CCCCXIX.—*Derivatives of Kojic Acid.*

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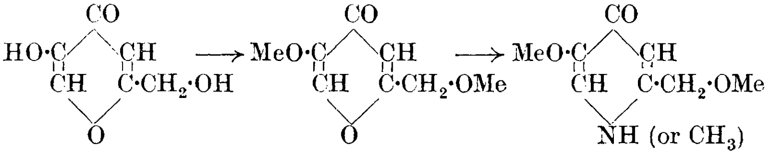
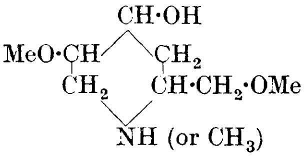
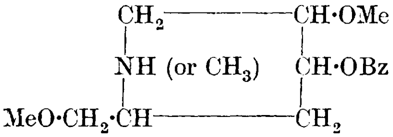
As kojic acid can readily be obtained by the action of various strains of *Aspergillus* on carbohydrates, its derivatives were investigated. A promising field appeared to lie in deriving from it synthetic drugs of local anæsthetic value of the β-eucaine type as outlined in the following scheme.



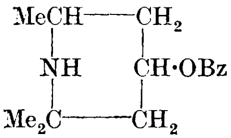
(I) Kojic acid (II) (III)



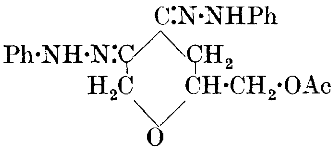
(IV)



(V)



(VI) β-Eucaine



(VII)

Diazomethane only methylated the nuclear hydroxy-group (position 5). The hydroxymethyl group was then readily methylated by means of dry silver oxide and methyl iodide. Derivatives of the type (III) were easily obtained by the action of gaseous ammonia or methylamine on a methyl-alcoholic solution of either the mono- or the di-methyl ether of kojic acid. These reactions proceeded readily in the cold except in the case of ammonia and the monomethyl ether, where heating under pressure was necessary, the reaction going smoothly at 90° in a sealed tube. All attempts to reduce these pyridones to the type (IV) were unsuccessful, as they appeared to be unaffected by the ordinary reducing agents, either acid or alkaline, and were not hydrogenated in the presence of palladium or platinum. Indeed, the only action of sodium and boiling amyl alcohol on 5-methoxy-1 : 2-dimethyl-4-pyridone was demethylation of the methoxy-group in about 30% of the base.

When the method employed by Willstätter in the reduction of tropinone (*Annalen*, 1903, **326**, 47) was followed with 5-*methoxy*-2-*methoxymethyl*-1-*methyl*-4-*pyridone* or 5-*methoxy*-2-*hydroxymethyl*-1-*methyl*-4-*pyridone*, the product was 5-methoxy-1 : 2-dimethyl-4-pyridone, which Yabuta (J., 1924, **125**, 586) obtained by the action of methyl sulphate on the 4 : 5-dihydroxy-2-methylpyridine which he had produced by reducing 5-methoxy-2-methoxymethyl-4-pyridone by means of red phosphorus and hydriodic acid.

Yabuta was unable to obtain comenic acid from kojic acid owing to the instability of the γ-pyrone ring. We obtained the methyl ether of comenamic acid with fair ease by oxidising 5-*methoxy*-2-*hydroxymethyl*-4-*pyridone* with nitric acid. This substance was made by Yabuta (*loc. cit.*, p. 583) by the action of ammonia on comenic acid methyl ether, and its preparation as described above affords further direct proof of Yabuta's constitution of kojic acid. On treatment with diazomethane both the nitrogen atom and the carboxyl group were methylated.

Owing to the failure to reduce the pyridone ring directly an attempt was made to obtain the corresponding tertiary alcohol by the Grignard reaction, methyl iodide and bromobenzene both being used. Addition compounds of a flesh-pink colour were formed, but their decomposition by water, dilute acid, or saturated ammonium chloride solution merely regenerated the initial material. Borsche and Bonacker (*Ber.*, 1921, **54**, 2678) had a similar experience with *N*-phenyl-4-pyridone. Their substance was, however, readily reduced to the hexahydro-alcohol by means of sodium and boiling ethyl alcohol.

As Braun, Braunsdorf, and Räth (*Ber.*, 1922, **55**, 1666) have shown that the most efficient local anæsthetics are obtained when the alcoholic group for esterification is in the γ-position to the nitrogen atom, an attempt was made to convert the hydroxymethyl group of kojic acid into a β-hydroxyethyl group through the chloromethyl and the cyanomethyl compound. The chloromethyl compound, although readily formed in good yield, appeared, however, to be completely resinified by boiling with aqueous-alcoholic potassium cyanide.

As a fully reduced base with an alcoholic group could not be produced, an attempt was made, but without success, to form a benzoyl ester by the interaction of potassium and silver benzoate with the product of the action of phosphorus pentachloride on 5-methoxy-2-methoxymethyl-*N*-methyl-4-pyridone.

Petrenko-Kritschenko and Plotnikoff (*Ber.*, 1897, **30**, 2801) obtained dibenzalacetone by boiling 2 : 6-diphenyltetrahydro-γ-pyrone in alcohol faintly acidified with hydrochloric acid. An attempt was accordingly made to obtain a piperidone derivative by applying this reaction to hydrogenated 5-methoxy-2-hydroxymethyl-γ-pyrone, followed by addition of methylamine with ring closure. The products were, however, syrups devoid of basic properties.

The experiments on the hydrogenation of kojic acid and its derivatives were, however, of interest. In the literature two references to the hydrogenation of kojic acid itself were found (Traetta-Mosca, *Ann. Chim. Applicata*, 1914, **1**, 477; *Z. physiol. Chem.*, 1924, **132**, 104). In the former an absorption of the equivalent of only four atoms of hydrogen is stated to have been observed, and in the latter an absorption of six atoms. In neither case, however, is an analysis of the product given. We found that kojic acid, its methyl ethers, and its diacetyl derivatives were all hydrogenated readily in the presence of colloidal palladium. In the case of kojic acid and its methyl ethers an absorption of the equivalent of six atoms of hydrogen was measured. The analysis, however, of the hydrogenation product of kojic acid itself showed the fixation of only four atoms of hydrogen. Much reliance, however, cannot be placed on these figures, as the substance was only purified by treatment with decolorising charcoal (norite), since it showed signs of decomposition on distillation even at a pressure of 1 mm. of mercury. The hydrogenation product obtained from the dimethyl ether of kojic acid was prepared on several different occasions, but the analytical figures obtained, although agreeing very closely with each other, consistently gave a carbon figure agreeing with a hexahydro-derivative and a hydrogen figure agreeing with a tetrahydro-derivative. The results are difficult to explain on any other grounds than that the product was actually a mixture. Demethylation had not taken place, as further methylation with methyl iodide and dry silver oxide left the analysis figures unchanged and the methoxy-content (Zeisel) was only 2% below the theoretical value. The material slowly yielded a crystalline phenylhydrazone : this would seem to indicate the presence of the tetrahydro-derivative (ketonic), although there is just the possibility of the phenylhydrazine having produced a ketone by oxidation of a secondary alcoholic group.

When the diacetyl derivative of kojic acid was hydrogenated, ten atoms of hydrogen were apparently taken up. The product was distilled under reduced pressure and was obviously a mixture, as it tended to yield three distinct fractions. From the two higher-boiling fractions, on treatment with phenylhydrazine, a phenylhydrazone, $C_{20}H_{22}O_3N_4$, was obtained, m. p. 207°, for which the constitution (VII) is tentatively put forward.

It was not found possible to hydrogenate the mono- or the dibenzoyl derivative of kojic acid under the conditions employed with kojic acid and its methyl and acetyl derivatives.

EXPERIMENTAL.

5-Methoxy-2-hydroxymethyl-γ-pyrone.—Dry, finely powdered kojic acid was slowly added to an ethereal solution of diazomethane (slightly more than 1 equiv.). The precipitate obtained, which gave no coloration with ferric chloride, was recrystallised from methyl alcohol (yield, almost quantitative) and then from ether–ethyl alcohol, forming colourless needles, m. p. 165° (Found: C, 53·8; H, 5·4; OMe, 18·9. $C_7H_8O_4$ requires C, 53·8; H, 5·1; OMe, 19·8%). *5-Methoxy-2-hydroxymethyl-γ-pyrone* is moderately readily soluble in water, alcohol, and acetic acid, but dissolves only to a very slight extent in other organic solvents.

5-Methoxy-2-methoxymethyl-γ-pyrone.—To a solution of 6 g. of 5-methoxy-2-hydroxymethyl-γ-pyrone in 50 c.c. of hot methyl alcohol under reflux, 10 g. of dry, finely powdered silver oxide and 12·5 g. of methyl iodide were added. When the vigorous reaction had subsided, the same weights of silver oxide and methyl iodide were again added. When all action had ceased, the liquid was boiled gently during 20 minutes. The solution was filtered from the silver iodide, and the latter repeatedly extracted with small quantities of hot methyl alcohol. The combined extracts, after treatment in the cold with decolorising charcoal (darkol), were evaporated to dryness and the residual mass of somewhat oily crystals was taken up in dry ether. On concentration of the ethereal solution the dimethoxy-derivative was obtained (yield, more than 90%) as colourless platelets, m. p. 89—90° (Found: OMe, 35·6. Calc. for $C_8H_{10}O_4$: OMe, 36·9%), moderately easily soluble in boiling ether, light petroleum and benzene and readily soluble in cold water, alcohol, and chloroform. The colourless crystals soon became pale yellow on keeping and the solutions in water and alcohol of even the colourless crystals were yellow.

5-Methoxy-2-methoxymethyl-1-methyl-4-pyridone.—Dry monomethylamine was passed into a cooled solution of 5 g. of 5-methoxy-2-methoxymethyl-γ-pyrone in 15 c.c. of methyl alcohol until the weight had increased by 5 g. After an hour the alcohol and most of the methylamine were evaporated in the cold by means of a pump. The residual dark oily crystals were kept over-night over concentrated sulphuric acid in an evacuated desiccator and were then washed with a very little ice-cold acetone. The *pyridone*, thus obtained almost colourless (yield, over 80%), distilled at 265—270°/15 mm. with considerable charring (pressures of about 1 mm. are to be recommended) and set to a hard mass, m. p. 113°. This crystallised from toluene, in which it was very sparingly soluble, in small silky needles, m. p. 57°, on slow cooling (the substance has a great tendency to come down on cooling as an oil which later solidifies as a hard skin). In an evacuated desiccator over concentrated sulphuric acid, the crystals lost three molecules of water of crystallisation; the fine anhydrous powder melted at 113° (Found: H_2O, 23·0; C, 59·1; H, 7·4; N, 7·7; OMe, 32·5. $C_9H_{13}O_3N,3H_2O$ requires H_2O, 22·8; C, 59·0; H, 7·1; N, 7·6; OMe, 33·9%). This substance is very readily soluble in water, alcohol, chloroform, and pyridine, and slightly soluble in ether, benzene, and light petroleum. Its aqueous solution gives a yellow coloration with a drop of ferric chloride. It forms a picrate which, after recrystallisation from hot water, melts at 191°. When the anhydrous base was boiled with dry methyl iodide during several hours, a crystalline *methiodide* was obtained which rapidly turned brown on exposure to light. It melted at 116—118° with evolution of gas bubbles (Found: I, 38·9. $C_{10}H_{16}O_3NI$ requires I, 39·1%).

5-*Methoxy*-2-*hydroxymethyl*-1-*methyl*-4-*pyridone*.—A rapid stream of dry monomethylamine was passed into a warm methyl-alcoholic solution of 5-methoxy-2-hydroxymethyl-γ-pyrone (4 g. in 45 c.c.) until on cooling no precipitate formed. After standing at room temperature for an hour, the solution was evaporated, on the water-bath until crystals began to form, and then to dryness in a vacuum desiccator. The *product* on recrystallisation from methyl alcohol, after treatment with charcoal, consisted of 3·1 g. of almost colourless needles, m. p. 203—204° (Found: C, 56·9; H, 6·8; N, 8·4. $C_8H_{11}O_3N$ requires C, 56·8; H, 6·5; N, 8·3%). It was readily soluble in alcohol, water, or acetic acid, but only very slightly soluble in other organic solvents.

5-*Methoxy*-2-*hydroxymethyl*-4-*pyridone*. — This was prepared (yield, over 90%) by heating 5-methoxy-2-hydroxymethyl-γ-pyrone with 125% of its weight of aqueous ammonia (*d* 0·88) in a sealed tube at 90° for about 2 hours. The product, consisting of crystals and a dark liquid, was submitted to filtration, and the filtrate concentrated almost to dryness. The residue was dissolved in methyl alcohol and treated with charcoal. On concentration and cooling, the *pyridone* separated in fine, almost colourless, rectangular prisms, which were dried in an evacuated desiccator over sulphuric acid for 15 hours. They lost water of crystallisation at 120° in a capillary tube and finally melted at 173—175° (Found: C, 48·9; H, 6·6. $C_7H_9O_3N,H_2O$ requires C, 48·6; H, 6·4%). With ferric chloride solution, the pyridone gave an orange coloration. The picrate is readily recrystallised from hot water and melts at 181—182°.

Action of Concentrated Nitric Acid on 5-*Methoxy*-2-*hydroxymethyl*-4-*pyridone*. *Methyl Ether of Comenamic Acid* (5-*Methoxy*-4-*pyridone*-2-*carboxylic Acid*).—A solution of 2 g. of 5-methoxy-2-hydroxymethyl-4-pyridone in 10 c.c. of nitric acid (*d* 1·42) and 2 c.c. of nitric acid (*d* 1·5) was kept at room temperature for several days. A small crystalline precipitate separated. The mother-liquor was diluted with water (80 c.c.) and evaporated slowly on a sand-bath, water being frequently added to keep the acid dilute; about 1·7 g. of a white crystalline product were thus obtained, m. p. 236—237° (decomp.) after recrystallisation from dilute nitric acid. It turned yellow in air and was strongly acid to litmus [Found by titration with *N*/10-caustic soda and phenolphthalein: equiv., 117·5. *Comenamic acid methyl ether nitrate* ($C_7H_7O_4N,HNO_3$) requires equiv., 116]. The free acid, liberated by caustic soda as a curdy white precipitate, crystallised from hot water in spore-like clusters of microscopic needles, m. p. 267° with evolution of gas when heated quickly (Found after drying over sulphuric acid in a desiccator: equiv., 173·3. Calc. for $C_7H_7O_4N$: equiv., 169). It retained traces of water persistently and tended to give off carbon monoxide when heated at 120° in a vacuum (Found in material dried over phosphoric oxide: C, 49·3; H, 4·4; N, 8·1. Calc. for $C_7H_7O_4N$: C, 49·7; H, 4·1; N, 8·3%). Yabuta (*loc. cit.*, 1924) gives m. p. 269°. The picrate, crystallised from hot water, had m. p. 225° (decomp.).

In the hope that the methyl ester would give more conclusive results an ethereal solution of diazomethane was added to the acid, suspended in ether, until effervescence ceased. The white gummy product, recrystallised from ethyl alcohol, gave almost white, somewhat soft crystals which rapidly turned yellow on keeping and had a pleasant smell reminiscent of new-mown hay. When heated slowly in a capillary tube, they softened at 94° and melted at 134° to a crimson liquid. Analysis showed that both the nitrogen atom and the carboxyl group had been methylated (Found in material dried for 3 weeks over phosphoric oxide: C, 54·5; H, 5·9. $C_9H_{11}O_4N$ requires C, 54·8; H, 5·6%).

This *ester* forms a picrate, m. p. 205—207°, readily crystallisable from hot ethyl alcohol.

5-*Methoxy*-1 : 2-*dimethyl*-4-*pyridone*.—To a solution of 5-methoxy-2-methoxymethyl-1-methyl-4-pyridone (3 g.) in water (60 c.c.), mechanically stirred and kept cold in running water, sodium amalgam (120 g. of 3%) was added during 4 hours, the solution being kept faintly acid by the gradual addition of hydrochloric acid (10%). The colourless solution was decanted from the mercury and filtered, and the product precipitated by the addition of finely powdered sodium hydroxide to small quantities of the solution at a time with cooling and stirring. The fine colourless needles thus obtained were dried on a porous tile and then over sulphuric acid. They were separated from traces of alkali by solution in hot acetone. The hydrated base was precipitated from the acetone solution by addition of a few drops of water. It melted at 95°, readily lost three molecules of water over concentrated sulphuric acid in a vacuum, and when anhydrous melted at 150° (Found : H_2O, 26·3 ; C, 62·7 ; H, 7·3 ; N, 9·1. Calc. for $C_8H_{11}O_2N,3H_2O$: H_2O, 26·1 ; C, 62·7 ; H, 7·2 ; N, 9·15%). This substance is only slightly soluble in the usual solvents with the exception of water, alcohol and acetone. It gives a deep yellow colour with aqueous ferric chloride, and forms a picrate, m. p. 208° after recrystallisation from water, and a hydrochloride, m. p. 216—217°.

By an exactly similar process of reduction and isolation the same substance was prepared from 5-methoxy-2-hydroxymethyl-1-methyl-4-pyridone (m. p. and mixed m. p. of the hydrated and the anhydrous form). It appears to be identical with the substance described by Yabuta (*loc. cit.*).

5-*Hydroxy*-1 : 2-*dimethyl*-4-*pyridone*.—A boiling solution of 5-methoxy-1 : 2-dimethyl-4-pyridone (3 g.) in amyl alcohol was gradually treated with sodium (10·5 g.). The hydrochloride of the base was isolated in the usual way, and from it 1·8 g. of unchanged base were obtained by decomposition with sodium hydroxide. The alkaline mother-liquor was made faintly acid with dilute hydrochloric acid and evaporated to dryness. An alcoholic extract of the dried residue gave on evaporation a new hydrochloride which quickly turned brown in the air ; m. p. 236—238° (decomp.). This was decomposed with aqueous ammonia. The solution became acid on evaporation, and gave an intense purple coloration with ferric chloride, indicating demethylation of the 5-methoxy-group. The substance (0·8 g.) was recrystallised from acetone containing 5% of alcohol and formed faintly pink, prismatic crystals, m. p. 273—274° after darkening at 250° and sintering at 263°. A Zeisel determination showed that no methoxyl group was present (Found : C, 60·6 ; H, 6·8 ; N, 9·9. $C_7H_9O_2N$ requires C, 60·5 ; H, 6·5 ; N, 10·1%). The copper salt formed pale green platelets.

Hydrogenation Products of Kojic Acid.—The apparatus used for hydrogenation was an all-glass model of that described by Franck (*Chem.-Ztg.*, 1913, **37**, 958).

Hydrogenation of kojic acid. A solution of 1·42 g. of kojic acid in 10 c.c. of water was mixed with 5 c.c. of 1% gum arabic solution, 5 c.c. of 1% palladous chloride solution, and 20 c.c. of methyl alcohol and shaken in the presence of electrolytic hydrogen under a pressure of 2 atmospheres. In 35 minutes, 650 c.c. of hydrogen were absorbed (calc. for the addition of 6 hydrogen atoms, 672 c.c.). This result was repeatedly confirmed and tested against the hydrogenation of pure cinnamic acid.

The colloidal palladium was precipitated by the addition of methyl alcohol and removed, the filtrate concentrated at diminished pressure at 60°, and the syrupy residue dried over sulphuric acid in a vacuum and distilled at 1 mm. pressure. The substance did not distil readily and the temperature gradually rose to 220°. The distillate was amber-yellow and had a smell of caramel (Found after drying over phosphoric oxide for 12 hours: C, 52·1; H, 7·0%). This result agrees with neither of those required for the hexahydro- and the tetrahydro-derivative. A different sample was therefore purified only by repeated treatments with decolorising charcoal, and dried as above. It was a very viscous syrup which rapidly darkened on keeping (Found: C, 49·0; H, 7·1. The tetrahydro-derivative, $C_6H_{10}O_4$, requires C, 49·3; H, 6·9%. The hexahydro-derivative, $C_6H_{12}O_4$, requires C, 48·7; H, 8·1%).

Hydrogenation of 5-methoxy-2-methoxymethyl-γ-pyrone. The pyrone (1·3 g.) in 5 c.c. of water was mixed with 3 c.c. of 1% aqueous gum arabic, 3 c.c. of 1% aqueous palladous chloride, and 10 c.c. of methyl alcohol and shaken under 2 atmospheres pressure in presence of pure hydrogen. In 20 minutes, 538 c.c. were absorbed (calc. for 6 atoms hydrogen, 514 c.c.). The product, isolated as already described in the case of hydrogenated kojic acid, was a colourless mobile oil, b. p. 98°/1 mm. It had a sharp burning taste, was soluble in water, alcohol, ether and chloroform, and was not hygroscopic. When it was mixed with phenylhydrazine, heat developed but crystals were slow to form. After addition, however, of a little glacial acetic acid bright yellow crystals formed in the course of 24 hours; m. p. 175° after recrystallisation from absolute alcohol. An oxime or a semicarbazone could not be formed.

A satisfactory analysis of hydrogenated 5-methoxy-2-methoxymethyl-γ-pyrone was not obtained (Found: C, 54·5, 54·6, 54·5, 54·65; H, 8·2, 8·1, 8·15, 8·1. $C_8H_{14}O_4$ requires C, 55·2; H, 8·05%. $C_8H_{16}O_4$ requires C, 54·55; H, 9·1%).

The derivative was unchanged after treatment with dry silver oxide and methyl iodide and gave the same analytical figures as before (Found: OMe, 32·3. $C_8H_{14}O_4$ requires OMe, 35·6%. $C_8H_{16}O_4$ requires OMe, 35·2%). The same substance was obtained by methylation of hydrogenated kojic acid with methyl sulphate and sodium hydroxide. The fact that a hydrazone is formed might point to this being a tetrahydro-derivative, but the low carbon figure cannot be explained.

Hydrogenation products of acetylated kojic acid. To 11·3 g. of diacetyl kojic acid, dissolved in 40 c.c. of ethyl alcohol, were added 8 c.c. of 2% platinic chloride solution, 4 c.c. of 2% gum arabic, and a few drops of 0·5% palladium chloride solution along with 30 c.c. of water and the whole was shaken in the presence of electrolytic hydrogen under a pressure of 2 atmospheres. The absorption ceased after 5780 c.c. (calculated to N.T.P.) had been taken up (calc. for 10 equivs., 5634 c.c.). The product was isolated in the usual way and distilled at a pressure of 10—12 mm. Three fractions were collected, (1) b. p. 80—120° (0·8 g.), (2) b. p. 138—144° (2·6 g.), (3) b. p. 180° (1·2 g.), but the material showed no tendency to accumulate at any definite temperatures. Each of these fractions was redistilled before analysis [Found: (1) C, 57·5; H, 8·0; Ac, 26·9; (2) C, 54·5; H, 7·7; Ac, 27·4; (3) C, 53·9; H, 7·5; Ac, 29·3%].

From fraction (1) and *p*-nitrobenzoyl chloride a compound was obtained which, after recrystallisation from hot water, gradually darkened on heating and finally melted to a dark brown liquid at 112—115°. There was not sufficient of this substance for a full analysis.

Fractions (2) and (3) readily reacted with phenylhydrazine to give a derivative which crystallised from alcohol in feathery yellow needles, m. p. 207° (Found: C, 65·5, 65·5; H, 6·1, 6·1; N, 15·4. $C_{20}H_{22}O_3N_4$ requires C, 65·6; H, 6·0; N, 15·3%). The substance was apparently a diphenylhydrazone or an osazone (VII).

Action of Methyl-alcoholic Methylamine on Diacetyl Kojic Acid.—As the bridge oxygen atom in kojic acid itself is not readily substituted by ammonia or primary amines, but such replacement takes place smoothly with the methyl ethers, it was of interest to investigate the action of methyl-alcoholic methylamine on the diacetyl derivative. It is well known that this reagent rapidly hydrolyses esters, but there was just a possibility that the imino-group would simultaneously be introduced. This was not the case, however, as an almost quantitative yield of the *methylamine* salt of kojic acid was obtained, m. p. 130° after sintering at 125° (Found: C, 48·6; H, 6·4; N, 8·0. $C_7H_{11}O_4N$ requires C, 48·6; H, 6·4; N, 8·1%). The identity was further established by a mixed melting point with authentic methylamine kojate prepared from methylamine and pure kojic acid. It readily yielded kojic acid on treatment with dilute acids, and evolved methylamine with sodium hydroxide in the cold. On treatment with picric acid, methylamine picrate was obtained, m. p. and mixed m. p. 206°.

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