

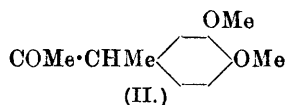
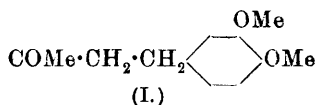
LXIV.—*The Pungent Principles of Ginger. Part I.*  
*A New Ketone, Zingerone (4-Hydroxy-3-methoxy-*  
*phenylethyl Methyl Ketone) occurring in Ginger.*

By HIROSHI NOMURA.

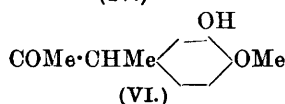
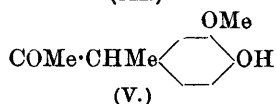
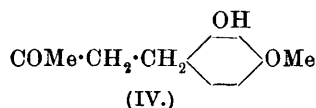
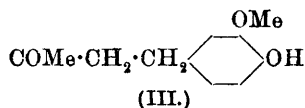
THRESH assigned the name "gingerol" to the pungent principle of ginger, and Garnett and Grier (*Pharm. J.*, 1907, [iv], **25**, 118) claimed to have isolated it. However, no account of an investigation of its composition and constitution is to be found in the literature, and the present work was undertaken to determine the constitution of the pungent principle.

The new ketone, to which the name "zingerone" is assigned, was obtained by extracting ginger with ether, followed by the treatment described on p. 770, and was proved to have the formula  $C_{11}H_{14}O_3$ . It yields monobenzoyl and monoacetyl derivatives, and the existence of one methoxyl group in it was proved. The methyl derivative,  $C_{12}H_{16}O_3$ , is readily converted into its oxime,  $C_{12}H_{17}O_3N$ , by hydroxylamine, which points to the presence of one carbonyl group. When the methyl derivative is oxidised with potassium permanganate in alkaline solution, veratric acid is obtained, and therefore the new ketone must be a 1:3:4-derivative of benzene.

Since sodium hydrogen sulphite combines with the new ketone and with its methyl derivative and the latter is oxidisable with difficulty by an ammoniacal solution of silver nitrate, the group,  $CO \cdot CH_3$ , appears to exist in both compounds. If this is the case, the constitutional formula of the methyl derivative must be either (I) or (II), and the constitution of the original ketone must be



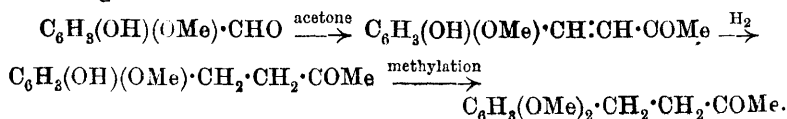
(III), (IV), (V), or (VI), according as the methyl derivative has the constitution (I) or (II) respectively. In order to decide between



these, the following two methods may be used.

I. The constitution of the methyl derivative may be determined by examining its products of oxidation by sodium hypobromite or hypochlorite. If the constitutional formula of the methyl derivative is once determined, that of the original ketone could be determined by the introduction of the ethyl group and subsequent oxidation.

II. If the constitution of the methyl derivative is (I), it could be synthesised by the reduction of the condensation product of vanillin and acetone, and subsequent methylation according to the following scheme:



According as the intermediate product in this synthesis agrees with the new ketone or not, the constitution of the latter must be either (III) or one of (IV), (V), and (VI). In the latter case, if the methyl derivative is identical with the above synthetical 3:4-dimethoxyphenylethyl methyl ketone, the constitution of the new ketone should be (IV). If this experiment fails to yield the methyl derivative, the constitutional formula of the latter is necessarily (II), and that of the new ketone can be determined by the oxidation of its ethyl derivative.

Since the yield of the ketone from ginger is poor, the second method is preferable to the first. Fortunately, by the reduction of the condensation product of vanillin and acetone, a substance identical with the new ketone was obtained. Its identity was further proved by comparing its benzoyl derivative and the oxime of its methyl ether with the corresponding derivatives of the naturally occurring ketone.

The constitution of the new ketone was, moreover, confirmed by the first method, namely, by the production, from the methyl derivative, of bromoform and  $\beta$ -3:4-dimethoxyphenylpropionic acid by oxidation with sodium hypobromite, and by the formation, from the ethyl derivative, of ethylvanillic acid by means of potassium permanganate in alkaline solution. There is no doubt, therefore, that the constitution of the new ketone is (III). The investigation of the other pungent principle and the synthesis of the substances analogous to the new ketone are now in progress.

#### EXPERIMENTAL.

Dry powdered ginger (367 kilos.) was extracted with ether in the cold and the ethereal extract evaporated to a syrupy consistency. The syrup was dissolved in a small quantity of ether and

shaken with 2 per cent. sodium hydroxide for three hours. The quantity of sodium hydroxide solution required for the extraction of the pungent principles from the syrup was determined by a preliminary experiment, 500 c.c. of 2 per cent. sodium hydroxide being necessary for 100 grams of the syrup. The pungent principles in the alkaline solution were deposited by means of carbon dioxide free from hydrochloric acid and extracted with ether. The ethereal solution was washed with 2*N*-sodium carbonate solution to remove any acid, and then with water until the alkaline reaction disappeared, dried over anhydrous sodium sulphate, and evaporated. The yield of residual oil was about 1 per cent. of the original ginger. It was distilled under 0.5—1 mm. pressure until the temperature of the oil-bath reached 320°, after the previous distillation of volatile substance under 13—23 mm. pressure. The whole of the distillate was diluted with ether and shaken with an excess of a concentrated solution of sodium hydrogen sulphite, whereby the bisulphite compound of the new ketone separated. This was collected, washed with ether until the washing was colourless, and decomposed with a concentrated solution of sodium carbonate. The oil was extracted with ether, the ethereal solution washed several times with water, dried over anhydrous sodium sulphate, and evaporated. The yield of oil thus obtained was 0.04 per cent. of the original material. On cooling and continuous agitation with a minute quantity of the solid ketone, the oil solidified to a somewhat brown mass, which melted at 40—41° after recrystallisation from light petroleum (b. p. 50—70°) or a mixture of ether and light petroleum. The colourless crystals thus purified gave the following results on analysis:

0.0944 gave 0.2350 CO<sub>2</sub> and 0.0629 H<sub>2</sub>O. C=67.89; H=7.45.

0.0900 „ 0.2243 CO<sub>2</sub> „ 0.0600 H<sub>2</sub>O. C=67.97; H=7.46.

0.2559 „ 0.2812 AgI. Me=7.03.

0.1615 in 19.64 benzene gave  $\Delta t = -0.217^\circ$ . M.W.=189.

C<sub>11</sub>H<sub>14</sub>O<sub>3</sub> requires C=68.00; H=7.27; IMe=7.74 per cent.

M.W.=194.

Zingerone gives a red coloration with Millon's reagent, dissolves to a green-coloured solution with alcoholic ferric chloride, and reduces ammoniacal silver nitrate solution on warming. There is no visible decomposition on shaking the ketone with 2 per cent. sodium hydroxide for several hours.

The phenylhydrazone and semicarbazone were not obtained in the pure state, owing to the instability of the compounds and the small quantities of ketone used for the preparation.

*Benzoyl Derivative.*—Half a gram of zingerone dissolved in 30 c.c. of 5 per cent. sodium hydroxide solution was shaken with

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3 c.c. of benzoyl chloride for two hours; the precipitate was collected and washed with water. After being dried in the desiccator, the substance was twice recrystallised from absolute alcohol with the addition of animal charcoal, when it separated in colourless crystals melting at 126—127°. The yield was 0.35 gram after one crystallisation:

0.1058 gave 0.2803 CO<sub>2</sub> and 0.0590 H<sub>2</sub>O. C=72.25; H=6.24.

C<sub>18</sub>H<sub>18</sub>O<sub>4</sub> requires C=72.45; H=6.08 per cent.

*Acetyl Derivative.*—Seven grams of zingerone were boiled for one hour under a reflux condenser with 7 grams of fused sodium acetate and 25 grams of acetic anhydride. After the removal of the excess of acetic anhydride under diminished pressure, the product was extracted with ether and the ethereal solution washed with a dilute solution of sodium carbonate and then with water until it became free from alkali. The dried ethereal solution was evaporated and the residual oil purified by distillation under diminished pressure. During the first distillation, almost the whole quantity distilled at 202—206°/14 mm., the main portion distilling at 204—206°. The yield was 7.1 grams. On repeating the operation, the substance boiled constantly at 204—205° under the same pressure:

0.1787 gave 0.4317 CO<sub>2</sub> and 0.1107 H<sub>2</sub>O. C=65.89; H=6.93.

C<sub>13</sub>H<sub>16</sub>O<sub>4</sub> requires C=66.07; H=6.83 per cent.

On allowing it to remain for a few days, the oil solidified and melted at 40—42°, the melting point of the original ketone. It differs, however, from the latter in that the crystals give no coloration with ferric chloride in alcoholic solution and liquefy when mixed with the ketone. It is sparingly soluble in light petroleum, but readily so in alcohol or benzene. The result of the oxidation of this acetyl derivative with potassium permanganate in the presence of magnesium sulphate was unsatisfactory.

*Methylzingerone.\**—The ketone (5.7 grams) was dissolved in 30 c.c. of 5 per cent. sodium hydroxide solution and shaken with 3.5 c.c. of methyl sulphate for half an hour. After removing the unchanged ketone by shaking with 5 c.c. of 10 per cent. sodium hydroxide solution, the product was extracted with ether, the ethereal solution washed several times with water, and shaken with a concentrated solution of sodium hydrogen sulphite. The

\* When the determination of the constitution of the ketone was complete and that of the other pungent principle in progress, the compounds which correspond with the methyl derivative and its oxime were synthesised by Kaufmann and Radosević (*Ber.*, 1916, 49, 675). The description of the melting points of these compounds is in agreement with those of the above methyl derivative and its oxime respectively.

bisulphite compound was collected, washed with ether, decomposed with sodium carbonate, and the product extracted with ether. The ethereal solution was washed with water, dried over anhydrous sodium sulphate, and evaporated. The residual oil was then distilled under diminished pressure, when almost the whole quantity passed over at  $188-189^{\circ}/17.5$  mm. The yield was 2.8 grams. On repeating the distillation, a colourless oil boiling at  $186^{\circ}/16$  mm. was obtained:

0.1258 gave 0.3166  $\text{CO}_2$  and 0.0885  $\text{H}_2\text{O}$ .  $\text{C}=68.64$ ;  $\text{H}=7.87$ .

$\text{C}_{12}\text{H}_{16}\text{O}_3$  requires  $\text{C}=69.19$ ;  $\text{H}=7.75$  per cent.

After several months, the oil partly solidified. On stirring with a glass rod, the whole solidified with the evolution of heat, and melted at  $55-56^{\circ}$ . The compound was oxidised with difficulty by an ammoniacal solution of silver nitrate.

*Methylzingeroneoxime*.—A mixture of methylzingerone (1 gram), hydroxylamine hydrochloride (0.35 gram), and sodium acetate (0.7 gram) was dissolved in dilute alcohol and boiled for two hours under a reflux condenser. In order to isolate the product, the alcohol was removed by gentle evaporation, the oily oxime, which, however, readily solidified, collected, washed with water, and dried. The yield was 1 gram. The crystals were several times recrystallised from dilute methyl alcohol with the addition of animal charcoal, when they separated in colourless needles melting at  $93-93.5^{\circ}$ :

0.1395 gave 8.04 c.c.  $\text{N}_2$  at  $22^{\circ}$  and 754.5 mm.  $\text{N}=6.45$ .

$\text{C}_{12}\text{H}_{17}\text{O}_3\text{N}$  requires  $\text{N}=6.28$  per cent.

*Ethylzingerone*.—Seven grams of zingerone and 2.1 grams of potassium hydroxide were dissolved in warm methyl alcohol, and the residue left on the evaporation of the methyl alcohol was heated for three hours under a reflux condenser with 30 c.c. of absolute alcohol and 20 grams of ethyl iodide. The alcohol and the excess of ethyl iodide were removed, when a brown mass separated, which was washed with 2 per cent. sodium hydroxide to remove the unchanged ketone, and then with water until it became neutral. The mass was now crystallised from dilute alcohol and then from light petroleum (b. p. below  $60^{\circ}$ ) with the addition of animal charcoal. The yield was 6 grams after one crystallisation from dilute alcohol. The crystals thus purified were colourless and gave the following results on analysis:

0.1523 gave 0.3926  $\text{CO}_2$  and 0.1160  $\text{H}_2\text{O}$ .  $\text{C}=70.30$ ;  $\text{H}=8.52$ .

$\text{C}_{13}\text{H}_{18}\text{O}_3$  requires  $\text{C}=70.23$ ;  $\text{H}=8.16$  per cent.

The compound melts at  $66^{\circ}$ , and is soluble in ether or methyl or ethyl alcohol, but insoluble in water.

*Oxidation of Methylzingerone with Potassium Permanganate.*

The compound (2.3 grams; 1 mol.) and 100 c.c. of 2*N*-sodium carbonate solution were heated under a reflux condenser, and 390 c.c. of a 3 per cent. solution of potassium permanganate (corresponding with 5 mols. of oxygen) were slowly run in. The boiling was continued until the colour of the permanganate disappeared, and the product was cooled and filtered from the precipitated manganese dioxide. The filtrate and washings of the manganese dioxide were treated with ether to remove any unchanged methylzingerone, evaporated to a small bulk, and acidified with hydrochloric acid, when a yellow acid (1.8 grams) separated, which after recrystallisation from water with the addition of animal charcoal and drying at 100—110° melted at 180—181°. The acid prepared by the above method was colourless (Found, C=59.13; H=5.82.  $C_9H_{10}O_4$  requires C=59.31; H=5.53 per cent.), and the melting point was not changed by admixture with veratric acid.

*Oxidation of Ethylzingerone with Sodium Hypochlorite.*

This oxidation was carried out in an exactly similar manner to that employed in the oxidation of the methyl derivative. The acid obtained melted at 195—196° (Found, C=61.39; H=6.31.  $C_{10}H_{12}O_4$  requires C=61.20; H=6.17 per cent.) and did not depress the melting point of ethylvanillic acid.

*Oxidation of Methylzingerone with Sodium Hypochlorite.*

Two grams of the substance were suspended in an excess of an alkaline solution of sodium hypochlorite and warmed on the water-bath until a clear solution was obtained and no chloroform evolved. The solution was rapidly cooled, acidified with sulphurous acid, evaporated to a small bulk, and extracted with ether. The ethereal solution was dried over anhydrous sodium sulphate, evaporated, and the residue was recrystallised from water, from which two different acids were obtained.

The one melted at 180—181° after drying at 100—110°, and this melting point was not depressed by admixture with veratric acid. The other melted at 95—99°, but it could not be purified owing to lack of substance. It is, however, probable that the substance is  $\beta$ -3:4-dimethoxyphenylpropionic acid (m. p. 98—99°).

*Oxidation of Methylzingerone with Sodium Hypobromite.*

The compound (3.1 grams) was shaken for two hours with an alkaline solution of sodium hypobromite, which was prepared by dis-

solving 2.3 c.c. of bromine in ice-cooled sodium hydroxide solution (6 grams in 100 c.c. of water), when the reaction of the hypobromite vanished. The product was then extracted with ether, and the ethereal solution (A) and the alkaline solution (B) were treated in the following way.

(A) The ethereal solution was washed with water until it became free from alkali, and the greater part of the ether evaporated. The residual solution was freed from any unchanged methylzingerone by shaking with a concentrated solution of sodium hydrogen sulphite, washed with sodium carbonate solution, and then with water until free from alkali. The ethereal solution thus purified was dried over anhydrous sodium sulphate and evaporated. The residual oil (2.1 grams) on distillation gave 0.8 gram of oil boiling at 147—148° and possessing the characteristic odour of bromoform.

(B.) After evaporating to a small bulk, the aqueous solution was acidified with hydrochloric acid, extracted with ether, washed several times with a saturated solution of sodium chloride, and dried over anhydrous sodium sulphate. On distilling off the ether from the ethereal solution, 2.6 grams of a yellow syrup were obtained, which did not solidify on keeping for a few days. The syrup was now dissolved in a small quantity of 2*N*-sodium carbonate solution, the solution digested with animal charcoal, filtered, and acidified with hydrochloric acid, when a yellow oil separated which on keeping overnight partly solidified to crystals. The crystals were collected, freed from the last traces of oil by draining on a porous tile, and recrystallised from water with the addition of animal charcoal. The crystals thus purified melted at 98—99° after being dried over sulphuric acid in the desiccator, and were proved to have the constitution of  $\beta$ -3:4-dimethoxyphenylpropionic acid by the mixed melting-point method. The yield of the impure crystals was 0.55 gram.

*Synthesis of Zingerone (4-Hydroxy-3-methoxyphenylethyl Methyl Ketone),*  $\text{CH}_3\cdot\text{CO}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{C}_6\text{H}_3(\text{OMe})\cdot\text{OH}$ .

The intermediate compound in this synthesis, namely, 4-hydroxy-3-methoxystyryl methyl ketone,  $\text{CH}_3\cdot\text{CO}\cdot\text{CH}:\text{CH}\cdot\text{C}_6\text{H}_3(\text{OMe})\cdot\text{OH}$ , has been described by Francesconi and Cusmano (*Gazzetta*, 1908, **38**, ii, 70), who, however, give no details of its preparation. It was therefore synthesised in the following way.

Seventy c.c. of 10 per cent. sodium hydroxide solution were added to a solution of 25 grams of vanillin in 100 c.c. of acetone, and after being allowed to remain for four days, the solution was acidified with dilute hydrochloric acid, when a yellow precipitate was obtained. The precipitate was collected, washed with water



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until free from chloride, and crystallised from dilute alcohol, from which it separated in yellow crystals melting at 128—129°. The yield was 28 grams after one crystallisation.

Six grams of this compound were suspended in 100 c.c. of absolute ether and reduced for nine hours by means of hydrogen in the presence of platinum black. The hydrogen absorbed was about 800 c.c. (at 23—24° and 752—754 mm.). After filtering off the platinum black, the filtrate and ethereal washings were evaporated, and the residual oil on distillation boiled constantly at 187—188°/14 mm. The yield was 4·8 grams. The oil was twice recrystallised from a mixture of ether and light petroleum (b. p. below 60°). The crystals thus obtained melted at 40—41°:

0·1629 gave 0·4058 CO<sub>2</sub> and 0·1090 H<sub>2</sub>O. C=67·94; H=7·49.

0·1244 „ 0·3113 CO<sub>2</sub> „ 0·0850 H<sub>2</sub>O. C=68·25; H=7·64.

C<sub>11</sub>H<sub>14</sub>O<sub>3</sub> requires C=68·00; H=7·27 per cent.

The substance sustained no lowering of the melting point by mixing with the naturally occurring ketone. The benzoyl derivative and the oxime of the methyl ether melted respectively at 126—127° and 93—93·5°, and these melting points were not altered when the respective compounds were mixed with the corresponding derivative of the naturally occurring ketone.

The isolation of zingerone was made for the first time in the laboratory of the Agricultural College, Tokyo Imperial University, under Professor Umetaro Suzuki, and after my coming to the Science College, Tohoku Imperial University, the work was resumed under the guidance of Professor Riko Majima. Since then, the separation of the ketone has been effected more easily, and its constitution studied with satisfactory results. The author wishes to express his hearty thanks to the professors for their kind suggestions.

AGRICULTURAL COLLEGE, IMPERIAL UNIVERSITY OF  
TOKYO, AND SCIENCE COLLEGE,  
IMPERIAL UNIVERSITY OF SENDAI.

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