171. *Experiments on the Synthesis of Substances Related to the Sterols. Part IX.*

By Robert Robinson and James Walker.

In a recent communication (this vol., p. 50) Hewett stated that Robinson and Schlittler (J., 1935, 1288) "accepted" a view expressed by Cook and Hewett (J., 1933, 1105) to the effect that certain difficulties in the use of 1-keto-1 : 2 : 3 : 4-tetrahydrophenanthrenes for the synthesis of the sterol type of ring system could probably be overcome by the use of analogous derivatives of *as.*-octahydrophenanthrene.

The work of Robinson and Schlittler was greatly delayed in publication and our plans were in no way influenced by the comments of Cook and Hewett on their experiences. Furthermore the idea that oestrone, a derivative of octahydrophenanthrene, might be synthesised from simpler derivatives of the same polycyclic hydrocarbon does not appear to us to be particularly original and we " accepted " this view long ago in a more general form.

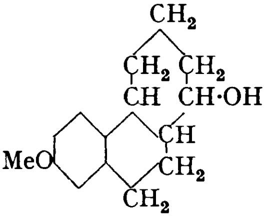
Hewett (*loc. cit.*) also comments on the fact that the method of Robinson and Schlittler for the synthesis of β-*m*-methoxyphenylethyl*cyclo*hexane-2 : 6-dione is lengthy. Unfortunately this is the case, but the process is the only known satisfactory method of preparation and we have now effected improvements at various stages (see Experimental). The ring closure of the dione to a phenanthrene derivative is a simple operation and can be brought about in various ways; we have retained the original method,* which is convenient and gives a yield exceeding 90%. In the hope of improving the preparation of 5-keto-8-*m*-methoxyphenyloctoic acid we have studied the formation of Grignard reagents from γ-*m*-methoxyphenylpropyl iodide and chloride. The organo-magnesium derivatives were readily produced and, after reaction with methyl chloroformate and hydrolysis of the product, γ-*m*-methoxyphenylbutyric acid was isolated. Interaction of γ-*m*-methoxyphenylpropylmagnesium chloride and β-chloropropionyl chloride afforded a mixture of products, including one that gave analytical data agreeing with the composition $C_{13}H_{17}O_2Cl$. The substance would appear to be the expected β-*chloroethyl* γ-m-*methoxyphenylpropyl ketone*, but its boiling point is abnormally high and in order to resolve the dubiety the investigation is being continued and extended to the zinc compounds.

Some further stages in one of the attempted syntheses of oestrone have now been realised and the first stereochemical hurdle has been safely negotiated.

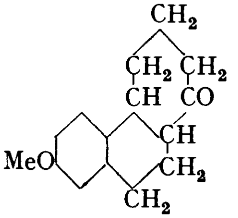
The reduction of 1-keto-7-methoxyhexahydrophenanthrene (Robinson and Schlittler, *loc. cit.*) to a ketomethoxyoctahydrophenanthrene could not be directly accomplished, although many conditions were tried. This contrasts with the practicability of the catalytic reduction of α-octalone to α-decalone (Hückel and Blohm, *Annalen*, 1933, **502**, 136) and of 2-keto-4-phenyl-$\Delta^{1:9}$-octalin to 2-keto-4-phenyldecalin (Rapson and Robinson, J., 1935, 1286).

The product of the catalytic reduction of the ketomethoxyhexahydrophenanthrene was a solid *methoxyoctahydrophenanthrol*-a (I), apparently stereoisomeric (different *p*-nitrobenzoate) with that obtained by reduction of the unsaturated ketone with sodium and alcohol (Robinson and Schlittler, *loc. cit.*). The isomeride (a) is probably a derivative of *cis*-decalin, because it is almost homogeneous and yet gives a mixture of labile and stable ketones on oxidation. The diagnosis of these substances is not conclusive, but the indication is that the labile ketone includes rings fused in the *cis*-position.

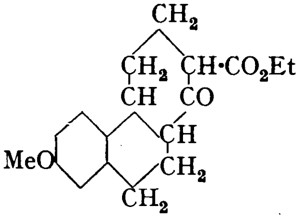
The first attempt to oxidise the alcohol (I) was made with Beckmann's mixture and a naphthalene derivative was produced. This substance has been previously obtained by Butenandt and Schramm (*Ber.*, 1935, **68**, 2083), but no derivatives were described; it has also been mentioned without details by Cohen, Cook, and Hewett (this vol., p. 52).



(I.)



(II.)



(III.)

Under milder conditions of oxidation, chromic acid in an acetic acid medium effected partial conversion of (I) into the related ketone (II), but the yield was not very satisfactory.

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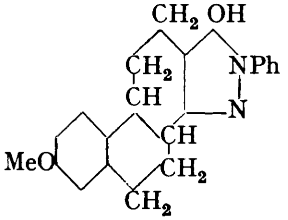
* The use of 80% sulphuric acid, as recommended by Hewett (*loc. cit.*), is also feasible but not a great improvement. We are familiar with the application of this reagent to such cyclisations : subject to correction and within our knowledge it was first used by Perkin, Rây, and Robinson (J., 1927, 2097) for the dehydration of β-*m*-methoxyphenoxypropionic acid with formation of methoxychromanone.

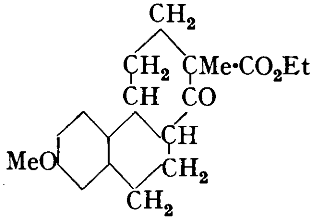
The ketone was isolated in the form of its semicarbazone or by means of Girard's reagent and was eventually crystallised but only in part. The oily ketone afforded further crystals only after isomerisation under the influence of hot aqueous oxalic acid.

The crystallised ketone was homogeneous and *X*-ray crystallographic analysis, kindly carried out by Miss D. M. Crowfoot, made it very probable that it was the *trans*-modification. This is in harmony with the evidence for isomerisation of a more labile ketone and the conclusion is important because the stereochemical configuration of (II) is evidently that which is characteristic of oestrone in respect of the fusion of the *cyclo*hexane rings.

The *trans*-ketone (II) was condensed with ethyl oxalate in the presence of sodium ethoxide; the resulting diketo-ester decomposed, on heating, with formation of the β-keto-ester (III). This substance was characterised by conversion into a *phenylpyrazolone* (or *hydroxypyrazole*) (IV). Methylation of the ester (III) afforded (V), which gives no ferric reaction. The expression (V) applies to four optically inactive stereoisomeric forms, of which two could be obtained from the *trans*-ketone (II), and the next phase of this section of our work must be concerned with the isolation of one or both of the stereoisomerides.

(IV.)





(V.)

EXPERIMENTAL.

Grignard Reagents from γ-m-*Methoxyphenylpropyl Iodide and Chloride.*—(A) γ-*m*-Methoxyphenylpropyl iodide (10·4 g.) was brought into reaction with magnesium (1·0 g.) in anhydrous ether (60 c.c.) and the mixture was eventually gently refluxed on the steam-bath until most of the metal had disappeared. An excess of methyl chloroformate was then introduced and, after the vigorous reaction had subsided, the product was worked up in the known manner. The γ-*m*-methoxyphenylbutyric ester produced was hydrolysed by means of aqueous methyl-alcoholic potassium hydroxide and the resulting γ-*m*-methoxyphenylbutyric acid was isolated (3·5 g.), m. p. 49—50° (Found: C, 68·1; H, 7·2. Calc. for $C_{11}H_{14}O_3$: C, 68·0; H, 7·2%). In a similar experiment with the chloride the yield was definitely improved, but a part of the product was lost.

(B) The reagent was prepared from magnesium (3·0 g.) and γ-*m*-methoxyphenylpropyl chloride (21 g.) in ether (100 c.c.), the mixture being finally refluxed for 3 hours. It was then cooled and added with vigorous stirring to a solution of β-chloropropionyl chloride (20 g.) in ether (50 c.c.). Under these conditions we thought it possible that a chloroethyl ketone might be formed and this substance would doubtless be convertible into (V) or the related alcohol by successive condensation with ethyl sodiomethylmalonate, two cyclisations, and reduction. After the usual treatment the following fractions were obtained: (a) 5·8 g. of a colourless mobile oil, b. p. up to 130°/0·2 mm., darkening on keeping; (b) 2·1 g. of a colourless oil, b.p. 130—180°/0·35 mm.; (c) 6·7 g. of a somewhat viscous oil, b. p. above 180°/0·35 mm. and mainly above 205°/0·27 mm. On redistillation, (c) gave 1·62 g., b. p. up to 195°/0·27 mm., $n_D^{14.5^\circ}$ 1·5290; 2·3 g., b. p. 200—212°/0·27 mm., a colourless viscid oil, $n_D^{14.5^\circ}$ 1·5456 (Found: C, 65·0; H, 7·1; Cl, 14·4. $C_{13}H_{17}O_2Cl$ requires C, 64·9; H, 7·1; Cl, 14·8%); and finally a fraction, b. p. 212—240°/0·27 mm., a viscous oil, $n_D^{14.5^\circ}$ 1·5602. The analysis cited confirms an earlier estimation and it is difficult to explain the results on any basis other than the assumption that this fraction consists essentially of the expected β-*chloroethyl* γ-m-*methoxyphenylpropyl ketone*.

Methyl 5-*Keto*-8-m-*methoxyphenyloctoate.*—γ-*m*-Methoxyphenylbutyryl chloride and ethyl sodio-α-acetylglutarate were condensed in benzene solution, and the product treated in the earlier stages by the method previously described (*loc. cit.*). The mixture of methyl esters ultimately obtained was, however, completely separated (cf. this vol., p. 193) by one fractionation into methyl γ-*m*-methoxyphenylbutyrate, distilling up to 165°/0·3 mm., and, with no intermediate fraction, *methyl* 5-*keto*-8-m-*methoxyphenyloctoate*, distilling without residue at 180—187°/0·2 mm.

as a limpid, nearly colourless, viscous oil, $n_D^{16°}$ 1·5095 (Found: C, 68·9; H, 8·0. $C_{16}H_{22}O_4$ requires C, 69·1; H, 7·9%).

From 242 g. of γ-*m*-methoxyphenylbutyric acid (treated in lots of 33 g.), there were obtained 154·2 g. (60%) of methyl γ-*m*-methoxyphenylbutyrate and 86·5 g. (25%) of methyl 5-keto-8-*m*-methoxyphenyloctoate.

β-m-*Methoxyphenylethyl*cyclo*hexane*-2 : 6-*dione*.—Methyl 5-keto-8-*m*-methoxyphenyloctoate (32·8 g.) was treated with alcohol-free sodium ethoxide (J., 1935, 1290), and ice-water added to the reaction mixture. The strongly alkaline aqueous layer was extracted twice with ether and acidified with dilute sulphuric acid; the precipitated dihydroresorcinol compound (25·1 g.; 87%), after being washed with water and ether and dried in a vacuum, had m. p. 150°, and was evidently pure as first isolated. The dihydroresorcinol derivative (25 g.) when treated as described previously afforded 1-keto-7-methoxy-1 : 2 : 3 : 4 : 9 : 10-hexahydrophenanthrene (21·1 g.) in 91% yield.

7-*Methoxy*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydrophenanthr*-1-*ol*-a (I).—(A) The last-named ketone (19·1 g.) in methyl alcohol (230 c.c.) was shaken with a 2% palladised strontium carbonate catalyst (15 g.) in hydrogen under 2—3 atmospheres excess pressure. Absorption of the gas was regular and continuous and ceased when slightly less than 2 mols. had been absorbed in about 9 hours. The filtered solution was evaporated; the vitreous residue (19 g.) distilled at 164—169°/0·2 mm. as an extremely viscous syrup, which set to a colourless stiff glass when cold. Rubbing with methyl alcohol induced crystallisation and from this solvent the compound separated as a powder, which softened at 99—104° and cleared at 105° This m. p. was unaltered on further separation from methyl alcohol (Found: C, 77·5; H, 8·3. $C_{15}H_{20}O_2$ requires C, 77·6; H, 8·6%). The *compound* separated from ethyl acetate as a microcrystalline powder, which sintered at 106°, softened from 108°, and cleared at 111°.

(B) The ketone (1·2 g.) in pure ether (30 c.c.) was shaken in hydrogen under a slight pressure with colloidal palladium (0·1 g. of palladium chloride, 0·2 g. of gum arabic, and 90 c.c. of water). Steady absorption of hydrogen occurred, slightly more than 2 mols. being absorbed in a few hours. The product isolated (1·1 g.) did not react with Brady's reagent and it crystallised readily on nucleation with the tetrahydro-compound obtained as in (A).

The p-*nitrobenzoate* was obtained by the action of a slight excess of *p*-nitrobenzoyl chloride on the compound (40 mg.) in dry pyridine (0·5 c.c.) at room temperature. After 12 hours the mixture was treated with water and the *ester* was extracted in ether–ethyl acetate, the extract being washed with zinc chloride solution and dilute sodium carbonate solution. The ester separated from ethyl alcohol as a very pale yellow, micro-crystalline powder, m. p. 125—126° after sintering at 120° (Found: C, 69·2; H, 6·2; N, 4·0. $C_{22}H_{23}O_5N$ requires C, 69·3; H, 6·0; N, 3·7%).

2 : 4-*Dinitrophenylhydrazone of* 1-*Keto*-7-*methoxy*-1 : 2 : 3 : 4-*tetrahydrophenanthrene*.—The above methoxyoctahydrophenanthrol (1·1 g.) was treated with Beckmann's mixture (30 c.c.) with shaking and warming on the steam-bath for about 45 minutes. The product was extracted with ether and the extract was washed with dilute sodium carbonate solution, dried, and evaporated. The crude product (0·75 g.) was distilled at 0·2 mm.; the distillate (*ca.* 0·4 g.) gave an immediate precipitate with Brady's reagent in warm alcoholic solution. The *hydrazone* was very sparingly soluble in the usual solvents and crystallised from pyridine in bright red needles, m. p. 304° (decomp.) (Found: C, 62·1; H, 4·5. $C_{21}H_{18}O_5N_4$ requires C, 62·1; H, 4·4%).

1-*Keto*-7-*methoxy*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydrophenanthrene* (II).—(A) The above methoxyoctahydrophenanthrol (14 g.) in glacial acetic acid (70 c.c.) was mixed with a concentrated solution of chromic acid (4·5 g.; slight excess) in water. The solution was warmed to *ca.* 60° on the water-bath at intervals during 1¼ hours, kept for 12 hours at room temperature, and again warmed at 60° for ½ hour. The reaction mixture was added to ether and water (*ca.* 300 c.c.) and the ethereal solution was separated, washed with sodium bicarbonate solution, dried, and evaporated. The crude reddish-brown oil (13·6 g.) was treated at room temperature in alcoholic solution (40 c.c.) with a concentrated aqueous solution of semicarbazide hydrochloride (7 g.) and sodium acetate (9 g.) and the *semicarbazone* (6·6 g.) which separated in the course of a few hours was collected and dried in a vacuum. It was very sparingly soluble in methyl and ethyl alcohols and separated from a large volume of butyl alcohol in small, stout, colourless prisms, m. p. 225° (decomp.) (Found: C, 67·1, 67·2; H, 7·1, 7·4. $C_{16}H_{21}O_2N_3$ requires C, 66·9; H, 7·3%).

When refluxed for an hour with 20% aqueous oxalic acid, the semicarbazone was quantitatively hydrolysed. The ketone was extracted with ether and the extract, washed with dilute sodium carbonate solution, dried, and evaporated, yielded a semi-solid product; crystallisation from methyl alcohol, or light petroleum, afforded colourless needles, m. p. 109° (Found: C, 78·3; H, 7·8. $C_{15}H_{18}O_2$ requires C, 78·3; H, 7·8%).

The 2 : 4-*dinitrophenylhydrazone* separated immediately as an orange precipitate when a warm solution of the ketone (34 mg.) in ethyl alcohol (0·5 c.c.) was mixed with a similar solution of 2 : 4-dinitrophenylhydrazine (30 mg.) containing a trace of concentrated sulphuric acid. The compound separated from ethyl acetate, containing a few drops of light petroleum, in small orange prisms, m. p. 209·5° (decomp.) after sintering at 205° (Found: C, 61·4; H, 5·3. $C_{21}H_{22}O_5N_4$ requires C, 61·5; H, 5·4%).

(B) The methoxyoctahydrophenanthrol (12·5 g.) in glacial acetic acid (60 c.c.) was oxidised during 1 hour on the steam-bath with chromic acid (4·0 g.; 10% excess) in 75% acetic acid (20 c.c.). The reaction mixture was treated as before and the crude product was dissolved in 65% ethyl alcohol (60 c.c.) and boiled under reflux for 1·5 hours with Girard's pyridine betaine-hydrazide reagent (*Chem. Zentr.*, 1935, I, 959) (12 g.). The alcoholic solution was cooled, mixed with ether, and added to water (*ca.* 250 c.c.). The aqueous solution was rapidly separated, washed with ether, mixed with concentrated hydrochloric acid (90 c.c.), and warmed on the water-bath for ½ hour. The ethereal solution furnished 7·43 g. of unchanged alcohol after drying, evaporation, and vacuum distillation. The ketone was isolated from the hydrolysis by means of ether, and the crude product (5·0 g.) on distillation in a vacuum furnished a colourless viscous oil (4·3 g.), b. p. 165—173°/0·23 mm. On crystallisation from methyl alcohol, only a part (1·35 g.) of this material separated in the crystalline form and the mother-liquor furnished a non-crystallising oil. The oil was refluxed with 20% oxalic acid solution for an hour and isolated as before; crystallisation from methyl alcohol then furnished a further quantity (1·1 g.) of crystalline material. The oil (1·8 g.) from the second mother-liquor was submitted again to treatment with oxalic acid, yielding still more crystalline material (0·6 g.). The residual oil finally obtained probably contained a small amount of the dehydro-ketone (see above), as was indicated qualitatively by the red colour of the precipitate obtained with Brady's reagent.

Crystallisation from light petroleum gave crystals better suited for *X*-ray analysis than those separating from methyl alcohol and we are grateful to Miss D. M. Crowfoot for the following report:

The crystals were in the form of needles elongated along *b* and flattened on (100). Optically they were positive, α along *b*, γ about 5° from *c* in the obtuse angle. Optic axial angle large, double refraction high. There is a marked *b* cleavage.

The *X*-ray measurements gave: $a = 12{\cdot}0$; $b = 8{\cdot}1$; $c = 12{\cdot}9$ A.; $\beta = 105°$; $n = 4$ for $\rho = 1{\cdot}245$; $h0l$ absent for $h + l$ odd, also apparently $0kl$ for k odd; $0k0$ absent for k odd; space group, $P2_1/n$.

This space group indicates that there are present two enantiomorphic molecules related by the *n* glide plane. Following the optics, the arrangement of the molecules is most probably with the length closely along *c* (γ), the width in *a* (β) and thickness in *b* (α).

(020) is, however, not nearly so powerful a reflection as (120) and there is therefore most probably slanting of the molecules across this plane. This requires fairly close packing all round, and while it is just possible to fit a *cis*-form into the cell, it appears much more probable that it is the *trans*-form which is present.

Ethyl 1-*Keto*-7-*methoxy*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydrophenanthrene*-2-*carboxylate* (III).—Methoxyoctahydrophenanthrone (4·0 g.) and ethyl oxalate (2·65 g.) were mixed with pure dry ether (65 c.c.), a small amount of the ketone remaining in suspension. Freshly prepared alcohol-free sodium ethoxide (1·44 g.) was added to the mixture in lumps, which were disintegrated by means of a glass rod. The sodium ethoxide rapidly dissolved with slight evolution of heat and soon afterwards the separation of an orange sodio-derivative commenced. After 2 days at room temperature, ice-water and dilute sulphuric acid were added and the ethereal solution was rapidly separated, dried, and concentrated; the orange-brown syrup obtained gave a blood-red colour with alcoholic ferric chloride. The crude product was heated at 180—190° for 3 hours, a fairly brisk effervescence taking place during the first hour. On distillation in a vacuum, unchanged ketone was not recovered and a yellow viscous syrup (3·41 g.) distilled at 195—205°/0·35 mm., $n_D^{16°}$ 1·5645. The product gave with alcoholic ferric chloride a violet colour, changing to brown on the addition of ether. It was characterised as the related phenyl-pyrazolone derivative.

The keto-ester (0·29 g.) was mixed with phenylhydrazine (0·16 g.) and heated on a boiling water-bath for 3 hours. The yellow solid obtained was cooled, triturated with ether, collected, and washed with much ether, giving a colourless powder (0·18 g.) very sparingly soluble in the usual solvents. The substance separated from 60% aqueous pyridine in clusters of colourless, microscopic, thin, trapezoidal plates, m. p. 258—260° (decomp.) after sintering at about 230° and slight softening from 245° (Found: C, 76·5; H, 6·3; N, 8·3. $C_{22}H_{22}O_2N_2$ requires C, 76·3; H, 6·3; N, 8·1%). It is evidently the expected 5-*hydroxy*-1-*phenyl*-3 : 4-(7′-*methoxy*-3′ : 4′ : 9′ : 10′ : 11′ : 12′-*hexahydrophenanthreno*-1′ : 2′)*pyrazole* (IV).

Ethyl 1-*Keto*-7-*methoxy*-2-*methyl*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydrophenanthrene*-2-*carboxylate* (V).—The above keto-ester (4·9 g.) in dry benzene (25 c.c.) was added to powdered potassium (0·7 g.; 10% excess) in benzene (25 c.c.). The potassium rapidly dissolved, giving a dark amber-coloured solution in about ½ hour. After 1 hour at room temperature the mixture was heated at 60° for 5 minutes, boiled for 2 minutes, and then cooled in melting ice. Methyl iodide (5 g.; *ca.* 2 mols.) was then added and there was no obvious immediate reaction, although gradually the appearance of the mixture changed. After 15 hours at room temperature and 2·5 hours at the boiling point, a further quantity (1·6 c.c.) of methyl iodide was added and the mixture was allowed to simmer for a further 3·5 hours. The solution, from which potassium iodide had not separated apparently owing to its being held in colloidal suspension, was cooled and mixed with ether and water and the washed and dried ethereal solution was evaporated. When the crude product (5·1 g.) was distilled under diminished pressure, a light yellow, viscous oil (4·4 g.) collected, mainly at 175—185°/0·09 mm., with a small amount up to 200° owing to slight superheating; $n_D^{15^\circ}$ 1·5508. On redistillation through a short column, there were obtained: (1) 1·0 g. of an almost colourless, viscous liquid, b. p. up to 180°/0·13 mm., and (2) 2·7 g. of a very viscous liquid, b. p. 180—192°/0·13 mm., $n_D^{14\cdot5^\circ}$ 1·5480 (Found: C, 72·5; H, 8·0. $C_{19}H_{24}O_4$ requires C, 72·2; H, 7·6%). The substance gave no ferric reaction in alcoholic solution and, as stated in the introduction, will be further examined in detail.

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