found: O·CH$_3$, 0·0; C, 80·4; H, 8·0. $C_{19}H_{24}O_2$ requires C, 80·3; H, 8·5%). Fraction 1C: m. p. 195° after previous softening. Fraction 1D: m. p. 147—148° after previous softening. Fraction 2A: m. p. *ca.* 184—188° (with darkening) after previous softening (Found: O·CH$_3$, 0·0; C, 80·1; H, 8·3. $C_{19}H_{24}O_2$ requires C, 80·3; H, 8·5%). Fraction 2B: m. p. 149° after previous softening (Found: C, 80·0; H, 8·3. $C_{19}H_{24}O_2$ requires C, 80·3; H, 8·5%).

The acid, therefore, is obtained in two isomeric forms. The main product is isomer-A (m. p. 196°), and isomer-B (m. p. 148°) is present in small amount only.

Hydrogenation of Ethyl 4 : 7-*Dimethoxy*-1 : 2-cyclo*pentenophenanthrylidene*-3′-*acetate*.—The ester (11 g.) in ethyl alcohol (120 c.c.) was shaken in hydrogen at 200—220°/65 atms. for 7 hours. On cooling, crystalline material had separated; a further 280 c.c. of alcohol were therefore added, and the boiling solution (coloured and possessing a slight fluorescence) filtered from the catalyst. On standing overnight, crystals were depositied (3·9 g.), m. p. 105°. These were taken up in boiling alcohol; on cooling, *ethyl* 4 : 7-*dimethoxy*-1 : 2-cyclo*pentenophenanthrene*-3′-*acetate* separated in pale yellow plates, m. p. 106—107° (Found: C, 75·8; H, 6·6. $C_{23}H_{24}O_4$ requires C, 75·8; H, 6·6%).

The mother-liquor was evaporated to a small volume; on standing, a small amount of amorphous material was deposited, followed by a further quantity of the above ester (1·4 g.), m. p. (recrystallised) 105—106°. This specimen was practically colourless. The substance in the mother-liquors could not be isolated.

In a second experiment the ester (11 g., unpurified product from the Reformatzky reaction) in ethyl alcohol (120 c.c.) was hydrogenated in the presence of Raney nickel at 200°/65 atms. for 8 hours. The product contained yellow crystals and was therefore brought up to a volume of 400 c.c. with more alcohol, and the solution boiled and filtered from the catalyst. On standing, pale yellow plates were deposited (3·9 g.), m. p. (recrystallised from alcohol) 105—107° (Found: C, 75·8; H, 6·9%). The filtrate was evaporated to a small bulk and a further crop of the dihydro-ester was obtained (1·4 g.), m. p. (recrystallised) 105—106°.

The mother-liquors were now evaporated completely, and the residue saponified with excess of methyl-alcoholic potassium hydroxide. After distillation of most of the methyl alcohol, with the addition of water to keep the volume constant, the product was acidified with dilute hydrochloric acid, and the precipitated acid collected and dissolved in boiling glacial acetic acid. On standing at room temperature there was no deposition, but on standing in the ice-chest the whole solidified and on gentle warming the acetic acid melted, leaving behind a small amount of buff-coloured material (350 mg.). This was crystallised from methyl alcohol (norit), giving the *dihydro-acid*, m. p. 197° (Found : C, 74·6; H, 6·1. $C_{21}H_{20}O_4$ requires C, 75·0; H, 6·0%).

The acetic acid mother-liquors failed to yield any further crystalline material.

Hydrogenation of Ethyl 4 : 7-*Dimethoxy*-1 : 2-cyclo*pentenophenanthrene*-3′-*acetate*.—The ester (3·7 g.) in ethyl alcohol (30 c.c.) was hydrogenated in the presence of Raney nickel at 200—220°/65 atms. for 8 hours. After removal of the catalyst and distillation of the solvent a pleasant-smelling, viscous liquid was left. This was saponified with excess of methyl-alcoholic potassium hydroxide, and the methyl alcohol evaporated with the addition of water. Acidification gave a sticky deposit of crude acids, which was dried, dissolved in boiling light petroleum (b. p. 100—120°), boiled with norit, filtered, and kept overnight. Nodules were deposited (fraction 1, 750 mg.). The mother-liquors were kept in the ice-chest and deposited a further amount of acid (fraction 2, 120 mg.). The petroleum mother-liquors were extracted with potassium carbonate solution; the alkaline layer, after boiling to free it from adhering solvent, was cooled and acidified, yielding another acid fraction, which was collected and dried (fraction 3, 2 g.).

These fractions were examined separately as follows : *Fraction* 1. This was dissolved in boiling glacial acetic acid; after standing at room temperature for 6 hours, the material deposited (nodules adhering in chains) was collected and dried, m. p. *ca.* 178° after previous softening (Found : C, 78·7; H, 8·1. $C_{20}H_{26}O_3$ requires C, 76·4; H, 8·3%).

The mother-liquors on standing in the ice-chest solidified. On gentle warming the acetic acid melted and the remaining solid material was collected and dried, m. p. *ca.* 180° after previous softening (Found : C, 78·5; H, 8·2%).

The mother-liquors were heated to boiling and diluted to cloudiness with water; the material deposited on cooling melted over a wide range. It was dissolved in hot methyl alcohol; on standing, material was deposited, which formed a viscous opalescent liquid at *ca.* 172° (after previous softening) but became clear and mobile at 178°.

Fraction 2. This melted at *ca.* 150—170° and was not further investigated.

Fraction 3. This was dissolved in boiling glacial acetic acid; on long standing, a small amount of material separated, m. p. 190—193° after recrystallisation (Found : C, 80·2; H, 8·6. $C_{19}H_{24}O_2$ requires C, 80·3; H, 8·4%). The mother-liquors slowly deposited a further fraction, m. p. *ca.* 140—150°.

Evidently the hydrogenation in this experiment went too far. Two methoxyl groups have been eliminated with formation of $C_{19}H_{24}O_2$ and the product, m. p. *ca.* 178°, 180°, is apparently a mixture of $C_{19}H_{24}O_2$ and $C_{20}H_{26}O_3$.

Ethyl 7-*Methoxy*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydro*-1 : 2-cyclo*pentenophenanthrene*-3′-*acetate* (XXVIII).—Ethyl 4 : 7-dimethoxy-1 : 2-*cyclo*pentenophenanthrylidene-3′-acetate (14 g., crude) in alcohol was hydrogenated at *ca.* 200°/65 atms. in the presence of Raney nickel catalyst for 16 hours, and the product filtered hot from the catalyst; the catalyst was washed several times with boiling alcohol. As there was still a considerable amount of dihydro-ester present, the hydrogenation was repeated after distillation of some of the alcohol. A second run was made, similar quantities being used; this time there did not appear to be any of the dihydro-ester present after one operation and the product was combined with the doubly reduced product from the first run, and the crude esters distilled. The following fractions were collected : (*a*) up to 210°/0·5 mm. (1·7 g.), (*b*) 218—222°/0·5 mm. (10·8 g.), (*c*) 234—254°/0·5 mm. (8·5 g.).

Fraction (*b*) was redistilled, and the middle portion collected (6·7 g.) (Found : C, 77·6; H, 8·6. $C_{22}H_{30}O_3$ requires C, 77·2; H, 8·8%). Fractions (*a*) and (*c*) and the first and the last runnings from the redistillation of (*b*) were combined, subjected to rehydrogenation under conditions similar to those previously employed, giving, finally, 10·5 g. of a distillate which was redistilled, giving the fractions : (*a*) 180—200°/0·4 mm. (2·6 g.), (*b*) 208—215°/0·4 mm. (6·5 g.) (Found : C, 77·0; H, 8·5%). The total yield of the required *ester* is therefore 13·2 g., which represents 84% of the final distillates.

DYSON PERRINS LABORATORY, OXFORD UNIVERSITY.

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