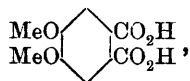


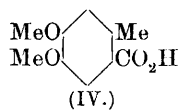
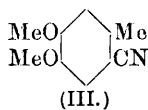
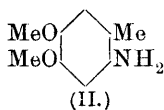
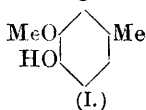
XCV.—*m*-Hemipinic and Asaronic Acids.

By BERNARD DUNSTAN WILKINSON LUFF, WILLIAM HENRY PERKIN, jun., and ROBERT ROBINSON.

AMONG the degradation products obtained by the oxidation of the alkaloids and other natural products with permanganate, there are few substances which are so frequently met with as *m*-hemipinic acid :

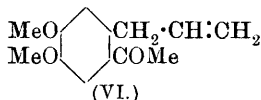
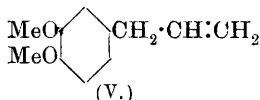


and yet, in spite of its importance, there is still great difficulty in obtaining this acid in quantity. As we were anxious to employ *m*-hemipinic acid in some synthetical experiments on which we are engaged, we undertook the present investigation in the hope of discovering a more convenient method for its preparation. The starting point selected was creosol (I), which is readily obtained in quantity, and this was methylated by means of methyl sulphate and potassium hydroxide in the usual manner. The creosol methyl ether, thus obtained, was nitrated, and the nitro-derivative reduced by tin and hydrochloric acid to 4:5-dimethoxy-*o*-toluidine (II), a crystalline substance which melts at 109°. This amino-derivative was next converted, by Sandmeyer's reaction, into 4:5-dimethoxy-*o*-toluonitrile (III), which melts at 81°, and, on hydrolysis with barium hydroxide, yields 4:5-dimethoxy-*o*-toluic acid (IV), an acid which had previously been prepared by Perkin and Weizmann (Trans., 1906, 99, 1651) by another process, namely, from the corresponding aldehyde by oxidation. At that time it was observed that *m*-hemipinic acid was also produced in small quantities, and we now find that 4:5-dimethoxy-*o*-toluic acid is quantitatively converted into *m*-hemipinic acid by oxidation with hot alkaline permanganate:



We have prepared considerable quantities of *m*-hemipinic acid in the way described above, but the process is still not convenient, principally on account of the time required to carry out the number of steps which have to be followed during the preparation.

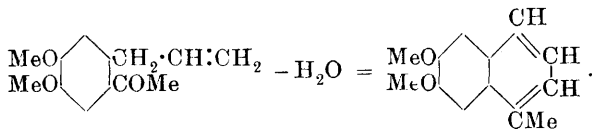
A second series of experiments was then instituted which seemed to promise well, and the starting point in this case was eugenol,  $\text{MeO} \cdot \text{C}_6\text{H}_3(\text{OH}) \cdot \text{CH}_2 \cdot \text{CH} \cdot \text{CH}_2$ , which was converted into eugenol methyl ether (V), and then treated with acetyl chloride in the presence of aluminium chloride, in the hope that acetyleneugenol methyl ether (VI) would result, which, on oxidation, should readily yield *m*-hemipinic acid:



Instead, however, of this ketone, we obtained a brown, resinous substance, which did not yield a semicarbazone, and from which nothing crystalline could be obtained by the action of solvents.

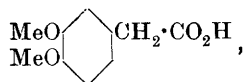
When this uninviting substance was distilled under diminished pressure, it yielded a beautifully crystalline substance,  $\text{C}_{13}\text{H}_{14}\text{O}_2$ ,

melting at  $114^{\circ}$ , the properties of which (p. 1140) clearly prove that it is 6:7-dimethoxy-1-methylnaphthalene. The formation of this interesting substance is evidently due to elimination of water from the methyl-ketone, and this internal condensation is probably the result of the dehydrating action of the aluminium chloride:



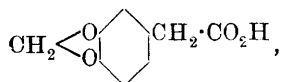
This naphthalene derivative gives *m*-hemipinic acid on oxidation, but the process is of no value as a method of preparation.

We have also carried out experiments on the oxidation of eugenol methyl ether itself in the hope of obtaining 4:5-dimethoxyphenyl-acetic acid:



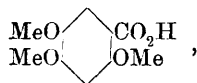
which we require for our synthetical experiments, but, although this acid is produced in this way, the yield is very small, owing to the fact that veratric acid is the principal product of the oxidation.

In the same way, we find that safrole,  $\text{CH}_2 \cdot \text{O}_2 \cdot \text{C}_6\text{H}_3 \cdot \text{CH}_2 \cdot \text{CH} \cdot \text{CH}_2$ , yields, on oxidation, principally piperonylic acid, only small quantities of piperonylacetic acid:



being obtained.

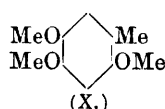
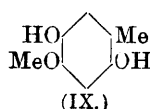
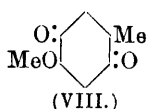
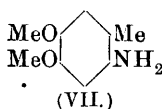
The synthesis of asaronic acid:



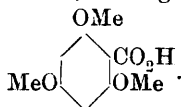
an account of which is included in this communication, was carried out as follows. We observed that 4:5-dimethoxy-*o*-toluidine (VII) is readily oxidised by ferric chloride to 4-methoxy-2:5-toluquinone (VIII),\* which crystallises in golden spangles, melts at  $170-172^{\circ}$ , and is readily reduced by sulphurous acid to 4-methoxy-2:5-toluquinol (IX). This substance melts at  $124^{\circ}$ , and yields, on treatment with methyl sulphate and potassium hydroxide, 2:4:5-trimethoxytoluene (m. p.  $55^{\circ}$ , X), which, on oxidation with hot

\* It is remarkable that the elimination of the methyl group, which is necessary for quinone formation, should take place so readily at the ordinary temperature.

alkaline permanganate, is converted, almost quantitatively, into asaronic acid:



Asaronic acid was first obtained by the oxidation of asarone, a substance which occurs in the root of *Asarum europaeum*, with permanganate (Butleroff and Rizza, *J. Russ. Phys. Chem. Soc.*, 1887, **19**, 3), and it was long thought that this acid was a derivative of phloroglucinolcarboxylic acid, having the constitution:

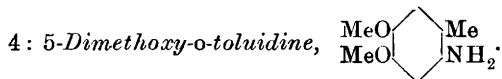


Gattermann and Eggers (*Ber.*, 1899, **32**, 289) succeeded, however, in synthesising the corresponding aldehyde from 1 : 2 : 4-trimethoxybenzene by the action of hydrogen cyanide in the presence of aluminium chloride. In this reaction, the aldehyde group always takes up the para-position with respect to a methoxy-group, and Gattermann and Eggers therefore represent the formation and constitution of the aldehyde, and therefore of asaronic acid, as follows:



The synthesis which we have described in this communication supports this view, and the constitution of asaronic acid may now be considered as definitely established.

#### EXPERIMENTAL.



The starting point in the preparation of this substance is creosol methyl ether,  $\text{C}_6\text{H}_3\text{Me}(\text{OMe})_2$  (1 : 3 : 4), which is readily obtained in quantity by the following process. Creosol,  $\text{C}_6\text{H}_3\text{Me}(\text{OMe})\cdot\text{OH}$  (1 : 3 : 4) (50 grams), is dissolved in methyl alcohol (100 c.c.), mixed with methyl sulphate (90 grams), and cooled to  $-10^\circ$ . A solution of potassium hydroxide (75 grams) in 150 c.c. of water is then added, with vigorous shaking, when a reaction sets in, which continues for about three minutes, and is then complete. The product is extracted with ether, the extract well washed with water, dried and evaporated, and the residue distilled, when pure creosol

methyl ether is obtained in an almost quantitative yield. It distils at  $218^{\circ}$ , and, on cooling, solidifies to a crystalline mass, melting at  $24^{\circ}$ .

The nitration of creosol methyl ether (compare Cousin, *Ann. Chim. Phys.*, 1898, [vii], **13**, 545) was carried out under the following conditions.

Creosol methyl ether (40 grams) dissolved in glacial acetic acid (200 c.c.) was added to a solution of concentrated nitric acid (25 grams) in glacial acetic acid (80 c.c.), the whole being kept cold by running water. Nitration took place readily, and, after leaving for a few minutes, the product gave, on dilution with water, a mass of yellow needles of nitrocreosol methyl ether,  $C_6H_2Me(OMe)_2 \cdot NO_2$  (1 : 4 : 5 : 2), which, after crystallising from alcohol, melted at  $119^{\circ}$ .

4 : 5-Dimethoxy-*o*-toluidine was obtained by reducing nitrocreosol methyl ether with tin and hydrochloric acid. The nitro-derivative (50 grams) was dissolved in hot alcohol (100 c.c.), granulated tin (70 grams) added, and then concentrated hydrochloric acid (150 c.c.) diluted with water (50 c.c.) gradually run in, and finally the whole was heated on the steam-bath for an hour. The excess of acid was partly neutralised by sodium hydroxide, the tin removed by hydrogen sulphide, and, after filtering, the filtrate was evaporated to a small bulk and rendered alkaline, when the base separated in glistening crystals, the yield being about 60 per cent. :

0.2238 gave 0.5323  $CO_2$  and 0.1600  $H_2O$ . C = 64.8 ; H = 7.9.

$C_9H_{13}O_2N$  requires C = 64.7 ; H = 7.9 per cent.

4 : 5-Dimethoxy-*o*-toluidine crystallises from a mixture of chloroform and light petroleum in clusters of needles, melting at  $109^{\circ}$ ; it is readily soluble in ether, alcohol, or hot water, and moderately so in chloroform. The alcoholic solution gives, on the addition of ferric chloride, a beautiful blue coloration, but this gradually fades, and long, golden-yellow needles of 4-methoxy-2 : 5-toluquinone separate (p. 1137). The *acetyl* derivative was prepared by heating with acetic anhydride in the usual manner, and crystallises from water in pearly plates, melting at  $141^{\circ}$  :

0.4262 gave 24.4 c.c.  $N_2$  at  $15^{\circ}$  and 764 mm. N = 6.8.

$C_{11}H_{15}O_3N$  requires N = 6.7 per cent.

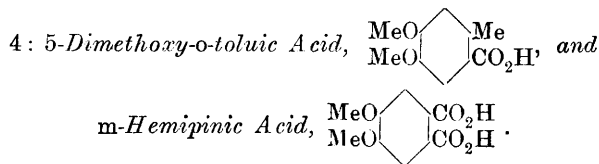


This substance was prepared from 4 : 5-dimethoxy-*o*-toluidine by the Sandmeyer reaction. The base (10 grams) was dissolved in hydrochloric acid (30 c.c.) and water (100 c.c.), and the solution

diazotised by the addition of sodium nitrite in the usual manner. The cuprous potassium cyanide solution (from 22 grams of potassium cyanide) was then added to the diazotised solution with constant shaking, and, after fifteen minutes, the whole was warmed to 80°. The product was then extracted with ether, the ethereal solution washed with sodium hydroxide, then with water, and dried. On removal of the ether, the nitrile was obtained as a crystalline mass, of which the yield was about 50 to 60 per cent. of that theoretically possible, and this crude product was employed, without further purification, for the preparation of 4:5-dimethoxy-*o*-toluic acid (see the next section). The nitrile is fairly soluble in hot water, and separates, on cooling, in silky needles, which melt at 81°:

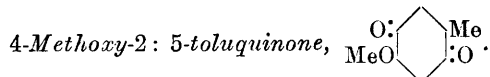
0.1532 gave 0.3806 CO<sub>2</sub> and 0.0876 H<sub>2</sub>O. C=67.7; H=6.3.

C<sub>10</sub>H<sub>11</sub>O<sub>2</sub>N requires C=67.8; H=6.3 per cent.



In preparing 4:5-dimethoxy-*o*-toluic acid, the crude nitrile was hydrolysed by boiling with barium hydroxide until ammonia ceased to be evolved, the product was filtered, and acidified with hydrochloric acid, when the acid was precipitated in a practically pure condition. It was identified by the fact that it melted at 145°, and that there was no alteration in melting point when it was mixed with a specimen of this acid which had been prepared by Perkin and Weizmann (Trans., 1906, **99**, 1651). The conversion of 4:5-dimethoxy-*o*-toluic acid into *m*-hemipipinic acid was carried out under the following conditions. The acid was dissolved in a slight excess of sodium hydroxide in a porcelain basin, and 5 per cent. alkaline permanganate added to the boiling solution until a permanent pink colour was produced. After destroying the excess of permanganate by the addition of a little alcohol, the filtrate and washings from the manganese precipitate were acidified with hydrochloric acid and evaporated to dryness. The residue was mixed with sand and extracted with ether in a Soxhlet apparatus, when it was observed that crystals soon began to separate from the ethereal extract, and, when extraction was complete, the ether was removed by evaporation and the residue crystallised from hot water. An acid was thus obtained in shining needles, which melted at temperatures ranging from 175° to 188° according to the

rate of heating, and was identified as *m*-hemipinic acid by conversion into the ethylimide and by its other properties. The amount obtained was almost that demanded by theory, and this fact emphasises again the remarkable stability of *m*-hemipinic acid towards alkaline permanganate.



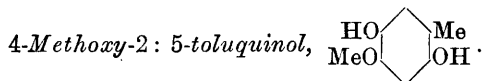
It has already been stated (p. 1135) that this interesting substance is produced when 4:5-dimethoxy-*o*-toluidine is oxidised with ferric chloride. In preparing it, a strong solution of ferric chloride is added to an aqueous solution of the hydrochloride of the base until further addition no longer produces a blue coloration.

The long needles, which separate after some time, are collected and purified by crystallisation from alcohol, from which the quinone separates in golden spangles:

0.1664 gave 0.3862 CO<sub>2</sub> and 0.0817 H<sub>2</sub>O. C=63.2; H=5.4.

C<sub>8</sub>H<sub>8</sub>O<sub>3</sub> requires C=63.1; H=5.2 per cent.

4-Methoxy-2:5-toluquinone softens at about 165°, and melts and decomposes at 170—172°; it is volatile in steam, and possesses the characteristic odour of quinone. It is soluble in hot water, alcohol, or benzene, but is very sparingly so in light petroleum or ether. The solution in ether gives, on the addition of an ethereal solution of magnesium methyl iodide, a bluish-green colour, a reaction which is characteristic of quinones.



When the quinone, just described, is suspended in warm water and a stream of sulphur dioxide passed, it gradually dissolves, and, on cooling, the dihydroxy-derivative separates in colourless needles:

0.1734 gave 0.3964 CO<sub>2</sub> and 0.1062 H<sub>2</sub>O. C=62.3; H=6.8.

C<sub>8</sub>H<sub>10</sub>O<sub>3</sub> requires C=62.3; H=6.5 per cent.

4-Methoxy-2:5-toluquinol melts at 124°, and is soluble in most organic solvents and in hot water; ferric chloride oxidises it to the quinone without the production of any characteristic coloration.

2:4:5-Trimethoxytoluene, C<sub>6</sub>H<sub>2</sub>Me(OMe)<sub>3</sub>, is prepared by methylating the dihydroxy-derivative just described. The substance (20 grams) is dissolved in methyl alcohol (75 c.c.), methyl sulphate (70 grams) is added, and, after the whole has been cooled to -10°, a solution of potassium hydroxide (60 grams) in water (120 c.c.) is added, when a vigorous reaction sets in. As soon as

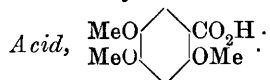
this has subsided, the product is extracted with ether, the ethereal solution washed, dried, and evaporated, when the trimethoxy-derivative remains as a syrup, which, on rubbing with a glass rod, soon solidifies :

0.1662 gave 0.4022  $\text{CO}_2$  and 0.1170  $\text{H}_2\text{O}$ .  $\text{C}=65.9$ ;  $\text{H}=7.8$ .

$\text{C}_{10}\text{H}_{14}\text{O}_3$  requires  $\text{C}=65.9$ ;  $\text{H}=7.7$  per cent.

2 : 4 : 5-Trimethoxytoluene melts at  $55^\circ$ , and crystallises from dilute methyl alcohol in leaflets; it is readily soluble in ether, alcohol, or light petroleum.

*Oxidation of 2 : 4 : 5-Trimethoxytoluene: Formation of Asaronic*



The oxidation of 2 : 4 : 5-trimethoxytoluene to asaronic acid was carried out under the following conditions. The finely-powdered substance (2 grams) was suspended in water (50 c.c.), heated to boiling, and a 5 per cent. alkaline solution of permanganate gradually added until the pink colour remained after boiling for three minutes. The slight excess was removed by the addition of alcohol, the filtrate and washings of the manganese precipitate acidified with hydrochloric acid until just acid to Congo-paper, and evaporated to dryness. The residue, mixed with sand, was extracted with ether in a Soxhlet apparatus, and in this way a colourless, crystalline acid was obtained, which separated from a mixture of light petroleum and benzene in glistening needles, melting at  $143^\circ$ . That this substance was asaronic acid was proved by adding a little nitric acid to its solution in glacial acetic acid and warming gently; effervescence set in, due to the evolution of carbon dioxide, and, on cooling, a pale yellow, crystalline solid separated, which melted at  $130^\circ$  and exhibited all the properties of 5-nitro-1 : 2 : 4-trimethoxybenzene (compare Fabinyi and Széki, *Ber.*, 1906, **39**, 3681).

#### *Oxidation of Eugenol Methyl Ether.*

Eugenol methyl ether,  $[3 : 4](\text{MeO})_2\text{C}_6\text{H}_3\cdot\text{CH}_2\cdot\text{CH}\cdot\text{CH}_2$ , and *iso*-eugenol methyl ether,  $[3 : 4](\text{MeO})_2\text{C}_6\text{H}_3\cdot\text{CH}\cdot\text{CH}\cdot\text{CH}_3$ , are readily prepared in almost quantitative yields by methylation with methyl sulphate in the way described in detail in the case of the preparation of the methyl ether of creosol (p. 1135). The oxidation of the methyl ether of eugenol was investigated in the hope of readily obtaining dimethoxyphenylacetic acid,  $[3 : 4](\text{MeO})_2\text{C}_6\text{H}_3\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$ , a substance of considerable importance in connexion with our synthetical researches on the alkaloids. The best results were obtained under the following conditions. Eugenol



methyl ether (30 grams) was dissolved in acetone (250 c.c.), the solution cooled in ice, and gradually treated with a cold saturated solution of permanganate (100 grams), when oxidation proceeded slowly at first, but afterwards more rapidly.

The filtrate from the manganese precipitate, after distilling off the acetone and concentrating somewhat on the water-bath, gave, on acidifying, a large quantity of a yellowish-brown precipitate, which was readily identified as veratric acid. The filtrate from this was concentrated and extracted with ether, and the ethereal extract shaken with sodium carbonate. The alkaline solution was boiled with animal charcoal, filtered, cooled in ice, and acidified, when a crystalline precipitate gradually separated, and the separation was much facilitated by rubbing the sides of the vessel with a glass rod. After crystallisation from water, the acid melted at  $97^{\circ}$ , and proved to be dimethoxyphenylacetic acid, but the yield was unsatisfactory, and seldom more than 4 to 5 grams from 30 grams of eugenol methyl ether. A similar process of oxidation applied to safrole,  $\text{CH}_2\text{:O}_2\text{:C}_6\text{H}_3\text{:CH}_2\text{:CH:CH}_2$ , yielded a mixture of piperonylic acid and piperonylacetic acid,  $\text{CH}_2\text{:O}_2\text{:C}_6\text{H}_3\text{:CH}_2\text{:CO}_2\text{H}$ , the latter being again produced in comparatively small quantity.

*The Action of Acetyl Chloride on Eugenol Methyl Ether in the presence of Aluminium Chloride. Formation of 6:7-Di-*



This interesting formation of a naphthalene derivative takes place under the following conditions. Eugenol methyl ether (30 grams), dissolved in carbon disulphide (50 c.c.) in a reflux apparatus, is mixed with powdered aluminium chloride (30 grams), and then acetyl chloride (16 grams), dissolved in an equal volume of carbon disulphide, is gradually added. The reaction becomes more vigorous as the acetyl chloride is added, and, when it has subsided, the product is heated on the steam-bath for one hour. The carbon disulphide is then decanted, and the residual aluminium compound decomposed by crushed ice and water, and, after adding 15 c.c. of concentrated hydrochloric acid, a current of steam is passed for about five minutes.

The whole is then extracted with ether, the ethereal solution washed with water, then with sodium hydroxide, dried, and the ether evaporated. Since the residue did not crystallise, and an attempt to prepare a semicarbazone was unsuccessful, it was distilled under 18 mm. pressure, when a considerable quantity passed over at  $180\text{--}190^{\circ}$  and again at  $190\text{--}220^{\circ}$ , a resinous mass being left.

On long standing, the two fractions deposited a crystalline substance, which was freed from oily impurity by contact with porous porcelain and then crystallised from alcohol, from which pearly leaflets, melting at  $114^{\circ}$ , separated:

0.1828 gave 0.5152  $\text{CO}_2$  and 0.1177  $\text{H}_2\text{O}$ .  $\text{C}=76.9$ ;  $\text{H}=7.1$ .

$\text{C}_{13}\text{H}_{14}\text{O}_2$  requires  $\text{C}=77.2$ ;  $\text{H}=6.9$  per cent.

In a determination of the molecular weight by the cryoscopic method:

0.177, in 17.8 c.c. benzene, gave  $\Delta t = -0.255^{\circ}$ . M.W.=195.

$\text{C}_{13}\text{H}_{14}\text{O}_2$  requires M.W.=202.

The following properties of the substance clearly indicate that it is 6: 7-dimethoxy-1-methylnaphthalene.

I. The substance was treated with concentrated nitric acid in glacial acetic acid solution; on dilution with water a nitro-derivative was precipitated, which was then reduced with tin and hydrochloric acid. The product was rendered alkaline, extracted with ether, and the oil obtained dissolved in hydrochloric acid and treated with sodium nitrite. The resulting diazo-solution, added to an alkaline solution of  $\beta$ -naphthol, yielded a blood-red dye, which turned blue on the addition of concentrated sulphuric acid, and the solution became red on dilution. These colour changes are characteristic of solutions of naphthalene azo-derivatives.

II. The substance was heated with hydriodic acid, extracted with ether, and the residue, obtained after evaporating off the ether, dissolved in alcohol and mixed with ferric chloride. A blue colour was produced, showing that the substance is a naphthol derivative, and not merely a derivative of catechol.

III. The substance yields *m*-hemipinic acid on oxidation. In this experiment, the crude substance (20 grams) was employed, and this was dissolved in acetone (200 c.c.) and oxidised with 5 per cent. permanganate solution and some potassium carbonate in a stoppered bottle on the shaking machine. When the pink colour remained permanent, the excess of permanganate was removed by sodium sulphite, and the filtrate from the manganese precipitate acidified with hydrochloric acid and evaporated to dryness. The residue, mixed with sand, was extracted in a Soxhlet apparatus, and the extract boiled with water and animal charcoal, filtered, and concentrated, when glistening needles separated, which melted at about  $178^{\circ}$ , and were easily identified as *m*-hemipinic acid.

The authors wish to state that much of the expense of this investigation was covered by a grant from the Chemical Society.

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