

CCA-224

547.812.5:547.823.07

Studies on 4-Pyrones and 4-Pyridones. I. The Preparation of 1-Aryl-3-hydroxy-4-pyridones and Related Compounds

V. Hahn and S. Kukulja*

Laboratory of Organic Chemistry, Faculty of Technology,
University of Zagreb, Zagreb, Croatia, Yugoslavia

Received October 26, 1961

By condensation of meconic acid, comenic acid, or comenic acid methyl ether with primary aromatic amines, 1-aryl-5-hydroxy-4-pyridone-2-carboxylic acids, or their methyl ethers, were obtained with satisfactory yields. Decarboxylation of the acids yielded 1-aryl-3-hydroxy-4-pyridones or the corresponding 1-aryl-3-methoxy-4-pyridones.

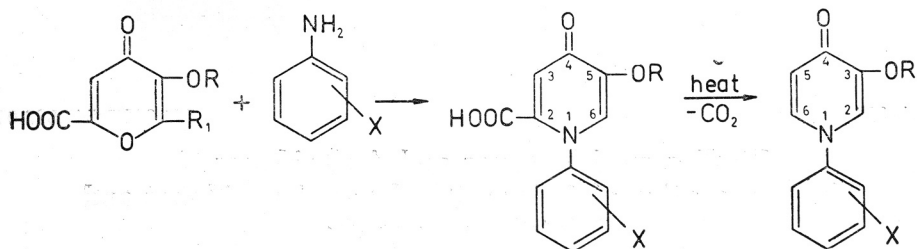
In the endeavour to prepare a number of 1-aryl-3-hydroxy-4-pyridones and the corresponding methyl ethers, needed as intermediates for further syntheses, it was deemed advisable to investigate the reaction of the readily available 3-hydroxy- and 3-methoxy-4-pyrone-carboxylic acids with primary aromatic amines.

A survey of the literature reveals that 3-hydroxy-4-pyrone-carboxylic acids react smoothly with ammonia¹⁻⁹ and with primary aliphatic amines¹⁰⁻¹⁵. There are not many data, however, concerning the reaction of the mentioned acids with primary aromatic amines. We found described only one attempt to condense comenic acid (5-hydroxy-4-pyrone-2-carboxylic acid) with aniline but this reaction has not been investigated in a more detailed manner¹⁰.

In the present communication we are describing the preparation of several 1-aryl-5-hydroxy-4-pyridone-2-carboxylic acids and the corresponding methyl ethers by condensation of primary aromatic amines with meconic acid (3-hydroxy-4-pyrone-2,6-dicarboxylic acid), comenic acid or comenic acid methyl ether, respectively. During the reaction of meconic acid with primary aromatic amines decarboxylation takes place, the carboxylic group in the vicinity of the hydroxylic group being split off, so that the same products are formed as in the reaction with comenic acid. The same phenomenon was observed by Kleipool and Wibaut in their study of the reaction of meconic acid with primary aliphatic amines¹⁴.

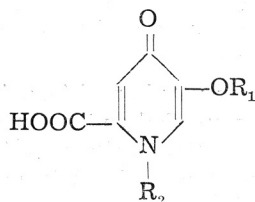
The condensation was carried out by refluxing an aqueous mixture of the acid with a slight surplus of the aromatic amine during 3—5 hours. After cooling the crude product separated in an average yield of about 70 per cent. It was purified by reprecipitation *via* the sodium salt and by following crystallization from 50 per cent acetic acid.

* Part of the Thesis of S. Kukulja, presented to the University of Zagreb, 1958, in partial fulfilment of the requirements for the degree of Doctor of Chemistry (Ph. D.)



$R=R_1=H$ comenic acid 1-aryl-5-hydroxy- 1-aryl-3-hydroxy
 $R=H, R_1=COOH$ meconic acid (or 5-methoxy)-4- (or 3-methoxy)-4-
 $R=CH_3, R_1=H$ comenic acid methyl ether pyridone-2-carboxy- -pyridones IX—XVI
 lic acids I—VIII

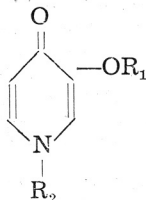
Table I. 1-Aryl-5-hydroxy- and 5-methoxy-4-pyridone-2-carboxylic acids



No.	R ₁	R ₂	M. p. °C
I	H	C ₆ H ₅ -	200
II	H	2-CH ₃ C ₆ H ₄ -	206
III	H	3-CH ₃ C ₆ H ₄ -	190
IV	H	4-CH ₃ C ₆ H ₄ -	197.5—198.5
V	CH ₃	C ₆ H ₅ -	176—177
VI	CH ₃	2-CH ₃ C ₆ H ₄ -	193
VII	CH ₃	3-CH ₃ C ₆ H ₄ -	177—178
VIII	CH ₃	4-CH ₃ C ₆ H ₄ -	176—177

All the prepared 1-aryl-5-hydroxy- (and 5-methoxy)-4-pyridone-2-carboxylic acids, which are listed in Table I, were easily decarboxylated to yield the corresponding 1-aryl-3-hydroxy-4-pyridones and 1-aryl-3-methoxy-4-pyridones, respectively. The decarboxylation was performed by heating the acids above the melting point as long as foaming could be observed. After cooling the 3-hydroxy derivatives solidified and could be recrystallized from water or from aqueous alcohol. The 3-methoxy derivatives were obtained as oily products which decomposed when heated in attempts to distil them under reduced pressure. They were converted into the hydrochlorides and the picrates which are well crystallized substances. The prepared bases and the corresponding hydrochlorides and picrates are listed in Table II.

Table II. 1-Aryl-3-hydroxy- and 3-methoxy-4-pyridones and the corresponding hydrochlorides and picrates.



No.	R ₁	R ₂	Salt	M. p. °C
IX	H	C ₆ H ₅	—	164
IXa	H	C ₆ H ₅	hydrochloride	197
IXb	H	C ₆ H ₅	picrate	172—174
X	H	2-CH ₃ C ₆ H ₄	—	206
Xa	H	2-CH ₃ C ₆ H ₄	hydrochloride	250—252
Xb	H	2-CH ₃ C ₆ H ₄	picrate	146
XI	H	3-CH ₃ C ₆ H ₄	—	158—159.5
XIa	H	3-CH ₃ C ₆ H ₄	hydrochloride	190.5—191.5
XIb	H	3-CH ₃ C ₆ H ₄	picrate	167—168
XII	H	4-CH ₃ C ₆ H ₄	—	196
XIIa	H	4-CH ₃ C ₆ H ₄	hydrochloride	215—216
XIIb	H	4-CH ₃ C ₆ H ₄	picrate	174
XIIIa	CH ₃	C ₆ H ₅	hydrochloride	180—181
XIIIb	CH ₃	C ₆ H ₅	picrate	150
XIVa	CH ₃	2-CH ₃ C ₆ H ₄	hydrochloride	196—197
XIVb	CH ₃	2-CH ₃ C ₆ H ₄	picrate	187—187.5
XVa	CH ₃	3-CH ₃ C ₆ H ₄	hydrochloride	185
XVb	CH ₃	3-CH ₃ C ₆ H ₄	picrate	163
XVIa	CH ₃	4-CH ₃ C ₆ H ₄	hydrochloride	204
XVIb	CH ₃	4-CH ₃ C ₆ H ₄	picrate	164—165

EXPERIMENTAL

All melting points are uncorrected.

1. *General procedure for the preparation of 1-aryl-5-hydroxy-4-pyridone-2-carboxylic acids*

A mixture of 0.1 mole of meconic acid (procedure A) or of comenic acid (procedure B), 0.11 mole of freshly distilled aryl amine (or the equivalent amount of amine hydrochloride) and 250 ml. of water was refluxed for 3—5 hours and then kept at room temperature overnight. The crop of dark crystals was filtered off, the crude product dissolved in a sodium carbonate solution and the remaining tar removed by filtration. The filtrate was acidified by adding concentrated hydrochloric acid drop by drop. The crystalline product which separated was filtered off and recrystallized several times from 50 per cent aqueous acetic acid. The products obtained with the same amine from meconic and comenic acid, respectively, were alike and there was no depression of the mixed melting point. The pure acids give a violet colour with a ferric chloride solution.

1-Phenyl-5-hydroxy-4-pyridone-2-carboxylic acid (I)

(In collaboration with B. Prohaska)

(A). A mixture of 25.4 g. of meconic acid (0.1 mole), 10.2 g. of aniline (0.11 mole) and 250 ml. of water was heated for 4 hours at 110—120° (bath temp.). The crude product having m.p. 182—187° (decomp.) was purified by reprecipitation. There was obtained 17.2 g. of crystals melting at 192—195° with decomposition which, after recrystallization, melted at 198—199° (decomp.); yield 10.75 g. or 43%. The analytical sample was crystallized from abs. ethanol with addition of dry ether yielding prismatic crystals of the *anhydrous* acid, m.p. 200° (decomp.).

Anal. C₁₂H₉NO₄ (231.20) calc'd.: C 62.34; H 3.92; N 6.06%
found: C 62.58; H 3.94; N 6.26%

(B). The mixture of 31.2 g. of comenic acid (0.2 mole), 20.4 g. of aniline (0.22 mole) and 500 ml. of water was heated for 4 hours at 115—120°. The crude product (35.2 g., 71%) melted after drying at 194—195° (decomp.). After reprecipitation there was obtained 27.2 g. of crystals having m.p. 198—199° (decomp.). This product showed to be identical with the product obtained by procedure A. After four recrystallizations from water the pure *monohydrate* of I, m.p. 188° (decomp.) was obtained.

Anal. C₁₂H₉NO₄ · H₂O (249.22) calc'd.: C 57.83; H 4.45; N 5.62%
found: C 57.82; H 4.34; N 5.71%

1-o-Tolyl-5-hydroxy-4-pyridone-2-carboxylic acid (II)

(A). The mixture of 15.24 g. of meconic acid, 7.1 g. of *o*-toluidine (0.066 mole), 5.6 ml. of concentrated hydrochloric acid (0.066 mole HCl) and 140 ml. of water was refluxed at 120—125° during 5 hours. There was obtained 10.0 g. (68%) of brown crystals, having m.p. 210—211° (decomp.). After purification colourless crystals melting at 206° (decomp.) were obtained.

Anal. C₁₃H₁₁NO₄ (254.23) calc'd.: C 63.67; H 4.52; N 5.71%
found: C 63.42; H 4.41; N 5.80%

(B) From 3.12 g. of comenic acid (0.02 mole), 2.36 g. of *o*-toluidine (0.022 mole), 1.9 ml. of concentrated hydrochloric acid (0.022 mole HCl) and 50 ml. of water, after heating at 110—118° for 1 hour, 2.91 g. (59%) of crude product having m.p. 210° (decomp.) was obtained. The pure acid melted at 206° (decomp.).

1-m-Tolyl-5-hydroxy-4-pyridone-2-carboxylic acid (III)

(A). From the mixture of 15.24 g. of meconic acid (0.06 mole), 7.1 g. of *m*-toluidine (0.066 mole), 5.6 ml. of conc. hydrochloric acid (0.066 mole HCl) and 150 ml. of water, heated for 4 hours at 120—125°, 10.85 g. (73%) of crude product melting at 195—196° (decomp.) was obtained. After reprecipitation and recrystallization colourless crystals having m.p. 190° (decomp.) were obtained.

Anal. C₁₃H₁₁NO₄ (254.23) calc'd.: C 63.67; H 4.52; N 5.71%
found: C 63.62; H 4.48; N 5.56%

(B). The mixture of 3.12 g. of comenic acid (0.02 mole), 2.36 g. (0.022 mole) of *m*-toluidine and 50 ml. of water was heated at 112—115° for 4 hours. The crude product (3.67 g., 75%) was purified to yield crystals melting at 191° (decomp.).

1-p-Tolyl-5-hydroxy-4-pyridone-2-carboxylic acid (IV)

(A). The condensation was carried out with the same amounts of reactants and in the same way as described for the *meta* isomer. The crude product was obtained in form of dark crystals melting at 210—211° (decomp.); average yield 73%. After reprecipitation and recrystallization crystals melting at 197.5° (decomp.) were obtained.

(B). The mixture of 3.12 g. of comenic acid (0.02 mole), 2.36 g. of *p*-toluidine, 1.9 ml. of conc. hydrochloric acid (0.022 mole HCl) and 50 ml. of water was heated for 1 hour at 110—115° to yield 3.35 g. (68.5%) of crude product having m.p. 207°

(decomp.). After purification colourless needles melting at 198.5° (decomp.) were obtained.

Anal. $C_{13}H_{11}NO_4$ (254.23) calc'd.: C 63.67; H 4.52; N 5.71%
found: C 63.27; H 4.40; N 5.90%

2. General procedure for the preparation of 1-aryl-5-methoxy-4-pyridone-2-carboxylic acids.

A mixture of 0.1 mole of comenic acid methyl ether¹⁵, 0.11 mole of freshly distilled aryl amine and 250 ml. of water was refluxed in an oil bath for 3 hours (bath temperature 105—120°). After cooling the crude product was filtered off and dried at 105° for 1 hour. It was purified by crystallization from 50 per cent acetic acid.

1-Phenyl-5-methoxy-4-pyridone-2-carboxylic acid (V)

From 17.0 g. of comenic acid methyl ether (0.1 mole) and 10.2 g. of aniline (0.11 mole), 16.6 g. of crude product (67.7%) having m.p. 181—183° (decomp.) was obtained. Two recrystallizations gave pure colourless prisms melting at 176—177°.

Anal. $C_{13}H_{11}NO_4$ (245.23) calc'd.: C 63.67; H 4.52; N 5.71%
found: C 63.85; H 4.68; N 5.98%

1-o-Tolyl-5-methoxy-4-pyridone-2-carboxylic acid (VI)

Condensation of 1.7 g. of comenic acid methyl ether (0.01 mole) with 1.17 g. of o-toluidine (0.011 mole) gave 1.85 g. (71.4%) of almost colourless crystals having m.p. 190—191° (decomp.). An analytical sample was recrystallized twice to yield colourless prisms melting at 193° (decomp.).

Anal. $C_{14}H_{13}NO_4$ (259.25) calc'd.: C 64.86; H 5.05; N 5.40%
found: C 65.14; H 5.08; N 5.38%

1-m-Tolyl-5-methoxy-4-pyridone-2-carboxylic acid (VII)

The preparation was carried out with the same amounts of reactants and in the same way as described for the *ortho* isomer. There was obtained 57.8% of crude product with m.p. 176° (decomp.). After recrystallization colourless crystals of the *monohydrate* of VII having m.p. 177—178° (decomp.) were obtained.

Anal. $C_{14}H_{13}NO_4 \cdot H_2O$ (277.27) calc'd.: C 60.64; H 5.45; N 5.05%
found: C 60.94; H 5.39; N 4.96%

1-p-Tolyl-5-methoxy-4-pyridone-2-carboxylic acid (VIII)

From the same amounts of reactants as described for the *ortho* isomer 1.9 g. (73.3%) of crude product melting at 187—188° (decomp.) was obtained. The pure acid, obtained in form of colourless crystals, melted at 176—177° (decomp.).

Anal. $C_{14}H_{13}NO_4$ (259.25) calc'd.: C 64.86; H 5.05; N 5.40%
found: C 64.60; H 5.07; N 5.31%

3. General procedure for preparation of 1-aryl-3-hydroxy- (or 3-methoxy-) -4-pyridones.

A small quantity (0.02 mole or less) of finely powdered 1-aryl-5-hydroxy- (or 5-methoxy-) 4-pyridone-2-carboxylic acid was placed in an open flask and cautiously heated above the melting point, with temporary shaking and stirring, as long as foaming persisted. When decarboxylation was finished, the melt was cooled to room temperature. While the 1-aryl-3-hydroxy-4-pyridones crystallized at once and could be purified by recrystallization from water, the 1-aryl-3-methoxy-4-pyridones were obtained as oily substances which could not be brought to crystallization.

Both the 1-aryl-3-hydroxy-4-pyridones and the 1-aryl-3-methoxy-4-pyridones could be easily converted into the well crystallized hydrochlorides and picrates.

1-Phenyl-3-hydroxy-4-pyridone (IX)

(In collaboration with B. Prohaska)

By decarboxylation of I the pyridone was obtained in a 88% yield. Crystallization from water yielded colourless silky needles melting at 164°.

Anal. C₁₁H₉NO₂ (187.19) calc'd.: C 70.58; H 4.85; N 7.48%
found: C 70.79; H 4.67; N 7.39%

Hydrochloride (IX a)

Colourless crystals from ethanol with addition of ether, m.p. 197°.

Anal. C₁₁H₁₀ClNO₂ (223.66) calc'd.: N 6.26%
found: N 6.34%

Picrate (IX b)

It was prepared by addition of the equivalent amount of sodium picrate to the hydrochloride IX a in aqueous solution. Yellow crystals from water, m.p. 172—174°.

Anal. C₁₇H₁₂N₄O₉ (416.30) calc'd.: N 13.46%
found: N 13.70%

1-o-Tolyl-3-hydroxy-4-pyridone (X)

Prepared from II by decarboxylation; yield 83%. The crude product was purified by recrystallization from water; prisms, melting at 206°.

Anal. C₁₂H₁₁NO₂ (201.21) calc'd.: C 71.62; H 5.51; N 6.96%
found: C 71.85; H 5.37; N 7.07%

Hydrochloride (X a)

Colourless crystals from ethanol-ether, having m.p. 250—252°.

Anal. C₁₂H₁₂ClNO₂ (237.68) calc'd.: C 60.63; H 5.09; N 5.89%
found: C 60.92; H 4.97; N 5.97%

Picrate (X b)

Yellow prisms from ethanol melting at 146°.

Anal. C₁₈H₁₄N₄O₉ (430.32) calc'd.: C 50.24; H 3.28; N 13.02%
found: C 50.43; H 3.02; N 13.09%

1-m-Tolyl-3-hydroxy-4-pyridine (XI)

By decarboxylation of 1.6 g. (0.006 mole) of III and subsequent crystallization from 50 per cent aqueous ethanol, 1.05 g. (87%) of almost colourless prisms, having m.p. 158—159.5°, were obtained. A second crystallization gave the pure product with the same melting point.

Anal. C₁₂H₁₁NO₂ (201.21) calc'd.: C 71.62; H 5.51; N 6.96%
found: C 71.41; H 5.34; N 7.23%

Hydrochloride (XI a)

It was obtained in form of the *monohydrate*. Colourless platelets from 96 per cent ethanol-ether melting at 190.5—191.5°.

Anal. C₁₂H₁₂ClNO₂ · H₂O (255.7) calc'd.: C 56.36; H 5.52; N 5.48%
found: C 56.68; H 5.44; N 5.49%

Picrate (XI b)

Yellow needles from dilute ethanol, m.p. 167—168°.

Anal. C₁₈H₁₄N₄O₉ (430.32) calc'd.: C 50.24; H 3.28; N 13.02%
found: C 50.50; H 3.16; N 13.30%

1-p-Tolyl-3-hydroxy-4-pyridone (XII)

Decarboxylation of 2.0 g. (0.008 mole) of IV yielded 1.45 g. (88.5%) of XII. After two crystallizations from water colourless silky needles having m.p. 196° were obtained.

Anal. C₁₂H₁₁NO₂ (201.22) calc'd.: C 71.62; H 5.51; N 6.96%
found: C 71.44; H 5.39; N 7.06%

Hydrochloride (XII a)

Colourless needles from ethanol-ether melting at 215—216°.

Anal. C₁₂H₁₂ClNO₂ (237.68) calc'd.: C 60.63; H 5.09; N 5.89%
found: C 60.76; H 4.81; N 5.71%

Picrate (XII b)

Yellow prisms from ethanol melting at 174°.

Anal. C₁₈H₁₄N₄O₉ (430.32) calc'd.: C 50.24; H 3.28; N 13.02%
found: C 50.34; H 3.17; N 13.33%

1-Phenyl-3-methoxy-4-pyridone (XIII)

Hydrochloride (XIII a)

From the oily product obtained by decarboxylation of 9.2 g. (0.038 mole) of V, 4.2 ml. of concentrated hydrochloric acid (0.05 mole HCl) and 10 ml. of ethanol, 7.5 g. (overall yield 83.8%) of almost colourless crystals having m.p. 176—178° was obtained. After two recrystallizations from abs. ethanol the pure colourless salt melting at 180—181° could be obtained.

Anal. C₁₂H₁₂ClNO₂ (237.68) calc'd.: C 60.63; H 5.09; N 5.89%
found: C 60.35; H 5.01; N 5.98%

Picrate (XIII b)

It was obtained from XIIIa and sodium picrate. Crystallization from ethanol yielded yellow crystals having m.p. 150°.

Anal. C₁₈H₁₄N₄O₉ (430.32) calc'd.: C 50.24; H 3.28; N 13.02%
found: C 50.07; H 3.27; N 13.29%

1-o-Tolyl-3-methoxy-4-pyridone (XIV)

Hydrochloride (XIV a)

Prepared by decarboxylation of 0.55 g. (0.002 mole) of VI and subsequent addition of 0.7 ml. of conc. hydrochloric acid. Yield 0.35 g., m.p. 190°. After several recrystallizations from abs. ethanol colourless prisms melting at 196—197° were obtained.

Anal. C₁₃H₁₄ClNO₂ (251.74) calc'd.: C 62.02; H 5.61; N 5.56%
found: C 61.73; H 5.31; N 5.59%

Picrate XIV b)

Yellow needles from dilute ethanol having m.p. 187—187.5°.

Anal. C₁₉H₁₆N₄O₉ (444.35) calc'd.: N 12.61%
found: N 12.90%

1-m-Tolyl-3-methoxy-4-pyridone (XV)

Hydrochloride (XV a)

Prepared from 1.0 g. (0.0035 mole) of VII in the same way as described for the *ortho* isomer. Yield 0.65 g., m.p. 171—172°. An analytical sample was obtained by two recrystallizations from abs. ethanol in form of the *semihydrate*; colourless prisms having m.p. 186°.

Anal. C₁₃H₁₄ClNO₂ · ½ H₂O (260.75) calc'd.: C 59.88; H 5.84; N 5.38%
found: C 60.03; H 5.76; N 5.58%

Picrate (XV b)

Yellow needles from ethanol melting at 163°.

Anal. C₁₉H₁₆N₄O₉ (444.35) calc'd.: N 12.61%
found: N 12.78%

1-p-Tolyl-3-methoxy-4-pyridone (XVI)

Hydrochloride (XVI a)

It was prepared from 0.7 g. (0.003 mole) of VIII by the same procedure as described for the *ortho* isomer. After recrystallizations from abs. ethanol the pure salt was obtained in form of colourless needles melting at 204°.

Anal. C₁₃H₁₄ClNO₂ (251.74) calc'd.: C 62.02; H 5.61; N 5.56%
found: C 62.16; H 5.66; N 5.42%

Picrate (XVI b)

Yellow needles from dil. ethanol having m.p. 164—165°.

Anal. C₁₉H₁₆N₄O₉ (444.35) calc'd.: N 12.61%
found: N 12.77%

Acknowledgement. We wish to express our thanks to the Fund for Scientific Research of the University of Zagreb for financial support during 1955—1956. One of the authors (S.K.) wishes to express his gratitude to »Pliva« Pharmaceutical and Chemical Works, Zagreb, for a fellowship during this research. We are also grateful to Mrs. I. Guštak-Mašek for the microanalyses, carried out in our micro-analytical laboratory.

REFERENCES

1. H. How, *Ann.* **88** (1851) 65.
2. T. Reibstein, *J. prakt. Chem.* [2] **24** (1881) 276.
3. H. Ost, *J. prakt. Chem.* [2] **29** (1884) 57.
4. H. Ost, *J. prakt. Chem.* [2] **27** (1883) 257.
5. G. A. Garkusha, *Zhur. Obschchei Khim.* **23** (1953) 1578.
6. I. S. Belonosov, *Zhur. Priklad. Khim.* **22** (1949) 1103.
7. I. S. Belonosov, *Zhur. Priklad. Khim.* **24** (1951) 113.
8. K. Takeuchi and K. Kaneko, *Japan. J. Pharm. & Chem.* **25** (1953) 22;
cf. *C. A.* **48** (1954) 676 i.
9. K. Heyns and G. Vogelsang, *Chem. Ber.* **87** (1954) 13, 1377 and 1440.
10. E. Mennel, *J. prakt. Chem.* [2] **32** (1885) 176.
11. J. P. Wibaut and R. J. C. Kleipool, *Rec. trav. chim.* **66** (1947) 24.
12. R. F. Bickel, *J. Am. Chem. Soc.* **69** (1947) 1901 and 1805.
13. A. F. Bickel, *J. Am. Chem. Soc.* **70** (1948) 326.
14. A. J. C. Kleipool and J. P. Wibaut, *Rec. trav. chim.* **69** (1950) 1041.
15. T. Yabuta, *J. Chem. Soc.* **125** (1924) 575.

IZVOD

Studije u redu pirona-(4) i piridona-(4). I. Priprava 1-aril-3-hidroksi-piridona-(4) i srodnih spojeva

V. Hahn i S. Kukulja

Kondenzacijom mekonske kiseline, komenske kiseline ili metiletera komenske kiseline s primarnim aromatskim aminima dobivene su u zadovoljavajućim iskorištenjima 1-aril-5-hidroksi-piridon-(4)-karbonske kiseline-(2), odnosno njihovi metileteri. Ove kiseline prevedene su dekarboksilacijom u 1-aril-3-hidroksi-piridone-(4) ili u odgovarajuće 1-aril-3-metoksi-piridone-(4).

ZAVOD ZA ORGANSKU KEMIJU
TEHNOLOŠKI FAKULTET
ZAGREB

Primljeno 26. listopada 1961.