

## The Conversion of Kojic Acid into Comenaldehyde and Comenic Acid

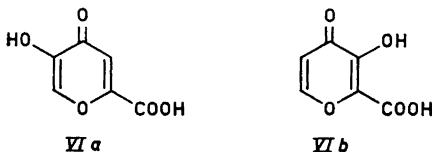
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Oxidation of kojic acid monomethylether (II) by active manganese dioxide yields a  $\gamma$ -pyrone aldehyde (III) that was demethylated by  $\text{AlCl}_3$  forming comenaldehyde (IV). The structure of comenic acid (VI) was confirmed by its preparation from kojic acid (I).

The structural relationship between kojic acid (I) and comenic acid (VI) has been established by the thorough investigations of Yabuta <sup>1,\*</sup>

The structure of kojic acid as 2-hydroxymethyl-5-hydroxy- $\gamma$ -pyrone has been recently confirmed by its conversion into 5-hydroxypicolinic acid by Heyns and Vogelsang <sup>3</sup>. Examination of the correctness of structure I had become necessary since Belonosov <sup>4</sup> had brought forward evidence that favored structure VIb for comenic acid, and the correctness of the structure of kojic acid depended on the correctness of the structure of comenic acid proposed as VIa by Peratoner and co-workers <sup>5,6</sup>.



The purpose of this research was to prepare unknown  $\gamma$ -pyrone aldehydes and to confirm the structure of comenic acid by its preparation from kojic acid. Several attempts had been made to prepare the aldehyde of kojic acid (IV, comenaldehyde) by either reduction of comenic acid derivatives <sup>7</sup> or direct oxidation <sup>8</sup> of kojic acid by mild oxidizing reagents as nitrosodimethylaniline, phenylhydroxylamine sulfonic acid,  $\text{H}_2\text{O}_2$  and  $\text{FeSO}_4$ , and methylene-blue and sunlight. The unknown comenaldehyde had not been obtained.

\* Kojic acid has been reviewed by A. Beélik <sup>2</sup>.

Also the conversion of kojic acid or its derivatives into comenic acid had not been successful. By direct catalytic oxidation kojic acid was destroyed and only traces of comenic acid could be detected by paper chromatography<sup>3</sup>.

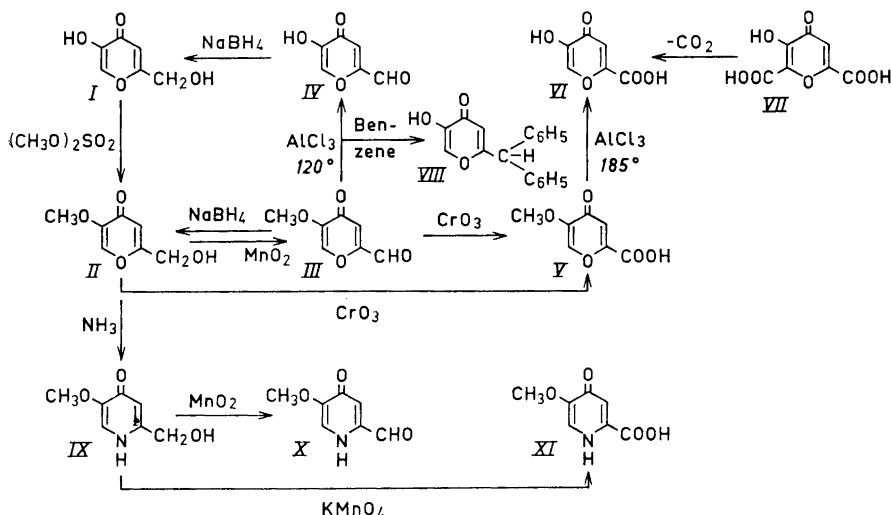
When we used active manganese dioxide for the oxidation of kojic acid in dioxane at room temperature the starting material was recovered unchanged. Oxidation in boiling dioxane only decreased the amount of starting material that could be recovered. Probably ring cleavage and degradation occurred since similar degradation reactions of ketols and glycols in boiling solvents in the presence of manganese dioxide have been described<sup>9</sup>.

The methyl ether of kojic acid (II, 2-hydroxymethyl-5-methoxy- $\gamma$ -pyrone), however, could be oxidized by manganese dioxide forming 2-formyl-5-methoxy- $\gamma$ -pyrone (III) in good yield<sup>10</sup>. All other attempts to prepare formyl substituted  $\gamma$ -pyrones by oxidation of the hydroxymethyl or methyl side chain have been unsuccessful<sup>11</sup>. The oxidation of II by manganese dioxide was carried out in boiling benzene or dioxane. Acetone otherwise successfully applied as solvent for oxidations with manganese dioxide<sup>12</sup> could not be used in the present case because the reaction product was adsorbed very strongly.

The presence of a formyl group in III was indicated unequivocally by the appearance of a strong C=O band at  $1705\text{ cm}^{-1}$  in the IR spectrum. The region between  $6.0$  and  $6.3\ \mu$  is characteristic for the  $\gamma$ -pyrone system<sup>13</sup>, and the C=O absorption of the  $\gamma$ -pyrone group in the compounds investigated (I–VI) was never found to be at higher frequencies than  $1670\text{ cm}^{-1}$ .

When III was treated with phenylhydrazine under mild conditions, a phenylhydrazone (m.p.  $205\text{--}206^\circ\text{C}$ ) was formed. The N-analysis of the product indicates that probably no further reactions of the hydrazine group and the  $\gamma$ -pyrone ring as studied by Thomas and Marxer<sup>14</sup> occurred under these conditions.

When III was oxidized in acetone by  $\text{CrO}_3/\text{H}_2\text{SO}_4$ , comenic acid methyl-ether (V) was formed immediately. The oxidation by  $\text{CrO}_3/\text{H}_2\text{SO}_4$  in acetone



was found to be a very convenient method for the preparation of V directly from kojic acid methylether (II).

The  $\gamma$ -pyrone ring system itself is reduced by  $\text{LiAlH}_4^{15}$  but the  $\gamma$ -pyrone aldehyde III was reduced selectively by  $\text{NaBH}_4$  in ethanol solution, forming 2-hydroxymethyl-5-methoxy- $\gamma$ -pyrone (II).

While all earlier attempts to prepare comenaldehyde (IV) had been unsuccessful the demethylation of III by  $\text{AlCl}_3$  without a solvent at  $120^\circ\text{C}$  yielded IV<sup>10</sup>. As with the  $\gamma$ -pyrone aldehyde III, the presence of a formyl group in comenaldehyde (IV) was indicated by IR spectroscopy by the appearance of a strong  $\text{C}=\text{O}$  band at  $1718\text{ cm}^{-1}$ . Treatment of IV with  $\text{NaBH}_4$  in ethanol solution did not affect the  $\gamma$ -pyrone group but yielded kojic acid by selective reduction. The presence of the OH group in IV was shown by absorption in the IR spectrum at  $3230\text{ cm}^{-1}$  and its enolic character was demonstrated by an intense red color reaction with  $\text{FeCl}_3$  in ethanol.

The UV spectra of the new  $\gamma$ -pyrone aldehydes were very similar to the corresponding alcohols (Table 1) and other 2,5 disubstituted  $\gamma$ -pyrones<sup>16,17</sup>.

Demethylation of III with  $\text{AlCl}_3$  in boiling benzene gave a solid compound that probably has the structure of 2-(diphenylmethyl)-5-hydroxy- $\gamma$ -pyrone (VIII), since this structure is supported by C,H-analysis, IR-spectrum and its red color reaction with  $\text{FeCl}_3$ . The analogous reaction of benzaldehyde in benzene solution in the presence of  $\text{AlCl}_3$  to form triphenylmethane has been reported earlier<sup>18</sup>.

In an attempt to demethylate comenic acid methylether by heating with pyridinium chloride at  $185^\circ$  for 2 h, only decomposition products were obtained. Attempted demethylation by  $\text{AlCl}_3$  at  $120-140^\circ\text{C}$  for 4 h without a solvent was unsuccessful. The starting material was recovered unchanged (90 %). Finally demethylation was achieved by heating V together with  $\text{AlCl}_3$  in a sealed tube at  $185^\circ\text{C}$ ; comenic acid (VI) was obtained in about 50 % yield. The identity was also proved by comparison of the UV and IR spectra of a sample of comenic acid obtained by decarboxylation of meconic acid (VII).

The present investigation was also extended to a  $\gamma$ -pyridone alcohol. Earlier described oxidations of 2-hydroxymethyl-5-methoxy- $\gamma$ -pyridone (IX) by aqueous  $\text{KMnO}_4^{19}$  or nitric acid<sup>20</sup> had resulted in the formation of comenaminic acid methylether (XI) but a  $\gamma$ -pyridone aldehyde had not been obtained. Application of active manganese dioxide in boiling dioxane, however, yielded 2-formyl-5-methoxy- $\gamma$ -pyridone (X). Formation of the formyl group in X was supported by the appearance of a strong  $\text{C}=\text{O}$  band in the IR spectrum

Table 1. UV-Spectra of  $\gamma$ -pyrones (in Methanol).

$\gamma$ -Pyrone	$\lambda_{\text{max}}^1$ (in $\text{m}\mu$ )	$\lambda_{\text{max}}^2$
Kojic acid (I)	218; $\epsilon = 1.2 \times 10^4$	269; $\epsilon = 8 \times 10^3$
Comenaldehyde (IV)	218; $1.3 \times 10^4$	272; $7 \times 10^3$
2-Hydroxymethyl-5-methoxy- $\gamma$ -pyrone (II)	216; $1.2 \times 10^4$	266; $9 \times 10^3$
2-Formyl-5-methoxy- $\gamma$ -pyrone (III)	216; $1.3 \times 10^4$	268; $9 \times 10^3$

at  $1708\text{ cm}^{-1}$ . The 2-formyl-5-hydroxy- $\gamma$ -pyridone (2-formyl-4,5-dihydroxy-pyridine) that could not be obtained by reduction<sup>21</sup> of comenaminic acid might now be available by demethylation of X.

*Added in proof.* In a recent publication [*J. Org. Chem.* **26** (1961) 2588] it has been claimed that the oxidation of kojic acid by chloranil in boiling ethanol yields a 6,6'-bipyron. However, the UV spectrum of this product is identical with that of kojic acid as reported earlier<sup>17</sup> and as found in the present work. Since the IR spectrum is also identical with that of kojic acid no evidence for a 6,6'-bipyron would be apparent.

### EXPERIMENTAL

The IR spectra were taken in KBr pellets on a Perkin Elmer model 21 instrument with the technical assistance of Ing. C. B. Skarstedt. The UV spectra were measured with a Cary Recording Spectrophotometer Model 11 MS. The microanalyses were carried out by Dr. O. Pfundt, Göttingen (Germany).

*Kojic acid (I)* was purchased from Fa. Th. Schuchardt, München (Germany), *Meconic acid (VII)* from K and K Laboratories, Jamaica, N. Y. (USA).

*Kojic acid monomethylether (II)* was prepared by the method described by Campbell, Ackerman and Campbell<sup>22</sup>. For the preparation of 2-hydroxymethyl-5-methoxy- $\gamma$ -pyridone (*IX*) the method described by Armit and Nolan<sup>20</sup> was applied. *Comenic acid (VI)* was prepared by decarboxylation of meconic acid (*VII*) according to Meyer<sup>23</sup>.

*Active manganese dioxide* was prepared by the method of Attenburrow *et al.*<sup>24</sup>

*2-Formyl-5-methoxy- $\gamma$ -pyrone (III)*. 600 mg of 2-hydroxymethyl-5-methoxy- $\gamma$ -pyrone were dissolved in 1000 ml of boiling benzene; 6 g of manganese dioxide were added and the mixture was refluxed for one hour. The solution was filtered and the  $\text{MnO}_2$  was washed with *ca.* 300 ml of benzene. From the filtered solution most of the benzene was removed by distillation, the rest of benzene (*ca.* 100 ml) was evaporated *in vacuo* at room temperature. Residue, colorless needles of *III*. Yield 410 mg (70 %), m.p.  $202^\circ\text{C}$  (sealed tube). Purification of *III* by sublimation at 12 mm/ $120^\circ\text{C}$ . (Found: C 54.75; H 3.91. Calc. for  $\text{C}_8\text{H}_6\text{O}_4$ : C 54.55; H 3.92).

*Reduction of III by NaBH<sub>4</sub>*. 100 mg of *III* and 70 mg of  $\text{NaBH}_4$  were dissolved in 50 ml of ethanol (95 %) and shaken for 18 h. Then 30 ml of water were added and the solution was extracted with 100 ml of chloroform. The chloroform solution was dried over  $\text{Na}_2\text{SO}_4$ , filtered and evaporated *in vacuo*. Yield 70 mg of *II* (70 %), m.p.  $161^\circ\text{C}$ , IR spectrum identical with authentic sample of *II*.

*Comenaldehyde (IV)*. 154 mg of *III* were mixed with 200 mg of sublimed  $\text{AlCl}_3$  and heated at  $120^\circ\text{C}$  for 3 h. The reaction mixture was decomposed by addition of 5 ml of HCl (10 %), and the aqueous solution was extracted continuously with ether for 14 h. The ether solution was evaporated *in vacuo*, yielding 130 mg (93 %) of yellowish crystals of *IV*. Recrystallization from boiling  $\text{CHCl}_3$  with addition of charcoal gave colorless crystals. The substance can be sublimed at  $100^\circ\text{C}/0.1\text{ mm}$ . M.p.  $162\text{--}163^\circ\text{C}$  (after drying *in vacuo* at  $10^{-2}\text{ mm}$ ). (Found: C 51.48; H 2.96. Calc. for  $\text{C}_8\text{H}_4\text{O}_4$ : C 51.44; H 2.88).

*Reduction of IV by NaBH<sub>4</sub>*. 15 mg of *IV* were dissolved in 5 ml of ethanol and 10 mg of  $\text{NaBH}_4$  in 1 ml of ethanol were added. After 3 h shaking 2 ml of HCl (10 %) were added and the solution was extracted continuously with ether for 15 h. The ether was removed *in vacuo*, and to the aqueous residue 15 ml of abs. ethanol were added. After evaporation *in vacuo* kojic acid (14 mg) crystallized. M.p.  $152^\circ\text{C}$ , IR spectrum identical with authentic sample of *I*.

*Comenic acid methyl ether (V), (a) from III*. 150 mg of *III* were suspended in 5 ml of acetone, and 1.3 ml of  $\text{CrO}_3/\text{H}_2\text{SO}_4$  solution prepared according to Bowden *et al.*<sup>25</sup> were added. The colorless solution turned green immediately and *V* precipitated. After 30 min 150 mg of *V* were isolated (90 %). M.p.  $282^\circ\text{C}$  (after recrystallization from  $\text{C}_2\text{H}_5\text{OH}/\text{H}_2\text{O}$ ). (Found: C 49.97; H 3.60. Calc. for  $\text{C}_7\text{H}_6\text{O}_5$ : C 49.42; H 3.56).

*(b) V from II*. 150 mg of *II* were dissolved in 5 ml of acetone and 3.5 ml of  $\text{CrO}_3/\text{H}_2\text{SO}_4$  solution<sup>25</sup> were added. After 24 h 120 mg (73 %) of *V* were isolated by filtration. M.p.  $282^\circ\text{C}$ , IR spectrum identical with *V* obtained from *III*.

*Comenic acid (VI)*. 150 mg of V and 250 mg of sublimed  $\text{AlCl}_3$  were mixed and heated in a sealed tube at  $185^\circ\text{C}$  for 4 1/2 h. The reaction product was decomposed with 5 ml of HCl (10 %) and the precipitate (70 mg) was recrystallized from boiling ethanol in presence of charcoal. M.p.  $285^\circ\text{C}$  (decomp.). The identity with comenic acid was proved by comparison with the IR and UV spectra \* of an authentic sample obtained by decarboxylation of meconic acid (VII).

*2-(Diphenylmethyl)-5-hydroxy- $\gamma$ -pyrone (VIII)*. 100 mg of III were dissolved in 200 ml of benzene, 500 mg of  $\text{AlCl}_3$  (subl.) were added, and the solution was refluxed for 45 h. The yellowish cloudy solution was evaporated, and the oily residue was decomposed by addition of 35 ml of  $\text{H}_2\text{O}$  and 4 ml of HCl (conc). This solution was extracted continuously with ether for 24 h. The ether solution was dried over  $\text{Na}_2\text{SO}_4$  and evaporated. The yellow oil crystallized (refrigerator) after addition of a few drops of ether. The crystalline product was recrystallized from benzene and decolorized by charcoal. Yield 72 mg of VIII. After sublimation at 0.1 mm/ $135^\circ\text{C}$  colorless crystals. M.p.  $150-152^\circ\text{C}$ . (Found: C 77.24; H 5.17. Calc. for  $\text{C}_{18}\text{H}_{14}\text{O}_3$ : C 77.68; H 5.07).

*2-Formyl-5-methoxy- $\gamma$ -pyridone (X)*. 50 mg of IX were dissolved in 50 ml of boiling dioxane, 500 mg of  $\text{MnO}_2$  were added and the mixture was refluxed for 90 min. The mixture was filtered and the  $\text{MnO}_2$  was washed with 30 ml of warm dioxane. From the filtrate the dioxane was removed *in vacuo* and an almost colorless crystalline residue was obtained (pyridine-like odor). M.p.  $176-178^\circ\text{C}$ , after sublimation at 0.1 mm/ $100^\circ\text{C}$ . (Found: C 54.58; H 4.69. Calc. for  $\text{C}_7\text{H}_7\text{NO}_3$ : C 54.90; H 4.61).

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\*  $\lambda_{\text{max}}^1$  223  $\mu\text{m}$ ;  $\lambda_{\text{max}}^2$  284  $\mu\text{m}$  ( $\text{H}_2\text{O}$ ). Reported <sup>16</sup>, 224; 290  $\mu\text{m}$ .