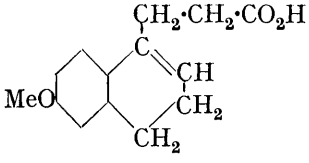
## 15. *Experiments on the Synthesis of Substances related to the Sterols. Part XVI.* 4-*Keto*-7-m-*methoxyphenylheptoic Acid and Some Derivatives.*

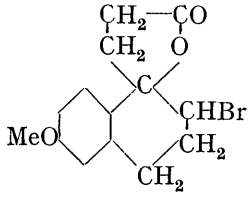
By K. H. Lin, J. Resuggan, Robert Robinson, and James Walker.

The keto-acid synthesis of G. M. and R. Robinson (J., 1925, **127**, 175; 1926, 2204; 1930, 745) gives good results in its application to the preparation of 4-*keto*-7-m-*methoxyphenylheptoic acid*, $MeO{\cdot}C_6H_4{\cdot}[CH_2]_3{\cdot}CO{\cdot}[CH_2]_2{\cdot}CO_2H$ (I). γ-*m*-Methoxyphenylbutyryl chloride is condensed with ethyl sodioacetylsuccinate, and the product hydrolysed with cold aqueous alcoholic potassium hydroxide and, after isolation and heating, with hot aqueous sodium hydroxide.

On treatment with sulphuric acid at — 10°, the methyl ester of this acid gives β-(6-*methoxy*-3 : 4-*dihydro*-1-*naphthyl*)*propionic acid* (II) as methyl ester. The action of bromine on a solution of (II) in aqueous sodium carbonate affords a *bromo-lactone* (III), the derivatives of which will be described in a subsequent paper.

(II.)

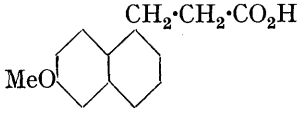


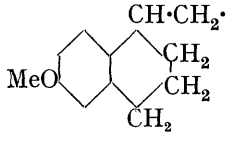




(III.)

When the dihydronaphthalene derivative (II) is heated with a trace of platinum-black, it is easily dehydrogenated with formation of β-(6-*methoxy*-1-*naphthyl*)*propionic acid* (IV), a fact which establishes the constitution of (II); catalytic reduction of (II) yields the tetrahydronaphthalene derivative (V).

(IV.)




(V.)

The main object of our work was to apply the Friedel–Crafts reaction to ketomethoxyphenylheptoic acid derivatives and it was hoped to couple them with the ester-chlorides of glutaric acid and α-methylglutaric acid so as to obtain substances of the type (VI);

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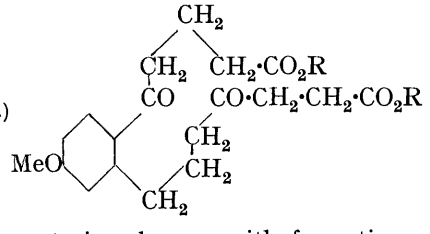
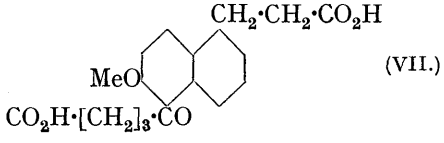
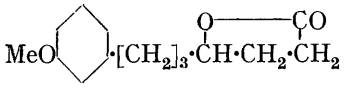


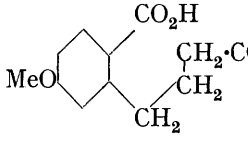




(VII.)

subsequent ring-closures with formation of near relatives of oestrone should not prove difficult. It was realised that (I) or its ester would probably be converted into a dihydronaphthalene under the influence of aluminium chloride and hence we worked at a low temperature and with an excess of the acid chloride. In this way methyl ketomethoxyphenylheptoate and γ-carbomethoxybutyryl chloride gave a reasonably good yield of condensed esters and after hydrolysis we were able to separate three crystalline acids, namely, the acid (IV), first isolated in this way, and *substances* $C_{19}H_{20}O_6$ and $C_{19}H_{24}O_6$. The compositions are those of the normal product less $H_2O$ and minus and plus two atoms of hydrogen. Both acids are saturated to permanganate and are apparently ketonic. They are clearly naphthalene and tetrahydronaphthalene derivatives respectively and owe

their formation to disproportionation under the influence of the catalyst. It is not certain, however, that they are closely related in structure. The acid $C_{19}H_{20}O_6$ is regarded as having the structure (VII), because it was recovered unchanged after treatment for 2 hours with boiling acetic anhydride in the presence of sodium acetate. The acid $C_{19}H_{24}O_6$ is changed by this treatment and, although this does not exclude the constitution of the tetrahydro-derivative of (VII), it certainly suggests that further investigation is desirable. When methyl ketomethoxyphenylheptoate was submitted to the conditions of this experiment, but without any acid chloride, the product was a neutral oil and on hydrolysis the acids (IV) and (V) were obtained. The dihydro-acid (II) was also present in the mixtures, but in order to purify (V), (II) was destroyed by oxidation with permanganate. In order to avoid the premature formation of the naphthalene ring in an undesired manner, we reduced the keto-acid (I) to the *lactone* of 4-*hydroxy*-7-m-*methoxyphenylheptoic acid* (VIII) and condensed this with *γ-carbethoxyvaleryl chloride*, $CO_2Et{\cdot}CHMe{\cdot}CH_2{\cdot}CH_2{\cdot}COCl$; the considerable fraction of b. p. compatible with the anticipated product could not be crystallised and hence no further mention of this experiment is made; the investigation will be continued employing γ-carbomethoxybutyryl chloride. The orientation of Friedel–Crafts reactions in this series is cleared up to a certain extent by the synthesis of a keto-

(VIII.) 


(IX.)

methoxyhexahydrophenanthrene described in the foregoing communication. It is confirmed by the synthesis of *γ-(2-carboxy-5-methoxyphenyl)butyric acid* (IX) from methyl γ-*m*-methoxyphenylbutyrate and phenylethylcarbamyl chloride by treatment with aluminium chloride and hydrolysis of the product.* The constitution of (IX) follows from its conversion into the known 6-methoxytetralone, in its turn obtainable from β-naphthol by a series of processes. This investigation is being extended in several directions.

## Experimental.

4-*Keto*-7-m-*methoxyphenylheptoic Acid* (I).—The process adopted was similar to that employed for the homologous acid (Part III, J., 1935, 1290; Part IX, J., 1936, 193). γ-*m*-Methoxyphenylbutyryl chloride (from 66 g. of the acid) was condensed with ethyl sodioacetosuccinate (74 g. of the ester and 8 g. of sodium) and the isolated product was shaken for 40 hours with 4·5% aqueous potassium hydroxide (3000 c.c.) and alcohol (250 c.c.). This addition of alcohol effects an improvement in the yield; also in the case of the preparation of ketomethoxyphenyloctoic acid. After this the normal process was followed and the crude mixed acids (78 g.) were esterified with diazomethane (from 78 g. of nitrosomethylurea). On distillation methyl methoxyphenylbutyrate (40 g.) and methyl ketomethoxyphenylheptoate (32 g.), b. p. 174°/0·3 mm., $n_D^{12°}$ 1·515, were obtained. The keto-ester was hydrolysed by heating with aqueous potassium hydroxide (120 c.c. of 25%) and methyl alcohol (10 c.c.), the oily acid obtained on acidification was dried in ethereal solution, and the solvent removed. It solidified on keeping and crystallised from light petroleum (b. p. 40—60°), containing a little benzene, in long, slender, colourless needles, m. p. 49—50° (Found : C, 67·2; H, 7·4. $C_{14}H_{18}O_4$ requires C, 67·2; H, 7·2%). The *semicarbazone* was readily formed and it crystallised from aqueous alcohol in colourless prisms, m. p. 117—118° (Found : C, 58·6; H, 6·9. $C_{15}H_{21}O_4N_3$ requires C, 58·6; H, 6·8%).

*Lactone of* 4-*Hydroxy*-7-m-*methoxyphenylheptoic Acid* (VIII).—The keto-acid was not reduced when it was treated with an excess of sodium amalgam (3%) in cold aqueous sodium hydrogen carbonate solution. A solution of 4-keto-7-*m*-methoxyphenylheptoic acid (26·5 g.) in alcohol (350 c.c.) was rapidly added to sodium (11 g.) heated in a bath at 160°. After 15 minutes, alcohol (150 c.c.) was added and after 30 minutes, when all the metal had disappeared, the alcohol was steam-distilled. A large excess of hydrochloric acid was added and next day the oil was isolated by means of ether and heated on the steam-bath for 10 minutes. The crude

* An application of a general process for the introduction of the carboxyl group embodied in patents of M. Wyler and Imperial Chemical Industries, Limited.

lactone was washed with aqueous sodium carbonate, dried in ethereal solution, and distilled; b. p. 178°/0·15 mm., $n_D^{12°}$ 1·5315 (15·5 g.) (Found: C, 72·1; H, 7·6. $C_{14}H_{18}O_3$ requires C, 71·8; H, 7·7%). Acidic material (6·5 g.) was recovered from the soda washings; this would not lactonise, nor did it form a semicarbazone and hence it was probably 7-*m*-methoxyphenylheptoic acid resulting from over-vigorous reduction.

β-(6-*Methoxy*-3 : 4-*dihydro*-1-*naphthyl*)*propionic Acid* (II).—Methyl ketomethoxyphenylheptoate (5 g.) was dissolved in concentrated sulphuric acid (25 c.c.) at − 10°; the solution was kept at this temperature for 3 hours and then poured on ice. The solid spiro-*lactone* was at once precipitated. It was collected by means of ether and obtained as a pale greenish oil (4·5 g.) which crystallised. Nearly colourless prisms, m. p. 60—61°, separated from a concentrated ethereal solution (Found: C, 73·5; H, 7·4. $C_{15}H_{18}O_3$ requires C, 73·2; H, 7·3%). The substance is insoluble in aqueous alkalis.

A mixture of the foregoing ester (4 g.) and methyl-alcoholic potassium hydroxide (60 c.c. of 12%) was boiled without condenser for ½ hour; water and hydrochloric acid were then added and the precipitate was collected and dried (3·9 g.). The substance crystallised from benzene–light petroleum and then from benzene in short colourless needles, m. p. 115° (Found: C, 72·6; H, 7·1. $C_{14}H_{16}O_3$ requires C, 72·4; H, 6·8%). On addition of bromine water to a solution of this *acid* in aqueous sodium carbonate an opaque milky liquid was produced. The *bromo-lactone* made in this way did not crystallise with facility and was probably a mixture of stereoisomerides. On keeping and stirring, the emulsion was slowly resolved, and about half of the product could be crystallised from light petroleum. The colourless needles, m. p. 100°, appeared to be homogeneous, but the analytical results were not sharp (Found: C, 53·2; H, 5·1; Br, 25·1. $C_{14}H_{15}O_3Br$ requires C, 54·7; H, 4·8; Br, 25·7%). Essentially the substance must be the bromo-lactone (III). The acid absorbed bromine very quickly in chloroform solution, and when the product was warmed with aqueous sodium acetate (perhaps not necessary) a bromo-lactone, crystallising readily from an alcoholic solution, was produced. This material was found on analysis to be a mixture of about equal parts of a mono- and a di-bromo-compound and it is evidently difficult to avoid nuclear bromination. This line of investigation is being pursued on account of the interesting synthetic possibilities it suggests.

β-(6-*Methoxy*-1-*naphthyl*)*propionic Acid* (IV).—This *acid*, obtained as described below, crystallises from benzene in colourless needles, m. p. 159° (Found in a specimen crystallised from light petroleum: C, 72·7; H, 6·2; MeO, 12·9. $C_{14}H_{14}O_3$ requires C, 73·1; H, 6·1; MeO, 13·4%). It retains solvent of crystallisation after drying in a vacuum and at 100° (Found: C, 74·7, 75·4; H, 6·1, 6·3%) and the benzene was recognised by Ramsden's test. It is stable to permanganate in alkaline solution, forms a very sparingly soluble bromo-derivative in warm chloroform solution, and is especially characterised by its sodium salt, which is very sparingly soluble in aqueous sodium carbonate.

A trace of platinum-black was added to about 0·5 g. of methoxydihydronaphthylpropionic acid, and the mixture carefully heated over a free flame. Hydrogen was evolved and when the evolution ceased the acid was distilled in a high vacuum. The solid distillate was converted into the sparingly soluble sodium salt, and the acid was recovered from this derivative and crystallised from benzene; m. p. 158—160°, alone or mixed with the analysed specimen.

β-(6-*Methoxy*-1 : 2 : 3 : 4-*tetrahydro*-1-*naphthyl*)*propionic Acid* (V).—Methoxydihydronaphthylpropionic acid (5 g.) was reduced in methyl-alcoholic solution (100 c.c.) by hydrogen under 2 atm. pressure and in the presence of palladised strontium carbonate (2·5 g. of 2%). 450 C.c. (theory, 480 c.c.) were absorbed in ½ hour. Evaporation of the filtered solvent afforded an oil (4·9 g.), stable to permanganate, and this gradually crystallised. The *tetrahydro-acid* crystallised from light petroleum (b. p. 40—60°) in colourless needles, m. p. 77° (Found: C, 72·1; H, 7·7. $C_{14}H_{18}O_3$ requires C, 71·8; H, 7·7%). The substance is freely soluble in most organic solvents. When the methyl ester of this acid (prepared with the help of diazomethane) was treated with γ-carbomethoxybutyryl chloride and aluminium chloride under the conditions of the experiment described below, the starting materials were largely recovered unchanged. This supports the view that the acid $C_{19}H_{24}O_6$ is not the tetrahydro-derivative of (VII).

*Condensation of Methyl Ketomethoxyphenylheptoate with γ-Carbomethoxybutyryl Chloride in the Presence of Aluminium Chloride.*—A mixture of the ester (10 g., 1 mol.), the acid chloride (15·5 g., 2·5 mols.), and carbon disulphide (20 c.c.) was rapidly added to powdered aluminium chloride (20 g., 4 mols.), vigorously stirred in carbon disulphide (100 c.c.) and cooled in melting ice. Stirring was continued for 3 hours and next day the carbon disulphide was decanted, ice added, and the mixture steam-distilled for a short time. The oily product (11 g.) was isolated by means of ether. It was dissolved in methyl alcohol (75 c.c.), mixed with methyl

sulphate (5 c.c.) and 5*N*-sodium hydroxide (30 c.c.), and refluxed for 1½ hours. After concentration on the steam-bath the diluted solution was acidified and the viscous acids were collected, washed with water, and dried. They were then exhaustively extracted with boiling light petroleum (b. p. 40—60°) and from this extract, colourless prismatic needles, m. p. 154—156°, separated. The acid was recrystallised from benzene, m. p. 156°, and was then freed from unsaturated impurities by means of permanganate. The recovered acid, m. p. 159°, was identified as β-(6-methoxy-1-naphthyl)propionic acid (above). On keeping, the viscous residue hardened and it was found that crystals were present; these were insoluble in methyl alcohol or acetone and the minimum of the latter solvent was used to dissolve the oil in which the solid was embedded. On recrystallisation from acetone, in which the substance was sparingly soluble, an *acid* was obtained in colourless microscopic prisms, m. p. 210° (Found: C, 66·1, 66·1; H, 5·7, 5·9; MeO, 9·5. $C_{19}H_{20}O_6$ requires C, 66·3; H, 5·8; 1MeO, 9·0%). The acetone solution was diluted with benzene and light petroleum (b. p. 40—60°); the precipitated oil, kept at 0°, gradually hardened. It was washed with ethyl acetate–light petroleum (1 : 4), then with the same solvents (1 : 2), and finally with ethyl acetate. The pale yellow solid residue crystallised from ethyl acetate–light petroleum (2 : 1) in nearly colourless, flat prisms, m. p. 144° (Found: C, 65·0, 65·3; H, 6·6, 6·9; MeO, 9·5. $C_{19}H_{24}O_6$ requires C, 65·5; H, 6·9; MeO, 8·9%). The combined mother-liquors were diluted with light petroleum, and the mixture kept in the ice-chest. On evaporation of the clear solution a considerable crop of methoxynaphthylpropionic acid was obtained, m. p. 158° after one recrystallisation; the oily residue was dissolved in a little ethyl butyrate and on keeping at 0°, crystals of the above *acid*, m. p. 144°, separated. In a similar way two further crops of this acid were obtained and the final small residue was an uncrystallisable oil. The acid $C_{19}H_{20}O_6$ is sparingly soluble in most organic solvents, but crystallises well from aqueous acetic acid. It is stable to permanganate in aqueous solution and affords a sparingly soluble semicarbazone; it also condenses with 2 : 4-dinitrophenylhydrazine. The acid $C_{19}H_{24}O_6$ is also stable to permanganate and forms a dinitrophenylhydrazone. On heating with a trace of platinum, extensive decomposition occurred and the product could not be purified. The behaviour of these acids towards acetic anhydride and sodium acetate has already been mentioned.

*Action of Aluminium Chloride on Methyl Keto*-m-*methoxyphenylheptoate*.—The keto-ester (5 g.) was added to powdered aluminium chloride (10 g.), stirred under carbon disulphide (50 c.c.) cooled in ice and water. The conditions were then identical with those of the experiment last described. The product (5 g.) was isolated in the usual manner and freed from a trace of acidic material. The mixed esters were hydrolysed by means of aqueous methyl-alcoholic sodium hydroxide on the steam-bath; the recovered acid (4·5 g.) crystallised rapidly and completely. On crystallisation from benzene, methoxynaphthylpropionic acid (2·4 g.) was obtained; this had m. p. 158° after recrystallisation, alone or mixed with the analysed specimen. The acids in the mother-liquor could not be fractionally crystallised and accordingly the unsaturated component was destroyed by addition of potassium permanganate to the solution in aqueous sodium carbonate. On acidification of the filtered solution, an oil separated and this crystallised on keeping at 0° (*ca.* 1·7 g.). The substance crystallised from light petroleum (b. p. 40—60°) in colourless needles, m. p. 76°, alone or mixed with authentic methoxytetrahydronaphthylpropionic acid.

*γ-(2-Carboxy-5-methoxyphenyl)butyric Acid* (IX).—A solution of phenylethylcarbamyl chloride (25·5 g., 1·5 mols.) and methyl *γ-m*-methoxyphenylbutyrate (20·8 g., 1 mol.) in carbon disulphide (50 c.c.) was added to powdered aluminium chloride (13·5 g., 1 mol.) at room temperature; a further equal quantity of aluminium chloride was then introduced. Next day the mixture was gently refluxed for 1½ hours and cooled, and the solvent decanted. The residue was washed with light petroleum, decomposed with ice and dilute hydrochloric acid, then heated on the steam-bath for 1 hour, and the oily product (35 g.) collected by means of ether. The material contained chlorine and it was refluxed for 4½ hours with potassium hydroxide (10 g.), water (20 c.c.), and methyl alcohol (60 c.c.). Methyl sulphate (10 c.c.) was added and after 40 minutes potassium hydroxide (10 g.) and water (20 c.c.) were introduced and the mixture was boiled for ¾ hour. It was then steam-distilled, and the residue acidified and isolated by means of ether. The residual oil (19·5 g.) contained nitrogen and did not crystallise; it was exhaustively extracted with boiling light petroleum and then (11 g.) hydrolysed by refluxing with acetic acid (25 c.c.) and concentrated hydrochloric acid (50 c.c.) for 7½ hours. Acetic acid was removed by steam distillation, the residue basified and steam-distilled to remove ethylaniline, and the *acid* liberated and collected (7 g.) by means of ether. On keeping a solution in benzene, a crop of prismatic crystals separated and these were recrystallised from ethyl acetate

and then from benzene–light petroleum, forming colourless prismatic needles, m. p. 173° after sintering at 165° (Found : C, 60·5; H, 6·0. $C_{12}H_{14}O_5$ requires C, 60·5; H, 5·9%). The acid was sparingly soluble in cold water and crystallised from water in colourless needles. It was boiled with an excess of acetic anhydride for 20 minutes, and the solution then distilled, finally in a high vacuum. When all the acetic anhydride had been removed, the residue evolved gas and, without significant loss, distilled as a pale yellow oil. This crystallised at once on cooling and after recrystallisation from aqueous alcohol was obtained in colourless plates, m. p. 81° alone or mixed with authentic 6-methoxytetralone. There were indications of the presence of an isomeric acid, but it could not be separated from the viscous substances in the mother-liquor. These still contained nitrogen, so the hydrolysis was incomplete. It is certain that the main product was the phenylethylamide of the acid described above, but owing to the difficulty of the separations any estimate of the yield would be valueless.

*γ-Carbethoxyvaleryl Chloride.*—Ethyl γ-cyano-α-methylbutyrate is conveniently obtained by the following modification of the method of Holmes, Thorpe, and Udall (J., 1900, **77**, 947). Ethyl cyanoacetate (133 g.) was added to alcoholic sodium ethoxide (27 g. of sodium in 400 c.c.), the solution cooled, and ethyl α-methylacrylate (135 g.) added in one portion. Heat was generated and the sodio-derivative dissolved. After 2½ hours, without heating or cooling, water (50 c.c.) was added and next day the solvent was distilled. When 300 c.c. had passed over, water (150 c.c.) was added, then 100 c.c. were distilled, and water (150 c.c.) was added; finally 250 c.c. were collected. The residue was acidified and exhaustively extracted with ether. The extract was dried over sodium sulphate and distilled, finally from a bath at 200° under 15 mm. pressure. The fraction up to 150° was collected and redistilled, b. p. 175—180°/140 mm. (87 g.). The residue afforded α-methylglutaric acid on hydrolysis with boiling 50% sulphuric acid. The hydrolysis of the nitrile ester was effected as follows. Concentrated sulphuric acid (30 c.c.) was very slowly added drop by drop to ethyl γ-cyano-α-methylbutyrate (15 c.c., 14·65 g.) cooled to — 10° and mechanically stirred. The mixture became very viscous and towards the end of the operation was stirred with difficulty; addition of the last portions of sulphuric acid again reduced the viscosity. After 10 minutes (keeping below 0°) the temperature was allowed to rise to that of the room for 20 minutes. The mixture was then cooled to — 10° and crushed ice (40 g.) was slowly added; the temperature did not rise above 5°. Arrangements were made to collect the evolved gas and aqueous sodium nitrite (65 c.c. of 30%) was gradually added with shaking. 3000 C.c. of gas were collected (of which only 2240 c.c. should theoretically be nitrogen). The reaction mixture was kept at 0° for 1½ hours, then saturated with sodium sulphate, and thrice extracted with chloroform (100 c.c. each time). The chloroform extract was washed with a little saturated sodium sulphate, dried, and distilled. The residue (13·1 g.) after removal of the solvent was fractionally distilled as follows : b. p. 85—109°/0·39 mm. (1·15 g.), b. p. 109—122°/0·33 mm. (6·6 g.) (Found : C, 54·9; H, 8·2. $C_8H_{14}O_4$ requires C, 55·1; H, 8·0%) (93·5% pure on titration with 0·1*N*-sodium hydroxide), b. p. 116·5—128°/0·23 mm. (3·55 g.). In another preparation the cyano-ester (29·3 g.) gave the acid ester (27·3 g. or 83%), b. p. 116—149°/0·4—0·7 mm.

The acid ester (53·1 g.) was mixed with purified thionyl chloride (65·2 c.c.) below 0° and after some time the mixture was refluxed for ½ hour. The product was fractionated : b. p. 17·5—80°/27—40 mm. (70·1 g.); b. p. 134—142°/15—16 mm. (48·8 g.). The first fraction on redistillation gave a further 2 g., b. p. 131—137°/17 mm. (yield, 86·4%). The substance was characterised by conversion into a β-naphthylamide, the anilide and *p*-toluidide being found unsuitable for the purpose.

The acid chloride was added to an ethereal solution of β-naphthylamine and *γ-carbethoxy-valero-β-naphthylamide*, $\beta\text{-}C_{10}H_7\cdot NH\cdot CO\cdot CH_2\cdot CH_2\cdot CHMe\cdot CO_2Et$, was isolated in the known manner and crystallised from 50% alcohol (Found : C, 72·4; H, 7·2; N, 4·9. $C_{18}H_{21}O_3N$ requires C, 72·2; H, 7·0; N, 4·7%). The substance was sparingly soluble in light petroleum (b. p. 60—80°) and crystallised therefrom in colourless needles, m. p. 76·5—77·5°.

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