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Original Scientific Paper

**Studies on 4-Pyrones and 4-Pyridones. III.\***  
**The Preparation of Some New 5-Hydroxy-1-aryl-4-pyridone-2-**  
**-carboxylic Acids and Related Compounds**

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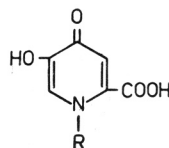
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By condensation of meconic acid with 4-chloroaniline, 4-bromoaniline, 3-nitroaniline and 1-naphthylamine, hitherto undescribed 5-hydroxy-1-aryl-4-pyridone-2-carboxylic acids (I—IV) have been prepared. Decarboxylation of the acids yielded several new 5-hydroxy-1-aryl-4-pyridones (V—VII). Esterification of I—IV, as well as of two earlier reported analogous acids<sup>1</sup> led to the formation of the corresponding esters (VIII—XIV) in good yield.

In the first paper of this series<sup>1</sup> it has been shown that by condensation of meconic acid (3-hydroxy-4-pyrone-2,6-dicarboxylic acid), comenic acid (5-hydroxy-4-pyrone-2-carboxylic acid), or comenic acid methyl ether with simple primary aromatic amines (aniline, *o*-, *m*-, or *p*-toluidine), the corresponding 5-hydroxy-1-aryl-4-pyridone-2-carboxylic acids, or their methyl ethers, can be prepared in a satisfactory manner.

Extending our work in this field, we prepared a number of analogous, hitherto undescribed, hydroxypyridone carboxylic acids having a halogen-

TABLE I  
 5-Hydroxy-1-aryl-4-pyridone-2-carboxylic Acids



No.	R	M. p. (° C)
I	4-Cl · C <sub>6</sub> H <sub>4</sub> (monohydrate)	236
II	4-Br · C <sub>6</sub> H <sub>4</sub> (monohydrate)	192—193
III	3-NO <sub>2</sub> · C <sub>6</sub> H <sub>4</sub>	256—257
IV	1-C <sub>10</sub> H <sub>7</sub>	203

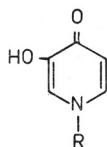
\* Part II. S. Kukolja and V. Hahn, *Croat. Chem. Acta* 33 (1961) 229.

\*\* Part of the Thesis of K. Blažević, presented to the University of Zagreb, 1964, in partial fulfilment of the requirements for the degree of Doctor of Chemistry (Ph. D.)

or nitro-substituted phenyl group, or an aryl group different from phenyl, in position 1, such compounds being of interest for further investigations.

Condensation of meconic acid with 4-chloroaniline, 4-bromoaniline, 3-nitroaniline and 1-naphthylamine respectively, carried out in the way described earlier,<sup>1</sup> led to the formation of the acids I—IV (Table I) with satisfactory yields (61—78% of crude product). After reprecipitation *via* the sodium salt and following crystallization from aqueous acetic acid the pure acids were obtained as almost colorless substances (I and II crystallizing with 1 mole of water), slightly soluble in water and in polar organic solvents.

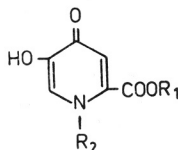
TABLE II  
3-Hydroxy-1-aryl-4-pyridones



No.	R	M. p. (° C)
V	4-Cl · C <sub>6</sub> H <sub>4</sub>	236—237
VI	4-Br · C <sub>6</sub> H <sub>4</sub>	247—248
VII	1-C <sub>10</sub> H <sub>7</sub>	216—217

When heated above the melting point, the acids I—IV decomposed with decarboxylation. From I, II and IV the corresponding 3-hydroxy-1-aryl-4-pyridones (V—VII) have been obtained in an average yield of about 80%. In the pure state these are colorless well crystallized substances having relatively high melting points. From III no well defined product of decarboxylation could be obtained.

TABLE III  
Esters of 5-Hydroxy-1-aryl-4-pyridone-2-carboxylic Acids



No.	R <sub>1</sub>	R <sub>2</sub>	M. p. (° C)
VIII	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	197—198
IX	C <sub>2</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	177—178
X	C <sub>2</sub> H <sub>5</sub>	4-CH <sub>3</sub> · C <sub>6</sub> H <sub>4</sub>	179—181
XI	C <sub>2</sub> H <sub>5</sub>	4-Cl · C <sub>6</sub> H <sub>4</sub>	203—204
XII	C <sub>2</sub> H <sub>5</sub>	4-Br · C <sub>6</sub> H <sub>4</sub>	204—205
XIII	C <sub>2</sub> H <sub>5</sub>	3-NO <sub>2</sub> · C <sub>6</sub> H <sub>4</sub>	182—183
XIV	C <sub>2</sub> H <sub>5</sub>	1-C <sub>10</sub> H <sub>7</sub>	182—183

In the present work several esters of 5-hydroxy-1-aryl-4-pyridone-2-carboxylic acids have also been prepared. According to the best known procedure for the preparation of esters of pyridone carboxylic acids<sup>2-4</sup> or pyrone carboxylic acids,<sup>5</sup> esterification of the acids I—IV was carried out by heating with absolute alcohol, a stream of dry hydrogen chloride being bubbled through the solution. In this way the ethyl esters XI—XIV could be obtained in high yields (77—94%). Besides, the methyl (VIII) and ethyl (IX) esters of the earlier described 5-hydroxy-1-phenyl-4-pyridone-2-carboxylic acid<sup>1</sup> and the ethyl ester (X) of 5-hydroxy-1-(4-tolyl)-4-pyridone-2-carboxylic acid<sup>1</sup> have been prepared by the same method. The obtained esters, listed in Table III, are well crystallized colorless substances, easily soluble in most polar organic solvents.

All of the prepared pyridones (I—XIV) give a dark red or violet color with ferric chloride solution.

#### EXPERIMENTAL

All melting points (m. p.) are uncorrected.

The ultraviolet spectra were recorded on a Perkin-Elmer spectrophotometer model 137 UV.

#### 1. 5-Hydroxy-1-aryl-4-pyridone-2-carboxylic Acids

The acids I—IV have been prepared essentially by the method described earlier<sup>1</sup>. The original procedure has been slightly modified in the course of this work.

##### 5-Hydroxy-1-(4-chlorophenyl)-4-pyridone-2-carboxylic acid (I)

A mixture of 7.6 g. (0.038 mole) of meconic acid, 4.9 g. (0.038 mole) of 4-chloroaniline, 2.8 ml. of concd. hydrochloric acid and 70 ml. of water was refluxed at 115—120° for 5 hrs. After standing overnight at room temperature the dark brown product was filtered off and dried. There was obtained 6.57 g. (61%) of crude acid which was dissolved in a 25% solution of sodium hydrogen carbonate and reprecipitated with glacial acetic acid. Crystallization from 80 per cent acetic acid yielded almost colorless crystals of pure *monohydrate of I*, melting at 236° with decomposition.

*Anal.* C<sub>12</sub>H<sub>8</sub>ClNO<sub>4</sub> · H<sub>2</sub>O (283.68) calc'd.: C 50.81; H 3.55; N 4.94%  
found: C 50.75; H 3.69; N 5.00%

##### 5-Hydroxy-1-(4-bromophenyl)-4-pyridone-2-carboxylic acid (II)

A mixture of 10 g. (0.5 mole) of meconic acid, 8.77 g. (0.051 mole) of 4-bromoaniline, 4 ml. of concd. HCl and 75 ml. of water, treated as described above, yielded 10.95 g. (67%) of crude II. After reprecipitation followed by crystallization from aq. acetic acid almost colorless crystals of the *monohydrate of II*, m. p. 192—193° (decomp.) were obtained.

*Anal.* C<sub>12</sub>H<sub>8</sub>BrNO<sub>4</sub> · H<sub>2</sub>O (328.13) calc'd.: C 43.92; H 3.07; N 4.27%  
found: C 43.88; H 3.30; N 4.22%

##### 5-Hydroxy-1-(3-nitrophenyl)-4-pyridone-2-carboxylic acid (III)

From 11.45 g. (0.057 mole) of meconic acid, 8.10 g. (0.059 mole) of 3-nitroaniline, 4.2 ml. of concd. HCl and 75 ml. of water, 12.35 g. (78%) of crude III was obtained. Reprecipitation and crystallization from aq. acetic acid yielded colorless crystals, m. p. 256—257° (decomp.).

*Anal.* C<sub>12</sub>H<sub>8</sub>N<sub>2</sub>O<sub>6</sub> (276.21) calc'd.: C 52.18; H 2.92; N 10.14%  
found: C 52.08; H 2.87; N 10.01%

##### 5-Hydroxy-1-(1-naphthyl)-4-pyridone-2-carboxylic acid (IV)

From the mixture of 4.0 g. (0.02 mole) of meconic acid, 3.0 g. (0.021 mole) of 1-naphthylamine, 1.5 ml. of concd. HCl and 40 ml. of water, treated in the usual way,

4.15 (74%) of crude IV was obtained. After reprecipitation and crystallization from aq. acetic acid colorless crystals melting at 203° (decomp.) have been obtained.

*Anal.* C<sub>16</sub>H<sub>11</sub>NO<sub>4</sub> (281.28) calc'd.: C 68.32; H 3.94; N 4.98%  
found: C 68.05; H 3.69; N 4.98%

## 2. 3-Hydroxy-1-aryl-4-pyridones

Decarboxylation of the 5-hydroxy-1-aryl-4-pyridone-2-carboxylic acids has been carried out according to the general procedure reported earlier<sup>1</sup>. For recrystallization of the crude products dilute (aqueous) ethanol proved to be the best solvent.

### 3-Hydroxy-1-(4-chlorophenyl)-4-pyridone (V)

The product of decarboxylation of 2.28 g. (0.008 mole) of I (monohydrate) was crystallized from 80 per cent ethanol to yield 1.34 g. (75%) of V. After repeated crystallizations colorless needles melting at 236—237° were obtained. UV-spectrum:  $\lambda_{\text{max}}$  302 m $\mu$ , log  $\epsilon$  4.21.

*Anal.* C<sub>11</sub>H<sub>8</sub>ClNO<sub>2</sub> (221.65) calc'd.: C 59.61; H 3.64; N 6.32%  
found: C 59.63; H 3.72; N 6.32%

### 3-Hydroxy-1-(4-bromophenyl)-4-pyridone (VI)

After one crystallization of the crude product of decarboxylation of 2.0 g. (0.006 mole) of II (monohydrate) from 80% ethanol 1.39 g. (86%) of VI was obtained. After repeated crystallization the pure product, m. p. 247—248°, was obtained. UV-spectrum:  $\lambda_{\text{max}}$  304 m $\mu$ , log  $\epsilon$  4.09.

*Anal.* C<sub>11</sub>H<sub>8</sub>BrNO<sub>2</sub> (266.11) calc'd.: C 49.65; H 3.03; N 5.26%  
found: C 49.88; H 3.09; N 5.23%

### 3-Hydroxy-1-(1-naphthyl)-4-pyridone (VII)

Prepared from IV (4.32 g., 0.015 mole) by decarboxylation. Yield 2.87 g. (79%) of crystallized VII. The pure product was obtained after several crystallizations from 60% ethanol, m. p. 216—217°. UV-spectra:  $\lambda_{\text{max}}$  292.5 m $\mu$ , log  $\epsilon$  4.27.

*Anal.* C<sub>15</sub>H<sub>11</sub>NO<sub>2</sub> (237.27) calc'd.: C 75.93; H 4.67; N 5.90%  
found: C 75.97; H 4.70; N 5.87%

## 3. Esters of 5-Hydroxy-1-aryl-4-pyridone-2-carboxylic Acids

### General Procedure

A mixture of 0.007—0.031 mole of 5-hydroxy-1-aryl-4-pyridone-2-carboxylic acid and 10—30 ml. of absolute alcohol was refluxed on a steam bath for 3—5 hrs., during which time dry hydrogen chloride was bubbled through the solution. To the resulting clear solution, which was concentrated, if necessary, under reduced pressure to about 5—10 ml., an approximately equal volume of water was added to facilitate crystallization. After cooling the crude crystalline ester was collected and recrystallized several times from ethanol or dilute aqueous ethanol.

### 2-Carbomethoxy-5-hydroxy-1-phenyl-4-pyridone (VIII)

From the mixture of 7.7 g. (0.031 mole) of 5-hydroxy-1-phenyl-4-pyridone-2-carboxylic acid (monohydrate)<sup>1</sup> and 30 ml. of abs. ethanol, treated with dry HCl for 3 hrs., 6.6 g. (87%) of crude product, m. p. 177—179°, separated after cooling. The pure ester, obtained by recrystallization from 35% ethanol, melted at 197—198°. UV-spectrum:  $\lambda_{\text{max}}$  310.5 m $\mu$ , log  $\epsilon$  4.09.

*Anal.* C<sub>13</sub>H<sub>11</sub>NO<sub>4</sub> (245.24) calc'd.: C 63.65; H 4.52; N 5.71%  
found: C 63.50; H 4.78; N 5.96%

### 2-Carbomethoxy-5-hydroxy-1-phenyl-4-pyridone (IX)\*

The mixture of 6.75 g. (0.027 mole) of 5-hydroxy-1-phenyl-4-pyridone-2-carboxylic acid (monohydrate)<sup>1</sup> and 25 ml. of abs. ethanol, treated with dry HCl for 5 hrs.,

\* In collaboration with B. P r o h a s k a.

yielded after dilution with water 5.6 g. (80%) of crude XI. Recrystallized from ethanol the pure ester melted at 177—178°. UV-spectrum:  $\lambda_{\max}$  309 m $\mu$ , log  $\epsilon$  4.04.

*Anal.* C<sub>14</sub>H<sub>13</sub>NO<sub>4</sub> (259.26) calc'd.: C 64.86; H 5.05; N 5.40%  
found: C 65.13; H 5.09; N 5.51%

#### 2-Carbethoxy-5-hydroxy-1-(4-tolyl)-4-pyridone (X)

2.32 g. (0.0095 mole) of 5-hydroxy-1-(4-tolyl)-4-pyridone-2-carboxylic acid<sup>1</sup> and 10 ml. of abs. ethanol, treated with dry HCl for 5 hrs., yielded after dilution with water 2.41 g. (93%) of crude product. After recrystallization from ethanol crystals melting at 179—181° were obtained. UV-spectrum:  $\lambda_{\max}$  308 m $\mu$ , log  $\epsilon$  3.87.

*Anal.* C<sub>15</sub>H<sub>15</sub>NO<sub>4</sub> (273.30) calc'd.: C 65.92; H 5.53; N 5.13%  
found: C 65.72; H 5.65; N 5.07%

#### 2-Carbethoxy-5-hydroxy-1-(4-chlorophenyl)-4-pyridone (XI)

4.05 g. (0.014 mole) of 5-hydroxy-1-(4-chlorophenyl)-4-pyridone-2-carboxylic acid (I) in 25 ml. of abs. ethanol, treated in the usual way with dry HCl for 3.5 hrs., gave, after concentration under reduced pressure and dilution with water, 3.75 g. (89%) of crude ester, m. p. 190—192°. After repeated crystallization colorless crystals melting at 203—204° were obtained. UV-spectrum:  $\lambda_{\max}$  312.5 m $\mu$ , log  $\epsilon$  3.93.

*Anal.* C<sub>14</sub>H<sub>12</sub>ClNO<sub>4</sub> (293.71) calc'd.: C 57.25; H 4.12; N 4.77%  
found: C 57.28; H 4.03; N 4.81%

#### 2-Carbethoxy-5-hydroxy-1-(4-bromophenyl)-4-pyridone (XII)

From 2.55 g. (0.008 mole) of II in 15 ml. of abs. ethanol, treated with dry HCl for 3 hrs. and worked up in the same manner as in the preceding preparation, there was obtained 2.47 g. (94%) of crude product. After recrystallization from dilute alcohol, colorless crystals, m. p. 204—205°. UV-spectrum:  $\lambda_{\max}$  315 m $\mu$ , log  $\epsilon$  3.88.

*Anal.* C<sub>14</sub>H<sub>12</sub>BrNO<sub>4</sub> (338.17) calc'd.: C 49.72; H 3.58; N 4.14%  
found: C 50.23; H 3.63; N 4.23%

#### 2-Carbethoxy-5-hydroxy-1-(3-nitrophenyl)-4-pyridone (XIII)

It was prepared in the same manner as XI. From 1.95 g. (0.007 mole) of III in 15 ml. of abs. ethanol, treated with dry HCl for 3.5 hrs., 1.65 g. (77%) of crude ester was obtained. Recrystallization from ethanol gave colorless crystals, m. p. 182—183°. UV-spectrum:  $\lambda_{\max}$  315 m $\mu$ , log  $\epsilon$  4.00.

*Anal.* C<sub>14</sub>H<sub>12</sub>N<sub>2</sub>O<sub>6</sub> (304.26) calc'd.: C 55.27; H 3.98; N 9.21%  
found: C 55.65; H 3.80; N 9.37%

#### 2-Carbethoxy-5-hydroxy-1-(1-naphthyl)-4-pyridone (XIV)

From the mixture of 2.81 g. (0.010 mole) of IV and 15 ml. of abs. ethanol, treated with dry HCl for 5 hrs. and diluted with water, 2.92 g. (96%) of crude product separated. After several recrystallizations from 50% ethanol the pure ester melted at 182—183°. UV-spectrum:  $\lambda_{\max}$  293 m $\mu$ , log  $\epsilon$  4.06.

*Anal.* C<sub>18</sub>H<sub>15</sub>NO<sub>4</sub> (309.33) calc'd.: C 69.89; H 4.89; N 4.53%  
found: C 69.80; H 4.63; N 4.48%

*Acknowledgment.* The authors are indebted to Mrs. E. Galogaža, Mrs. J. Zake, and Mrs. N. Zambeli for the microanalyses, as well as to Miss M. Momčilović for the ultraviolet spectra.

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### IZVOD

#### Studije u redu 4-pirona i 4-piridona. III. Priprava nekih novih 5-hidroksi-1-aril-4-piridon-2-karbonskih kiselina i srodnih spojeva

*K. Blažević i V. Hahn*

Provedena je kondenzacija mekonske kiseline s 4-kloranilinom, 4-bromanilinom, 3-nitranilinom i 1-naftilaminom na ranije opisani način,<sup>1</sup> te su na taj način priređene u zadovoljavajućem iskorišćenju 5-hidroksi-1-aril-4-piridon-2-karbonske kiseline I—IV koje ranije nisu bile opisane. Izvršena je dekarboksilacija navedenih kiselina, pa su tako dobiveni 5-hidroksi-1-aril-4-piridoni V—VII. Esterifikacijom kiselina I—IV kao i analogno građenih, ranije opisanih kiselina: 5-hidroksi-1-fenil-4-piridon-2-karbonske i 5-hidroksi-1-(4-tolil)-4-piridon-2-karbonske kiseline,<sup>1</sup> pripremljeni su odgovarajući esteri VIII—XIV u dobrom iskorišćenju.

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