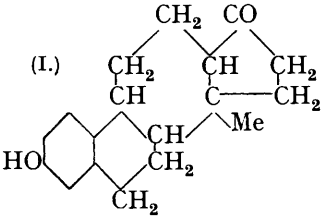
150. *Experiments on the Synthesis of Substances Related to the Sterols. Part I. Some Derivatives of Chrysene.*

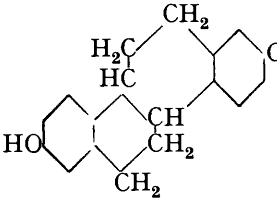
By G. R. Ramage and Robert Robinson.

Recent developments in the chemistry of the sterols, bile acids, and sex hormones (the literature of the last is summarised in *Ann. Reports*, 1932, 240) have been so rapid as to render feasible an attempt to supplement analysis by synthesis in these groups of natural products. The angle-methyl groups offer formidable difficulties in this connexion, but only one of these is present in ketohydroxyoestrin, the constitution of which may, as a working hypothesis, be represented as (I). (A communication by Butenandt and his collaborators read at the Chemical Society Discussion on March 16th gives experimental support to the phenanthrene skeleton assumed.) It is the purpose of the work now described to obtain ultimately a *nor*-derivative of (I), the physiological properties of which should be of much interest, especially in view of the work of Cook, Dodds, and Hewett (*Nature*, 1933, **131**, 56) which indicates that the oestrogenic property is not of a highly specific nature. The general idea underlying our scheme of synthesis is the preparation of symmetrical chrysene derivatives, one of the terminal rings of which will be modified so as to provide the necessary five-ring including a carbonyl group.

Thus it appeared probable that the phenol (II) could either be reduced to a hexahydro-derivative, then methylated, oxidised to a dibasic acid, and converted into a pyro-derivative, or alternatively might be changed by nitrous acid to a nitroso-derivative which could be transformed successively into a nitrile unsaturated acid, a dibasic unsaturated acid, a dibasic saturated acid, and a ketone. These considerations made it plain that chrysene derivatives must be synthesised, and that these should preferably be reduced in the two inner nuclei.

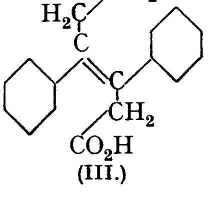
(I.)



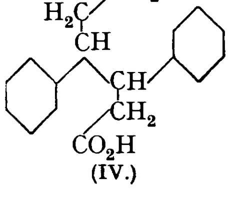


(II.)

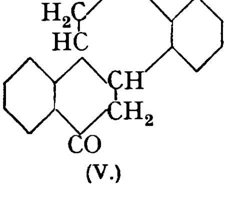
The first to devise a suitable synthesis was Beschke (*Annalen*, 1911, **384**, 143); this depended on the application of the Reformatzky reaction to benzil and its derivatives, and the essential stage was the double ring closure of dibasic acids of the type (III). An even more convenient method, indicated by Braun and Irmisch (*Ber.*, 1931, **64**, 2461), is very similar in principle to the process of Beschke but employs the saturated $\beta\gamma$-diphenyladipic acid (IV).



(III.)



(IV.)

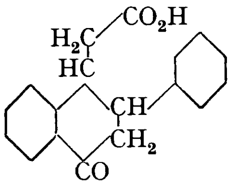


(V.)

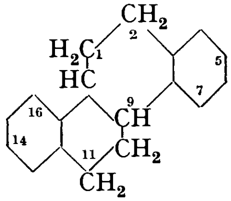
Isomeric forms of this acid were first obtained by Henle (*Annalen*, 1906, **384**, 16), who reduced cinnamic ester with amalgamated aluminium; the yield in the process was improved by Oommen and Vogel (J., 1930, 2148), who also obtained one of the acids in a condition of greater purity and determined the configuration of the isomerides. Braun and Irmisch (*loc. cit.*) submitted the acid chlorides of the *meso*- and *r*-βγ-diphenyladipic acids to the action of aluminium chloride and so obtained the *meso*- and *r*-diketohexahydrochrysenes (V).

As a by-product, keto-acids of the form (VI) were obtained. It was stated that diphenyladipic ester was obtained by the action of alcohol and concentrated hydrochloric acid on the *meso*-diketohexahydrochrysene. This observation we are unable to confirm, and the ring systems of the diketohexahydrochrysenes appear to exhibit normal stability. Braun and Irmisch carried out reductions of the diketohexahydrochrysenes, and obtained substances which they regarded as hexahydrochrysenes; the physical properties of their products do not tally with those which we have observed. Braun and Irmisch correctly retain the prefixes *meso*- and *r*- for the chrysene derivatives obtained from the respective diphenyladipic acids. It is, however, an interesting stereochemical point that *meso*-βγ-diphenyladipic acid must give rise to a *trans*-diketohexahydrochrysene, whereas *r*-diphenyladipic acid gives the *cis*-diketone. Here the prefixes *cis* and *trans* refer to the disposition of groups at the fused-ring positions of the central hexahydronaphthalene nucleus. In our own experiments in this field the isomeric diphenyladipic acids were submitted to the action of hot 85% sulphuric acid, a method used by Perkin, Rây, and Robinson for the preparation of 7-methoxychromanone (J., 1927, 2097) and with great success by R. D. Haworth in the synthesis of phenanthrene derivatives (*e.g.*, J., 1932, 1125). The formation of the diketohexahydrochrysenes was particularly smooth and it was later found that equally good results were obtainable by the use of the diphenyladipic esters. The isomeric ketones were, as already stated, perfectly stable substances and were reduced by means of amalgamated zinc and hydrochloric acid to homogeneous *hexahydrochrysenes* (VII). These substances furnished chrysene on being heated with selenium. The reduction of methyl 4-methoxycinnamate by amalgamated aluminium in moist ether affords a mixture of *methyl βγ-dianisyladipates-a* and *-b*, of which only the former has so far been employed (the b-series is in course of preparation); this isomeride is the more sparingly soluble and by analogy should be the *meso*-form.

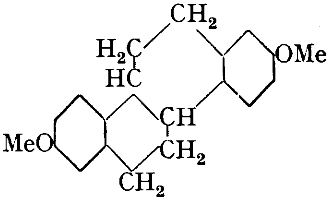
The ring-closure in this case cannot be conveniently effected by means of sulphuric acid, and we returned to a modification of the method of Braun and Irmisch (*loc. cit.*). βγ-Dianisyladipyl chloride was submitted to the action of aluminium chloride in tetrachloroethane solution; carbon disulphide was far less satisfactory. This *diketodimethoxyhexahydrochrysene* was reduced by Clemmensen's method to the *dimethoxyhexahydrochrysene* (VIII).



(VI.)



(VII.)



(VIII.)

The latter process offered considerable difficulty until it was found that the addition of anisole to the reaction mixture greatly facilitated the reduction. The substance (VIII) is the intermediate which we hope to be able to transform into a near relative of ketohydroxyoestrin, and this work is in progress.

EXPERIMENTAL.

trans-2 : 11-*Diketo*-1 : 2 : 9 : 10 : 11 : 18-*hexahydrochrysene* (V).—The reduction of methyl cinnamate under Oommen and Vogel's conditions (*loc. cit.*) gave *meso*- and *r*-diphenyladipates in 20% and 15% yields respectively. Methyl *meso*-diphenyladipate (1·5 g.) was added to conc. H_2SO_4 (18 c.c.) and H_2O (6 c.c.) and heated on the steam-bath with stirring for 3 hr. The ppt.

from three such expts., after addition of H_2O, was digested with hot Na_2CO_3 aq., washed, and dried (3·1 g.). *trans*-Diketohexahydrochrysene separates from BuOH in colourless diamond-shaped plates, m. p. 293°. The *bis-semicarbazone*, prepared in boiling BuOH, crystallised from AcOH (very sparingly sol.) in minute needles, m. p. 352° (Found : N, 22·6. $C_{20}H_{20}O_2N_6$ requires N, 22·3%). If the *meso*-acid is employed in the above prepn., the time of heating may be reduced to 1½ hr.

trans-1 : 2 : 9 : 10 : 11 : 18-*Hexahydrochrysene* (VII).—A mixture of the above-described diketone (3·0 g.), amalgamated Zn (20 g.), and conc. HCl (15 c.c.) was gently refluxed for 8 hr., and for a further equal period after addition of conc. HCl (12 c.c.). On cooling, the oil solidified, but the substance was isolated by means of C_6H_6 and distilled (2·0 g., b. p. 223°/12 mm.) as a colourless oil which rapidly solidified; it then crystallised from BuOH–EtOH (1 : 1) in long colourless prisms, m. p. 115° (Found : C, 92·0; H, 7·8. $C_{18}H_{18}$ requires C, 92·3; H, 7·7%).

cis-*Diketohexahydrochrysene* (V).—Methyl *r*-βγ-diphenyladipate (4·5 g.), treated like the *meso*-ester, furnished *cis*-diketohexahydrochrysene (2·7 g.), which crystallised from EtOH in glistening plates, m. p. 184° (Found : C, 82·4; H, 5·4. Calc. for $C_{18}H_{14}O_2$: C, 82·4; H, 5·3%).

cis-*Hexahydrochrysene* (VII).—The *cis*-diketone (2·0 g.) was reduced as described above for the *trans*-isomeride and afforded cis-*hexahydrochrysene* (1·2 g.), obtained on distillation as a colourless oil, b. p. 208°/12 mm., and then on crystn. from EtOH in elongated prisms, m. p. 75° (Found : C, 92·3; H, 7·8%).

Chrysene.—When either *cis*- or *trans*-hexahydrochrysene (1·0 g.) was heated with Se (5·0 g.) at 300° for 20 hr. a cryst. sublimate was formed, and this was melted down thrice in order to complete the oxidation. The sublimate was removed, combined with the residue from an extraction of the Se with C_6H_6, and distilled from Na; the distillate (0·8 g.), cryst. from C_6H_6, afforded pure chrysene (0·6 g.), m. p. 248° alone or mixed with an authentic specimen kindly supplied by Dr. A. C. Bottomley (Found : C, 94·6; H, 5·3. Calc. for $C_{18}H_{12}$: C, 94·7; H, 5·3%). The compound with *s*-trinitrobenzene was obtained from C_6H_6 as yellow needles, m. p. 186° (Sudborough, J., 1916, **109**, 1344).

Methyl 4-*Methoxycinnamate.*—Anisaldehyde (50 g.) and anhydr. AcOMe (150 c.c.) were added in one portion to sodium wire (9·5 g.), with cooling to control the ensuing vigorous reaction. After being heated on the steam-bath for 2 hr. with occasional stirring, the semi-solid mass was decomposed by dil. HCl, and the ester isolated partly by crystn. and partly by distillation of mother-liquors (yield, 62 g. of m. p. 89°) (Found : C, 69·0; H, 6·5. Calc. for $C_{11}H_{12}O_3$: C, 68·8; H, 6·3%).

Methyl βγ-*Dianisyladipate-a.*—A solution of methyl 4-methoxycinnamate (50 g.) in ordinary ether (1000 c.c.) was poured on amalgamated aluminium foil (90 g.). After the addition of H_2O (15 c.c.), the flask was cooled in running water during 8 hr. The filtered solution and the washings of the aluminium sludge were concentrated and finally methyl β-anisylpropionate (28 g.), b. p. 150°/14 mm., was removed by distillation as a colourless oil which solidified and crystallised from light petroleum in plates, m. p. 39° (Found : C, 68·1; H, 7·4. Calc. for $C_{11}H_{14}O_3$: C, 68·0; H, 7·2%). The undistilled residue (20 g.) was diluted with Et_2O, and the less sol. *methyl* βγ-*dianisyladipate-a* then separated (7·0 g.); recryst. from EtOAc–EtOH (1 : 1), it formed rectangular plates, m. p. 153° (Found : C, 68·4; H, 6·7. $C_{22}H_{26}O_6$ requires C, 68·4; H, 6·7%). By using ethyl 4-methoxycinnamate (Vorländer, *Annalen*, 1897, **294**, 295), the average yield of *ethyl* βγ-*dianisyladipate-a*, colourless elongated prisms from EtOH, m. p. 110° (Found : C, 69·9; H, 7·4. $C_{24}H_{30}O_6$ requires C, 69·6; H, 7·3%), was inferior to that obtained with the methyl ester.

βγ-*Dianisyladipic-a Acid.*—The methyl ester (8·0 g.) was refluxed for 3 hr. with a solution of KOH (10 g.) in H_2O (10 c.c.) and EtOH (20 c.c.). The ppt. obtained on addition of HCl aq. was dried; it crystallised from BuOH in colourless needles, m. p. 250° (Found : C, 67·5; H, 6·5. $C_{20}H_{22}O_6$ requires C, 67·1; H, 6·2%).

2 : 11-*Diketo*-5 : 14-*dimethoxy*-1 : 2 : 9 : 10 : 11 : 18-*hexahydrochrysene-a.*—A mixture of dianisyladipic-a acid (3·0 g.) and purified $SOCl_2$ (10 c.c.) was gently refluxed on the steam-bath until a clear solution resulted (¾—1 hr.); the excess of reagent was then removed by distillation, and the solid residue could be crystallised from C_6H_6 in needles, m. p. 162°. The crude chloride was coarsely powdered, covered with $C_2H_2Cl_4$ (20 c.c.), and finely powdered anhydr. $AlCl_3$ added; the mixture was maintained at 55—60° for 12 hr. and then decomposed by means of ice. The buff-coloured ppt. was washed by digestion with hot Na_2CO_3 aq. and then recrystallised from AcOH or anisole, forming colourless prisms, m. p. 285° (Found : C, 74·6; H, 5·7. $C_{20}H_{18}O_4$ requires C, 74·5; H, 5·6%). This *diketone* is very sparingly sol. in most org. solvents. The yield in the condensation exceeds 80%, but was not usually determined because it was found

that drying rendered the substance less readily sol. in anisole and this hindered the reduction described below.

5 : 14-*Dimethoxy*-1 : 2 : 9 : 10 : 11 : 18-*hexahydrochrysene-a* (VIII).—Diketodimethoxyhexahydrochrysene (from 3 g. of the acid) was mixed with amalgamated Zn (100 g.), anisole (10 c.c.), and conc. HCl aq. (12 c.c.) in a 100 c.c. round-bottomed flask, and the liquid refluxed for 20 hr. with occasional shaking. The anisole layer was combined with an extract of the Zn with the boiling solvent and was distilled in vac. from the steam-bath. The residue solidified in contact with EtOH (yield, 1·2 g.); it crystallised from anisole–EtOH (1 : 1), but, as it was still yellow, final purification was effected by distillation in vac. and recrystn. from AcOH, colourless needles, m. p. 185°, being obtained (Found : C, 81·7; H, 7·2. $C_{20}H_{22}O_2$ requires C, 81·6; H, 7·5%).

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THE DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, March* 31*st*, 1933.]