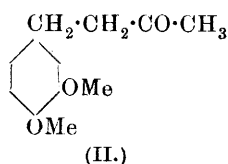
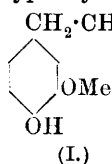


LXVI.—*The Pungent Principles of Ginger. Part II. Synthetic Preparations of Zingerone, Methylzingerone and Some Related Acids.*

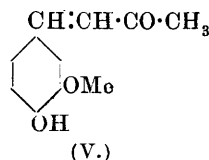
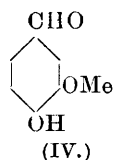
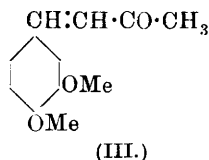
By ARTHUR LAPWORTH and FREDERICK HENRY WYKES.

IN Part I. evidence was adduced that the phenolic ketone, "zingerone," obtained from gingerol, the pungent oleo-resin of ginger, was 4-hydroxy-3-methoxyphenylethyl methyl ketone (I) or a position isomeride, and that "methylzingerone," the corresponding ketone from "methylgingerol," is its methyl ether, (II), 3:4-dimethoxyphenylethyl methyl ketone.



The authors have prepared these, and also several important acids that were required for purposes of comparison, by synthetic methods, which in certain cases represent the first direct syntheses of the compounds in question and in other cases are simpler or give better yields than previous methods.

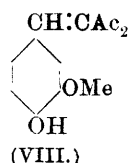
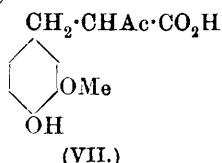
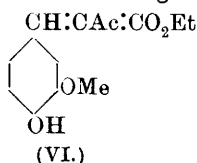
The synthesis of methylzingerone presented no difficulty, as 3:4-dimethoxystyryl methyl ketone (II), from veratraldehyde and acetone, is easily made in good yield and is readily reduced by sodium amalgam, giving 3:4-dimethoxyphenylethyl methyl ketone, which is identical with methylzingerone (II).



A similar process for preparing 4-hydroxy-3-methoxyphenylethyl methyl ketone by condensing vanillin (IV) with acetone and reducing the resulting 4-hydroxy-3-methoxystyryl methyl ketone (V) gave very poor yields at each stage, but the final product was

identical with zingerone. On the other hand, good yields were quickly obtained by the following process.

Vanillin (V) gives an excellent yield of ethyl vanillylideneacetate (VI) by Knoevenagel and Albert's method (*Ber.*, 1904, **37**, 4476); this unsaturated ester was easily reduced by means of sodium amalgam, and the product with excess of alkali was converted into an acid, doubtless *vanillylacetoacetic acid* (VII), which when heated lost the elements of carbon dioxide and was converted into zingerone (V).

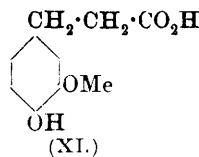
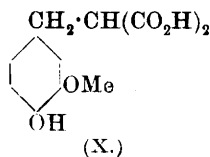
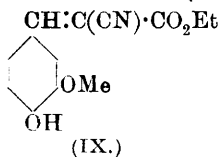


Synthetic zingerone was obtained in crystalline form, and had the characteristic sweet odour and pungent taste of the ketone from the decomposition of gingerol. The solid when used to infect samples of ketone obtained from the drug caused these to solidify for the first time. The properties of the synthetic ketone were identical in every respect with those of the compound from ginger.

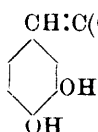
An attempt to imitate this synthesis through vanillylideneacetylacetone (VIII) was not successful, and the reduction products of the latter compound were not of the type expected.

The authors' work included some simple direct syntheses of hydroferulic acid (XI) and of hydrocaffeic acid (XIII). These have previously been obtained by the reduction of synthetic ferulic and caffeic acids (Tiemann and Nagai, *Ber.*, 1878, **11**, 650, 672) prepared by the Perkin "cinnamic acid synthesis." As the authors' methods, although obvious enough, are new, if not in principle, and are very easily carried out, the steps may be indicated.

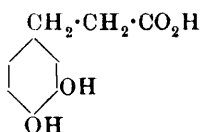
Vanillin (V) was condensed with diethyl malonate or ethyl cyanoacetate, yielding diethyl vanillylidenemalonate and ethyl vanillylidenecyanoacetate (IX) respectively. These were readily reduced at the double bond, and on subsequent hydrolysis with excess of alkali were converted into acids, doubtless vanillylmalonic acid (X) in both instances. The product when heated yielded hydroferulic acid (XI).



A precisely analogous process, applied to protocatechualdehyde instead of vanillin, gave hydrocaffeic acid (XIII) through the intermediate condensation product (XII).

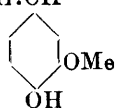
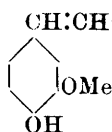


(XII.)



(XIII.)

It is worthy of remark that all the unsaturated phenolic ketones and esters (I, V, VIII, IX, and XII) give solutions in alkali which in the thinnest layers exhibit an intense yellow colour that disappears on reduction at the double bond. The effect is perhaps most pronounced with (XII), which exhibits with boric acid a reaction very like that associated with curcumin, the colouring matter of turmeric. The constitution which Kostanecki suggests for curcumin is



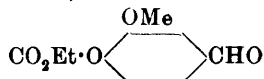
in which case it is obviously very closely related to the similar compounds dealt with in the present paper.

The question of the groupings essential to the pungency of gingerol, zingerone, and similar compounds is one which one of us is hopeful of reserving for a short time. So far, it would appear certain that the presence of the free phenolic hydroxyl group is essential, and also, not improbably, the ketonic carbonyl suitably disposed in a saturated chain attached to the phenolic residue.

EXPERIMENTAL.

I. *Synthesis of Zingerone (4-Hydroxy-3-methoxyphenylethyl Methyl Ketone).*

Preparation of Ethylcarbonatovanillin,



As vanillin and its acetyl and benzoyl derivatives did not readily condense with acetone, the ethylcarbonato-derivative, which is new, was prepared by adding one molecular proportion of ethyl chloroformate to vanillin dissolved in the requisite quantity of *N*-sodium

hydroxide. The derivative separated in the cold in small, white needles, and after an hour was collected and crystallised from hot alcohol.

Found: C=63·3; H=5·9.

$C_{11}H_{12}O_4$ requires C=63·5; H=5·8 per cent.

The substance crystallises from alcohol in slender needles and melts at 65°. It is slowly hydrolysed by cold dilute alkali. When it was dissolved in excess of acetone and the mixture treated with a little dilute sodium hydroxide, an intense yellow colour was produced, and apparently a small quantity of the desired condensation product was formed, as the neutral product of the reaction, when reduced with sodium amalgam, gave an oily mixture which had a pronounced pungent taste. The authors have not yet had opportunities to follow up these observations.

Reduction of Vanillylidene Derivatives of Acetylacetone and Ethyl Acetoacetate. Formation of Zingerone.

Vanillylideneacetylacetone, which was prepared by Knoevenagel and Albert's method (*Ber.*, 1904, **37**, 4480), forms an intensely yellow solution in sodium hydroxide; this colour is discharged by shaking the solution with sodium amalgam, and on saturating the resulting liquid with carbon dioxide, an oil, doubtless *vanillylacetylacetone*, $HO \cdot C_6H_3(OMe) \cdot CH_2 \cdot CH(CO \cdot CH_3)_2$, is deposited and ultimately tends to crystallise; as the oil when heated with acid or alkaline hydrolytic agents gave no product with the characters of vanillylacetone, its further investigation was not undertaken.

Ethyl vanillylideneacetoacetate, which was also obtained in nearly theoretical yield by Knoevenagel and Albert's method (*loc cit.*, p. 4476), crystallised in pale yellow needles melting at 112·5—113·5°, and as Knoevenagel and Albert give the melting point as 120—121°, the authors analysed their product. (Found, C=63·3; H=6·0. $C_{14}H_{16}O_5$ requires C=63·5; H=6·1 per cent.)

The ester was dissolved in 10 per cent. aqueous sodium hydroxide and the intensely yellow solution shaken violently with washed, fluid, sodium amalgam, the whole being kept very cool. When the solution no longer displayed a yellow colour in thin layers, it was separated from mercury, mixed with 35 per cent. of its weight of solid sodium hydroxide, and heated for about eight hours on the water-bath, when it was cooled, saturated with carbon dioxide, and extracted with ether to remove unhydrolysed *ethyl vanillylacetoacetate*, $OMe \cdot C_6H_3(OH) \cdot CH_2 \cdot CHAc \cdot CO_2Et$, an oily compound which represents the first stage in the reduction process.

The aqueous residue was next acidified and extracted with ether, the latter then being dried and evaporated. The oily extract was heated in a vacuum, when at first carbon dioxide was evolved, and the residual material distilled at $175\text{--}210^\circ/15\text{ mm}$.

In order to separate the products, the distillate was dissolved in aqueous sodium hydroxide, which was then saturated with carbon dioxide and extracted with ether ("phenolic extract"), the aqueous residue being subsequently acidified with hydrochloric acid and again extracted with ether ("acidic extract").

The "phenolic extract" when dried and evaporated left a brown oil. This was dissolved in *N*-sodium hydroxide solution and treated in the cold with ethyl chloroformate, when the bulk of the material in solution was converted into an oil which solidified on scratching the vessel with a glass rod. The solid was dissolved in ether, the solution dried, and allowed to evaporate spontaneously. Large, tabular crystals were deposited, which on recrystallisation from light petroleum formed colourless, hexagonal plates melting at 47.5° .

Found: C=62.7; H=6.7.

$\text{C}_{14}\text{H}_{18}\text{O}_5$ requires C=63.1; H=6.8 per cent.

The substance was identical in all respects with the ethyl-carbonato-derivative of the ketone ("zingerone") obtained from gingerol.

In order to obtain the free phenolic ketone, the foregoing compound was heated on the water-bath with dilute aqueous sodium hydroxide until a homogeneous liquid resulted. Excess of hydrochloric acid was then added and the cooled product extracted with ether. After drying and evaporating, the ethereal extract left a residue, which was distilled in a vacuum, when the distillate set to a crystalline mass.

The solid material, obtained as above, was purified by dissolving it in dry ether, adding enough petroleum to cause a turbidity, allowing the latter to settle, and then infecting the clear solution with a trace of solid 4-hydroxy-3-methoxyphenylethyl methyl ketone. On spontaneous evaporation, the liquid deposited lustrous, flat, colourless crystals which had the odour of the above ketone and melted at $36\text{--}37^\circ$.

Found: C=67.7; H=7.2.

$\text{C}_{11}\text{H}_{14}\text{O}_3$ requires C=68.0; H=7.3 per cent.

4-Hydroxy-3-methoxyphenylethyl methyl ketone obtained in this way had an extremely pungent taste and was in every respect identical in properties with "zingerone." As has already been mentioned, the "zingerone" from the natural source was not

obtained in crystalline condition until infected with a trace of the synthetic ketone, which had solidified spontaneously after distillation in a vacuum.

4-Hydroxy-3-methoxyphenylethyl methyl ketone is not the only product which is formed by reduction of ethyl vanillylideneacetate and subsequent hydrolysis. The "acidic extract" (compare p. 794) gave on evaporation a small quantity of an acid which was moderately soluble in cold water and readily so in hot; this formed colourless leaflets melting at 133—134°, and was at first believed to be hydrocaffeic acid, which also crystallises in leaflets and melts at 137—139°. The substance obtained as above, however, unlike hydrocaffeic acid, gives no coloration with ferric chloride, and when it is mixed with hydrocaffeic acid the mixture melts at 127—132°. A titration with alkali, using phenolphthalein as indicator, gave an equivalent for this acid of about 240; the quantity of this material obtained in the pure state was, however, too small to permit of further investigation.

*Oxidation and Reduction of 3:4-Dimethoxystyryl Methyl Ketone.
Formation of Dimethylcaffeic Acid and of Methylzingerone.*

3:4-Dimethoxystyryl methyl ketone was prepared by condensing veratraldehyde with acetone (compare Francesconi and Cusmano, *Gazzetta*, 1908, **38**, ii, 70 *et seq.*) and purifying it by recrystallisation from light petroleum. (Found: C=70.0; H=6.8. $C_{12}H_{14}O_3$ requires C=69.9; H=6.8 per cent.)

The compound crystallises from carbon tetrachloride in microscopic leaflets. When it is warmed with concentrated hydrochloric acid, it gives a deep red coloration, doubtless due to the intermediate formation of veratraldehyde, which gives a similar reaction.

3:4-Dimethoxystyryl methyl ketone is readily oxidised when shaken with aqueous sodium hypobromite, being converted into dimethylcaffeic acid, $C_6H_3(OMe)_2 \cdot CH:CH \cdot CO_2H$, which was isolated in small, flat needles (from water) melting at 180—181°.

Reduction of 3:4-dimethoxystyryl methyl ketone with the aid of Paal and Skita's or Willstätter's methods did not proceed in a very satisfactory manner, but when an alcoholic solution of the compound was shaken with liquid sodium amalgam, the bright yellow colour rapidly lost its intensity, and when this process was carried out in presence of excess of potassium hydrogen carbonate, good yields of the desired reduction product were obtained. It was isolated by diluting the aqueous-alcoholic solution with water, extracting with ether, and shaking the ethereal extract with

freshly prepared sodium hydrogen sulphite solution. The solid hydrogen sulphite compound was collected, washed with ether, dried, and then decomposed by warming it with excess of aqueous sodium carbonate. By extracting the resulting liquid with ether, 3:4-dimethoxyphenylethyl methyl ketone was obtained in quantity corresponding with about 80 per cent. of that theoretically possible. It was purified by crystallisation from methyl alcohol.

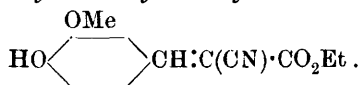
Found: C=69.4; H=7.8.

$C_{12}H_{16}O_3$ requires C=69.2; H=7.7 per cent.

The substance formed colourless, odourless needles melting at 55–56°, and its identity with "methylzingerone," obtained by methylating "zingerone" or by the decomposition of "methylgingerol," was established by the usual methods. Its colour reactions with hydrochloric acid and the properties of its oxime (long, white needles, m. p. 92°) were indistinguishable from those of the corresponding compounds obtained from "gingerol."

III. *Synthesis of Hydroferulic Acid.*

Ethyl Vanillylidenecyanoacetate,



Vanillin and ethyl cyanoacetate were mixed in molecular proportions and heated on the water-bath until a homogeneous liquid was obtained, when a few drops of piperidine were added and the heating was continued until a test portion solidified completely. Alcohol (twice the weight of vanillin present) was added, and the whole allowed to cool. The crystals obtained were washed with dilute hydrochloric acid, dried, and crystallised from alcohol. With material obtained from mother liquors, the total yield of condensation product approached that theoretically possible.

Found: C=62.2; H=5.3.

$C_{13}H_{13}O_4N$ requires C=63.1; H=5.3 per cent.

Ethyl vanillylidenecyanoacetate separates from alcohol in yellow needles melting at 107°. It dissolves in aqueous sodium hydroxide, giving a solution which shows an intensely yellow colour even in thin layers; it is reprecipitated unchanged from this solution on the addition of acids.

Formation of Hydroferulic Acid from Ethyl Vanillylidenecyanoacetate.

The reduction of ethyl vanillylidenecyanoacetate was accomplished by means of sodium amalgam in precisely the same manner

as was used for the reduction of ethyl vanillylideneacetoacetate (p. 793). The reduction product [mainly, no doubt, a mixture of vanillylcyanoacetic acid, $\text{HO}\cdot\text{C}_6\text{H}_3(\text{OMe})\cdot\text{CH}_2\cdot\text{CH}(\text{CN})\cdot\text{CO}_2\text{H}$, and its ethyl ester] was heated with excess of potassium hydroxide until the ester present had been completely hydrolysed, when excess of acid was added and the liquid extracted with ether. The latter was evaporated and the residue heated in a vacuum to expel carbon dioxide; the hydroferulic acid left was purified by converting it into its lead salt, which is very sparingly soluble in water, and decomposing the latter in aqueous suspension with hydrogen sulphide.

Hydroferulic acid, obtained in the above way, crystallises from hot water in stout, white needles melting at $89-90^\circ$. It dissolves readily in hot water, less readily in cold, and only sparingly in concentrated hydrochloric acid. Its aqueous solution gives no coloration with ferric chloride. (Found: $\text{C}=60.6$; $\text{H}=6.2$. $\text{C}_{10}\text{H}_{12}\text{O}_4$ requires $\text{C}=60.6$; $\text{H}=6.1$ per cent.) The acid agreed very closely in properties with those assigned by Tiemann and Nagai (*Ber.*, 1878, 11, 650) to the acid obtained by the reduction of ferulic acid.

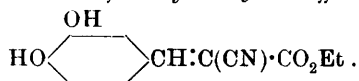
Diethyl vanillylidenemalonate, $\text{HO}\cdot\text{C}_6\text{H}_3(\text{OMe})\cdot\text{CH}:\text{C}(\text{CO}_2\text{Et})_2$, was prepared from vanillin and ethyl malonate by Knoevenagel and Albert's method (*loc. cit.*, p. 4481). It had the properties ascribed to it by these authors.

On reduction with sodium amalgam and subsequent treatment in the manner described in the case of ethyl vanillylideneacyanoacetate, it yields hydroferulic acid.

IV. *Synthesis of Hydrocaffeic Acid.*

Hydrocaffeic acid was prepared by Tiemann and Nagai (*Ber.*, 1878, 11, 672) by the reduction of synthetic caffeic acid. The following is a simple alternative synthesis.

Condensation of Protocatechualdehyde with Ethyl Cyanoacetate. Formation of Ethyl α -Cyanocaffeate,



This condensation was effected by means very similar to those used in similar condensations in previous sections, but it was found desirable to dilute the mixture of aldehyde and ester with a little absolute alcohol. The product, which was contaminated

with a brown impurity, was purified by extraction with benzene and recrystallisation therefrom.

Found: C=61·6; H=4·9.

$C_{12}H_{11}O_4N$ requires C=61·8; H=4·7 per cent.

Ethyl α -cyanocaffeate is a yellow, microcrystalline solid which melts somewhat indefinitely at 162—166°, and dissolves in alkali to give an intensely orange solution. A test-paper made by dipping paper in an alcoholic solution of this ester behaves towards boric acid in much the same way as does turmeric paper, that is, if moistened with boric acid solution and then heated it turns brown, but the temperature required is somewhat higher than with turmeric.

Formation of Hydrocaffeic Acid from Ethyl α -Cyanocaffeate.

A solution of ethyl α -cyanocaffeate in alkali was reduced with sodium amalgam until colourless. The resulting liquid, which very quickly turned brown on exposure to air, was made strongly alkaline by the addition of solid sodium hydroxide, boiled for two days under a reflux condenser, cooled, acidified, and extracted with ether. The ethereal extract gave an oil which soon deposited crystals; these were not isolated, but the whole was heated to expel carbon dioxide, then dissolved in water, treated with animal charcoal, and allowed to crystallise. The crystals of hydrocaffeic acid obtained in this way were hexagonal leaflets melting at 138—139°, were moderately soluble in cold water, readily so in hot, and their aqueous solution gave a green colour with ferric chloride, changing to a rich purple on the addition of ammonia. These properties correspond closely with those assigned to hydrocaffeic acid by Tiemann and Nagai (*loc. cit.*).

The authors have also found that hydrocaffeic acid is readily obtained from hydroferulic acid by heating it with dilute hydrochloric acid (about 5 per cent.) at 200° for six hours in a closed tube.

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