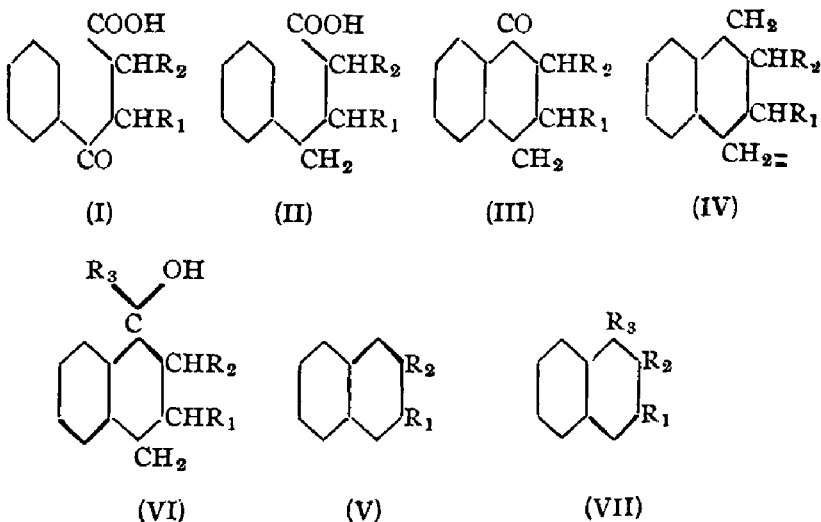


STUDIES IN THE γ -KETONIC ACIDS. PART II.

BY P. C. MITTER AND LAKSHMI KANTA DE.

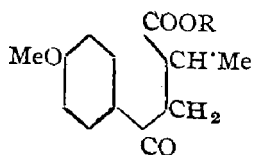
Methyl succinic anhydride has been condensed with phenol, anisole, resorcinol dimethyl ether and pyrogallol trimethyl ether giving rise to β -aroylpropionic acids, which have been reduced to the corresponding γ -arylbutyric acids. The latter have been cyclised to ketotetrahydronaphthalenes from which the corresponding naphthalenes have been obtained by dehydrogenation.

The condensation of methylsuccinic anhydride with aromatic hydrocarbons in the presence of aluminium chloride results in the production of a mixture of keto-acids (I, $R_1 = H$; $R_2 = Me$ and $R_1 = Me$; $R_2 = H$) which can be converted into substituted γ -arylbutyric acids (II, $R_1 = H$; $R_2 = Me$ and $R_1 = Me$; $R_2 = H$) by Clemmensen's method. On cyclisation the corresponding ketotetrahydronaphthalenes (III, $R_1 = H$; $R_2 = Me$ and $R_1 = Me$; $R_2 = H$) are produced. Further reduction by Clemmensen's method gives the tetrahydronaphthalene derivatives (IV, $R_1 = H$; $R_2 = Me$ and $R_1 = Me$; $R_2 = H$) whence by subsequent dehydrogenation by selenium the corresponding naphthalene hydrocarbons are obtained. Further alkyl groups can be introduced with the help of the Grignard reagent on the ketotetrahydronaphthalene derivatives. When the resulting carbinol (VI) is submitted to selenium dehydrogenation by simultaneous dehydration the naphthalene derivative (VII) is formed.

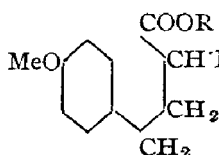


Mayer and Stamm (*Ber.*, 1923, **56**, 1424) condensed methyl succinic anhydride with benzene and obtained two isomeric products. Robertson and Waters (*J. Chem. Soc.*, 1933, 83) condensed veratrole with methylsuccinic anhydride in nitrobenzene and from the mixture of the isomeric products isolated 2 : 3-dimethoxy-6-methylnaphthalene by the scheme indicated above.

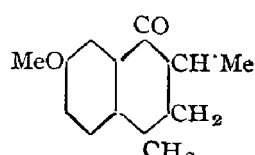
We have studied the condensation of phenol and various phenolic ethers with methylsuccinic anhydride with the object of synthesising various naphthalene derivatives with methyl groups in 6 or 7 positions. Anisole condenses with methylsuccinic anhydride in nitrobenzene solution at the ordinary temperature to give α -methyl- β -anisoylpropionic acid, m.p. 144°. Repeated fractional crystallisation of the condensation product from different solvents such as methyl alcohol, acetone, acetic acid and benzene, does not reveal the existence of an isomeric substance. The orientation of the methoxyl group has been proved by oxidising the product with moderately concentrated nitric acid in acetic acid solution to *p*-methoxybenzoic acid. A methyl alcoholic solution of the substance and salicylaldehyde at 0°, when saturated with hydrogen chloride, gives a bright red pyrylium derivative (Desai and Wali, *Proc. Indian Acad. Sci.*, 1937, **A**, 6, 135). Therefore, the presence of a CO-CH₂ group is established. This reaction also fixes definitely the position of the methyl group.



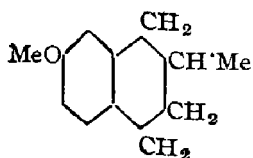
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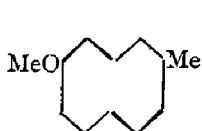
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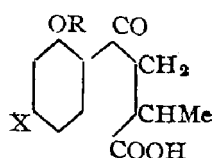
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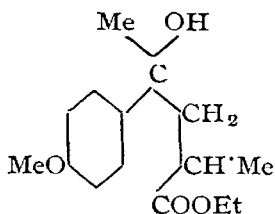
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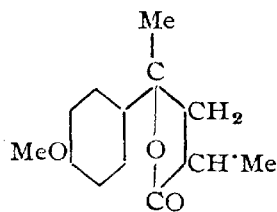
(XIV)



(XV)



(IX)



(X)

The keto-acid (VIII, R=H) gives an ester (VIII, R=Et), b.p. 185-87°/5 mm. When the keto-ester is allowed to react with methyl magnesium iodide (1 mol.) two products have been obtained, the hydroxy-ester (IX) and a small amount of the γ -lactone (X). The lactone can not be reduced by zinc dust and 10% sodium hydroxide solution even when boiled for 20 hours.

The keto-acid on reduction by Clemmensen's method gives α -methyl- γ -(*p*-methoxy)-phenylbutyric acid (XI, R=H), b.p. 180-82°/5 mm. It gives an ester (XI, R=Et), b.p. 146-48°/4mm. Dehydration of the acid (XI, R=H) with phosphorus pentoxide gives 1-keto-1:2:3:4-tetrahydro-2-methyl-7-methoxynaphthalene (XII). The selenium dehydrogenation of the tetrahydronaphthalene (XIII) gives 2-methyl-7-methoxynaphthalene (XIV).

1-Keto-1:2:3:4-tetrahydro-7-methoxy-2-methylnaphthalene (XII) gives on condensation with methyl magnesium iodide, a mixture evidently of the carbinol and the related lactone which can not be separated.

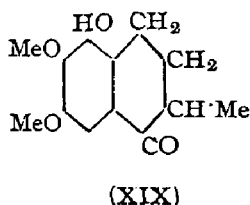
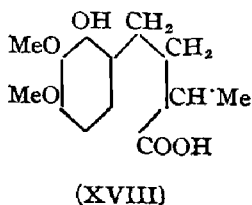
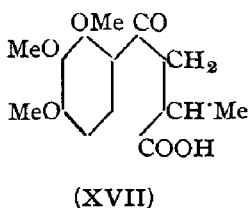
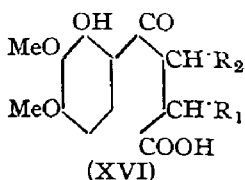
Phenol condenses with methylsuccinic anhydride in acetylene tetrachloride at 135-140° and gives α -methyl β -(*o*-hydroxy)-benzoylpropionic acid, m.p. 161° (XV, R=H; X=H). The product gives violet ferric reaction. The presence of a CO-CH₂ grouping in the keto-acid is proved by the formation of the pyrylium salt with salicylaldehyde and hydrogen chloride in methanol at 0°. The hydroxyketo-acid is methylated to α -methyl- β -(*o*-methoxy)-benzoylpropionic acid (XV, R=Me; X=H), m.p. 92-94°.

This substance is different from α -methyl- β -anisoylpropionic acid (VIII, R=H) whose constitution has been settled before. Further, the substance (m.p. 92-94°) has been proved to contain a CO-CH₂ grouping. Hence the condensation between phenol and methyl succinic anhydride has taken place in the *ortho* position with respect to the phenolic group. The keto-acid (XV, R=H; X=H) on Clemmensen's reduction gives α -methyl- γ -(*o*-hydroxy)-phenylbutyric acid (XV, R=H; X=H; CO replaced by CH₂), which does not cyclise with 85% sulphuric acid, but is sulphonated.

Resorcinol dimethyl ether condenses with methylsuccinic anhydride in nitrobenzene solution at the ordinary temperature to give a mixture of two substances. The mixture has been separated by repeated fractional crystallisation from methyl alcohol and acetone. The major portion of the condensation product crystallises in small needles, m.p. 130-31°. It gives reddish colouration with ferric chloride solution and a bright red pyrylium derivative is obtained with salicylaldehyde.

The second fraction crystallises in fine colourless needles, m.p. 141-42°, and gives faint pink colouration with ferric chloride showing that it has not been demethylated. The quantity is insufficient for an analysis. It is probably the second possible isomer. Following Perkin and Robinson (*J. Chem. Soc.*, 1908, 93, 506), we think the product (m.p. 130-31°) to be β -2 : 4-dimethoxybenzoyl- α -methylpropionic acid (XV, R = Me; X = OMe).

Pyrogallol trimethyl ether in nitrobenzene solution gives a mixture of two substances. One fraction, which is the major portion of the condensation product, crystallises in light yellow needles (XVI, R₁ = Me; R₂ = H), m.p. 155°, whilst the other component is a deep yellow needle-shaped crystalline solid, m.p. 175° (XVI, R₁ = H; R₂ = Me). These compounds give violet colouration with ferric chloride solution which points to the fact that the condensation products have been demethylated. The presence of a CO-CH₂ grouping in the compound (m.p. 155°) has been proved by the formation of a pyrylium derivative. That one methoxyl group is hydrolysed during the reaction is confirmed by a Zeisel estimation. As the other isomer, m.p. 175°, does not form the pyrylium derivative it has been concluded that in this case the methyl group is in the β -position with respect to the carboxyl group.



By using methyl iodide and anhydrous potassium carbonate in dry acetone solution, the methyl ester of the trimethoxy derivative has been obtained which on hydrolysis gives α -methyl- γ -(2 : 3 : 4-trimethoxy - benzoyl)butyric acid (XVII). The keto-acid (XVI, $R_1 = \text{Me}$; $R_2 = \text{H}$) on reduction by Clemmensen's method yields α -methyl- γ -(2-hydroxy-3 : 4-dimethoxy)-phenylbutyric acid (XVIII). Dehydration of this acid with 85% sulphuric acid gives 1-keto-1 : 2 : 3 : 4-tetrahydro-2-methyl-6 : 7-dimethoxy-5-hydroxynaphthalene (XIX), m.p. 130-32°. Further reduction of this ring ketone by Clemmensen's method gives 1 : 2 : 3 : 4-tetrahydro-2-methyl-5-hydroxy-6 : 7-dimethoxynaphthalene (XIX, CO replaced by CH_2).

E X P E R I M E N T A L.

α -Methyl- β -anisoylpropionic Acid.—To a solution of powdered anhydrous aluminium chloride (180 g.) in nitrobenzene (500 c.c.), cooled in iced water, a mixture of methylsuccinic anhydride (70 g.) and anisole (70 g.) was added drop by drop. The flask was constantly shaken, and the mass became reddish brown and viscous towards the end. After standing overnight, the mixture was then poured into ice and dilute hydrochloric acid (1 : 1) with shaking. After the removal of nitrobenzene and unchanged anisole with steam, the residue solidified on cooling. It was collected and then digested with sodium carbonate solution. The filtrate on acidification in the cold, gave the keto-acid which crystallised from water in plates, m.p. 144°, yield 105 g. The acid was repeatedly crystallised fractionally from different solvents, such as ethyl alcohol, acetone, methyl alcohol, acetic acid, benzene, ethyl acetate but no evidence was obtained of a second isomer. (Found : C, 64.61 ; H, 6.21. $\text{C}_{12}\text{H}_{14}\text{O}_4$ requires C, 64.86 ; H, 6.30 per cent).

The *semicarbazone*, prepared in the usual way, crystallised from alcohol, m.p. 162° (decomp.). (Found : N, 15.23. $\text{C}_{13}\text{H}_{17}\text{O}_4\text{N}_3$ requires N, 15.05 per cent).

Oxidation of the Keto-acid (m.p. 144°) to 4-Methoxybenzoic Acid.—Moderately concentrated nitric acid (2 c.c.) was added to a solution of the keto-acid (0.8 g.) dissolved in acetic acid (3 c.c.). The mixture after heating for 1 hour on the steam-bath was diluted with water and the precipitated acid was crystallised from alcohol, m.p. and mixed m.p. with anisic acid, 183-84°.

Pyrylium Derivative of α -Methyl- β -anisoylpropionic Acid.—A mixture of the keto-acid (0.2 g.) and salicylaldehyde (0.2 g.) in methyl alcohol (15 c.c.) was saturated with dry hydrogen chloride at 0°. The mixture gradually

became deep red and the precipitate was filtered after 12 hours. It was washed with a little ethyl alcohol containing hydrogen chloride and dried in a vacuum desiccator. It is readily soluble in dilute alkali, and does not melt even at 300°.

Ethyl α -methyl- β -anisoylpropionate was obtained by esterifying the keto-acid in the usual way, b.p. 185-87°/5 mm. (Found: C, 67'43; H, 7'02. $C_{14}H_{18}O_4$ requires C, 67'20; H, 7'20 per cent).

α -Methyl- γ -(p-methoxy)-phenylbutyric Acid.—The keto-acid (50 g.) and zinc filings (100 g.) amalgamated with 5% mercuric chloride solution were refluxed with 200 c.c. of hydrochloric acid (d 1.19) for 10 hours. A further quantity of hydrochloric acid (100 c.c.) was introduced and the heating continued for 2 hours. After cooling the acid was extracted with ether, the extract washed with a little water and dried over anhydrous sodium sulphate. After the removal of ether, the residue was distilled at 180-82°/5 mm., yield 42 g. (Found: C, 69'47; H, 7'71. $C_{12}H_{16}O_3$ requires C, 69'23; H, 7'69 per cent).

Ethyl α -methyl- γ -(p-methoxy)-phenylbutyrate was prepared by esterifying the acid by Fischer's method, b. p. 146-48°/4.5 mm. (Found: C, 70'82; H, 8'65. $C_{14}H_{20}O_3$ requires C, 71'18; H, 8'47 per cent).

1-Keto-2-methyl-7-methoxy-1 : 2 : 3 : 4-tetrahydronaphthalene.—The reduced acid (26.5 g.) was added to phosphorus pentoxide (80 g.) and heated on the steam-bath for about 8 hours. The benzene solution was removed and the residual phosphorus pentoxide decomposed with ice. The contents of the flask were steam distilled and a small quantity of oil in the distillate was extracted with benzene. The combined benzene solution was washed with dilute sodium carbonate solution, water and then dried over calcium chloride. The residue after removal of benzene, was distilled in *vacuo* at 150-52°/5 mm. The distillate was a pale greenish liquid which became reddish after a few days, yield 20 g. (Found: C, 75'45; H, 7'40. $C_{12}H_{14}O_2$ requires C, 75'78; H, 7'36 per cent).

The ketone gave a *semicarbazone* under the usual conditions as brownish crystals from alcohol, m.p. 197°. (Found: N, 17'32. $C_{13}H_{17}O_2N_3$ requires N, 17'0 per cent).

1:2:3:4-Tetrahydro-2-methyl-7-methoxynaphthalene.—A mixture of the foregoing ketone (8 g.) amalgamated zinc (35 g.) and concentrated hydrochloric acid (85 c.c.) was refluxed for 15 hours. Concentrated hydrochloric acid was added at intervals. The product was extracted with ether; the ethereal extract was washed with dilute sodium carbonate solution and then with water. It was then dried over anhydrous sodium sulphate. The residue

after removal of ether was distilled at $114-15^{\circ}/5$ mm., yield 4.5 g. (Found : C, 81.97 ; H, 9.02. $C_{12}H_{16}O$ requires C, 81.81 ; H, 9.09 per cent).

2-Methyl-7-methoxynaphthalene.—Dehydrogenation was effected by heating a mixture of 2-methyl-7-methoxy-1 : 2 : 3 : 4-tetrahydronaphthalene (3.5 g.) and selenium (6 g.) for 25 hours at $310-320^{\circ}$. The product was extracted with ether, washed with cold 5% sodium hydroxide solution and then with water. The dried extract (sodium sulphate) gave a brownish residue after removal of ether, which was crystallised from alcohol in shining flakes, m.p. $89-90^{\circ}$, yield 2 g. (Found : C, 83.83 ; H, 6.90. $C_{12}H_{12}O$ requires C, 83.72 ; H, 6.97 per cent). The *picrate*, prepared in hot alcoholic solution, crystallised in orange needles, m.p. 119° . (Found : N, 10.23. $C_{18}H_{15}O_8N_3$ requires N, 10.47 per cent).

Action of Methyl Magnesium Iodide on 1-Keto-1 : 2 : 3 : 4-tetrahydro-7-methoxy-2-methylnaphthalene.—To the Grignard reagent prepared from magnesium ribbon (1.4 g.) and methyl iodide (4.5 c.c.) in dry ether, a solution of the ketone (10 g.) in dry ether was added dropwise with shaking and ice-cooling and then left overnight.

The solid magnesium compound was decomposed with ice-cold 10% dilute sulphuric acid and then extracted with ether, washed with water, then with sodium bisulphite and again with water. The dried ethereal extract (sodium sulphate) was freed from solvent and the residue, distilled at $134-38^{\circ}/5.5$ mm. The product decolourised potassium permanganate solution and was found by analysis to be a mixture of carbinol and dehydrated product, yield 8 g. (Found : C, 79.54 ; H, 8.62. $C_{13}H_{18}O_2$ requires C, 75.72 ; H, 8.73. $C_{13}H_{16}O$ requires C, 82.97 ; H, 8.51 per cent).

Condensation of Methyl Magnesium Iodide with Ethyl α -Methyl- β -anisoylpropionate.—To a solution of 25 g. of the ester in absolute ether (60 c. c.) was added the Grignard reagent prepared from magnesium powder (2.6 g.), methyl iodide (7.5 c. c.) and dry ether (20 c. c.) drop by drop with stirring. Reaction set in at once. After standing overnight the product was decomposed with dilute ice-cold hydrochloric acid. The ethereal extract after washing with dilute sodium bicarbonate solution, ice-cold 5% sodium hydroxide solution and water, was dried over sodium sulphate and the residue from ether distilled at $183-85^{\circ}/6$ mm., yield 15 g. (Found : C, 67.94 ; H, 8.34. $C_{15}H_{22}O_4$ requires C, 67.66 ; H, 8.27 per cent).

The sodium hydroxide washing on acidification gave an oily product which was extracted with ether, washed with water and dried over anhydrous sodium sulphate. On removal of ether, the product distilled at $175-77^{\circ}/5$ mm., yield 5 g. The lactone is insoluble in sodium bicarbonate

solution. (Found : C, 71.07; H, 7.45. $C_{13}H_{16}O_3$ requires C, 70.90; H, 7.27 per cent).

α-Methyl-β-(o-hydroxy)-benzoylpropionic Acid.—To a mixture of phenol (50 g.), methylsuccinic anhydride (50 g.) and acetylene tetrachloride (300 c. c.) powdered anhydrous aluminium chloride (150 g.) was gradually added with constant shaking, the mass becoming brown towards the end. The mixture was then heated in an oil-bath at 135–140° for 6 hours and kept overnight. The product was decomposed by the addition of crushed ice and hydrochloric acid (1 : 1) and then distilled in steam. The keto-acid solidified on cooling and was crystallised first from water and then from alcohol in colourless needles, m. p. 161°. No isomeric product was obtained on fractional crystallisation, yield 30 g. (Found : C, 63.61; H, 5.93. $C_{11}H_{12}O_4$ requires C, 63.46; H, 5.76 per cent). A poor yield was obtained when the reaction was carried out at the ordinary temperature. The methyl ether was obtained by methylating with dimethyl sulphate and caustic soda solution. It crystallised from ligroin, m. p. 92–94°. (Found : C, 64.7; H, 6.27. $C_{12}H_{14}O_4$ requires C, 64.86; H, 6.30 per cent).

Pyrylium Derivative of α-Methyl-β-(o-hydroxy)-benzoylpropionic Acid.—A mixture of the keto-acid (0.1 g.) and salicylaldehyde (0.1 g.) in methyl alcohol (8 c. c.) was saturated with dry hydrogen chloride at 0°. After a few minutes the mixture became deep red and was left overnight. It was then poured into water containing hydrochloric acid. The crimson red precipitate was filtered and washed with water and dried in a desiccator. It dissolved in alkali with bluish red colouration and did not melt up to 330°. *α-Methyl-γ-(o-hydroxy)-phenylbutyric acid* was obtained by Clemmensen reduction of the keto-acid, b. p. 170–73°/5.5 mm. (Found : C, 67.83; H, 7.35. $C_{11}H_{14}O_3$ requires C, 68.04; H, 7.21 per cent).

Condensation of Resorcinol Dimethyl Ether with Methylsuccinic Anhydride.—To a cold solution of powdered anhydrous aluminium chloride (30 g.) in nitrobenzene (80 c. c.) was added a mixture of methylsuccinic anhydride (10 g.) and resorcinol dimethyl ether (15 g.) dropwise. The flask was constantly shaken during the addition. The mass became reddish brown towards the end and was left overnight. The mixture was then poured into ice and dilute hydrochloric acid (1 : 1) with shaking and then subjected to steam distillation to remove nitrobenzene and unreacted resorcinol dimethyl ether. The residual semi-solid mass was extracted with ether, washed with a little water and the ether removed. On crystallisation from water it melted indefinitely between 115° and 124°, yield 11 g.

On repeated fractional crystallisation from methyl alcohol and acetic acid, two products were isolated *viz.*, (i) pale brownish needles, m. p. 130–31°,

which gave reddish colouration with ferric chloride and (ii) colourless small needles, m. p. 142-43°, giving a very faint pink colouration with ferric chloride solution. [Found for the product (i): C, 61.66; H, 6.36. $C_{13}H_{16}O_5$ requires C, 61.90; H, 6.34 per cent].

When dry hydrogen chloride was passed to a methyl alcoholic solution of the substance (i) (0.1 g.) and salicylaldehyde (0.1 g.) the mixture gradually became deep red. After keeping overnight, it was poured into water when the pyrylium derivative was precipitated. It was filtered off, washed with water and dried in a desiccator. It did not melt up to 280°.

Condensation of Methylsuccinic Anhydride with Pyrogallol Trimethyl Ether.—A solution of aluminium chloride (210 g.) in nitrobenzene (600 c. c.) was cooled in ice-water and a mixture of methylsuccinic anhydride (75 g.) and pyrogallol trimethyl ether (105 g.) in nitrobenzene was slowly added to it. The mixture became brown and viscous and was left overnight. The aluminium chloride addition product was decomposed by ice-cold dilute hydrochloric acid (1 : 1) and then subjected to steam distillation to remove nitrobenzene and unreacted pyrogallol trimethyl ether. The residue solidified on cooling. It was filtered and extracted with hot sodium carbonate solution. The keto-acid was precipitated with hydrochloric acid in the cold and crystallised from water, m.p. 140-46°, yield 95 g.

After repeated fractional crystallisation from methyl alcohol, acetic acid and acetone two compounds were obtained, *viz.*

(i) Pale yellow needles, m.p. 155°, yield 18 g. (ii) Yellow needles, m.p. 175-76°, yield 6 g. Found for the compound (i): C, 58.33; H, 5.92; OMe, 23.46. $C_{13}H_{16}O_6$ requires C, 58.21; H, 5.97; OMe, 23.16 per cent. Found for the compound (ii): C, 58.46; H, 5.78. $C_{13}H_{16}O_6$ requires C, 58.21; H, 5.97 per cent. The substance (i) gave a pyrylium derivative, whilst (ii) did not.

The *semicarbazone* of the keto-acid (i) crystallised from alcohol, m.p. 208-9°. (Found: N, 12.65. $C_{14}H_{19}O_6N_3$ requires N, 12.92 per cent).

The acid was methylated in acetone solution with methyl iodide in presence of dry potassium carbonate. It crystallised from petroleum ether, m.p. 89-90°. (Found: C, 59.73; H, 6.57. $C_{14}H_{18}O_6$ requires C, 59.57; H, 6.38 per cent).

On Clemmensen's reduction, the keto-acid gave α -methyl- γ -(2-hydroxy-3:4-dimethoxy)-phenylbutyric acid as very fine needles from petroleum ether, m.p. 83-85°. (Found: C, 61.62; H, 7.06. $C_{13}H_{18}O_5$ requires C, 61.41; H, 7.08 per cent).

1-Keto-1:2:3:4-tetrahydro-2-methyl-5-hydroxy-6:7-dimethoxynaphthalene.—A mixture (35 c. c.) of 85 g. of pure sulphuric acid and 15 c. c. of

water was added to the reduced acid (8 g.) and the mixture heated on the water-bath for $1\frac{1}{2}$ hours. After cooling the mixture was poured into crushed ice and water and the product was extracted with ether. The ethereal extract was washed with water, then with sodium bicarbonate solution and finally with water, and then dried (sodium sulphate). After removal of ether the residue was crystallised from dilute methyl alcohol in needles, m.p. $130-32^\circ$, yield 6 g. (Found: C, 66.01; H, 6.91. $C_{13}H_{16}O_4$ requires C, 66.10; H, 6.78 per cent).

The *semicarbazone* crystallised from alcohol, m.p. $228-29^\circ$. (Found: N, 14.74. $C_{14}H_{19}O_4N_3$ requires N, 14.33 per cent).

1:2:3:4-Tetrahydro-2-methyl-5-hydroxy-6:7-dimethoxynaphthalene.—The ring ketone (5.5 g.) was reduced with amalgamated zinc (30 g.) and concentrated hydrochloric acid (80 c.c.), by heating for 15 hours, hydrochloric acid (5 c.c.) being added every hour. The product was extracted with ether, the ethereal extract was washed with a dilute solution of sodium bicarbonate and with water, and then dried over anhydrous sodium sulphate. The residue from ether distilled at $152-54^\circ/6$ mm. The distillate was a colourless liquid which solidified when kept in a vacuum desiccator, yield 3 g. (Found: C, 70.41; H, 8.35. $C_{13}H_{18}O_3$ requires C, 70.27; H, 8.11 per cent).

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