# SYNTHESIS OF FUSARIC ACID AND ITS ANALOGS

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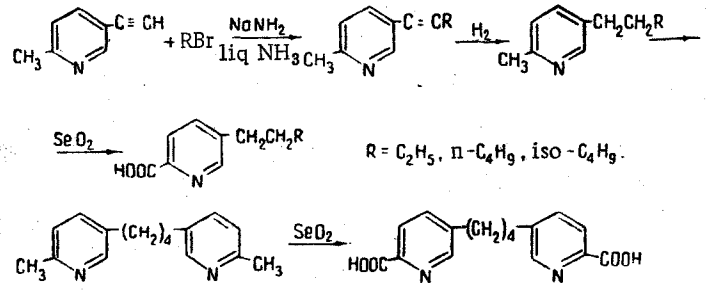
Fusaric acid (5-butylpicolinic acid) is a natural broad-spectrum antibiotic which suppresses the growth of a number of bacteria, fungi, and algae [1]. It is produced by pathogenic fungi of the genus Fusarium causing wilt in the cotton plant. The toxicity of fusaric acid is due to its capacity for binding the ions of heavy metals from metal-containing enzyme systems. Even in a concentration of $5 \times 10^{-3}$ M, this acid inhibits the activity of succinoxidase and cytochrome oxidase by 35%, and at $10^{-2}$ M by 100% [2].

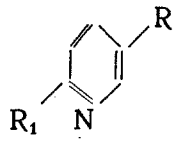
Several synthetic methods for obtaining fusaric acid have been reported [3–5]. However, they are fairly complex and do not enable analogs and homologs of this acid to be synthesized in the same way.

We have developed a simple and convenient method for obtaining fusaric acid and its homologs [6] starting from 2-methyl-5-ethynylpyridine, which is readily obtained from 2-methyl-5-vinylpyridine by bromination and dehydrobromination [7]. 2-Methyl-5-ethynylpyridine was alkylated by alkyl halides under the action of sodium halide or by tosylates in the presence of metallic sodium. The 2-methyl-5-alkynylpyridines formed were reduced to 2-methyl-5-alkylpyridines by the hydrogen liberated in the leaching of an aluminum–nickel alloy [8] and were then oxidized to the corresponding 5-alkylpicolinic acids with selenium dioxide [9].

Similarly, the oxidation of the hydrogenation product of bis-(6-methylpyrid-3-yl) diacetylene gave 1,4-bis (6-carboxypyrid-3-yl) butane.



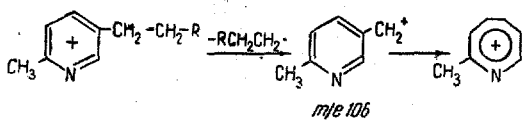

The individuality of the compounds synthesized was checked by thin-layer chromatography on alumina (activity grade II) in the benzene–methanol (25:1) system. The chromatographic mobility of the alicyclic acids was investigated on paper in the butan-1-ol–acetic acid–water (75:15:10) system. The table gives yields and constants of the compounds




The absence of absorption in the 1640–1680 $cm^{-1}$ and 2100–2200 $cm^{-1}$ regions is characteristic for the IR spectra of the 2-methyl-5-alkylpyridines, which shows the complete hydrogenation of the triple bond. There is only one absorption maximum in the UV spectrum of these compounds, in the 268 mμ region, which is characteristic of alkylpyridine bases [9]. The mass spectra of the 2-methyl-5-alkylpyridines [10] (figure) are characterized by a maximum peak of the fragmentary ion with m/e 106, the formation of which is due to the rupture of the 1, 2 C–C bond in the alkyl chain present in position 3 of the pyridine ring. The stability of the ion with m/e 106 is apparently due to the rearrangement of the fragment formed into an azatropilium ion (p. 112).

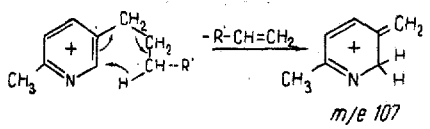
In addition, the mass spectra of all the 2-methyl-5-alkylpyridines have the peak of a rearranged ion with m/e 107 possibly formed by the transfer of hydrogen by a cyclic mechanism with the elimination of an olefin molecule (p. 112).

As was to be expected, the intensities of the peaks of these ions rise with an increase in the length of the chain. The subsequent decomposition of the ions with m/e 107 and 106 takes place in the same way for all the compounds investigated with the successive elimination of a molecule of HCN and of 2H and with the formation of ions with m/e 79 and 77 ($C_6H_7^+ + C_6H_5^+$).



m/e 106

The presence of branching in the chain of 2-methyl-5-isohexylpyridine is reflected in the mass spectrum of this compound. An ion with m/e 163 appears which is formed by the splitting off a methyl group and is not found in the mass spectra of the other alkylpyridines.



m/e 107

## Experimental

Synthesis of 2-methyl-5-alkynylpyridines. A. With stirring, 0.15 mole of 2-methyl-5-ethynylpyridine was added over 20 minutes to a solution of freshly prepared sodium amide (from 0.15 g-at of metallic sodium in 200 ml of liquid ammonia) and after 3 hr 0.3 mole of alkyl bromide was added rapidly (over 15 min.) Stirring was continued for another 4 hr, the ammonia was evaporated off, 200 ml of water was added, and the mixture was extracted with ether. The extract was dried with potassium carbonate, the ether was driven off, and the residue was vacuum-distilled. The distillation yielded only a small amount of unchanged 2-methyl-5-ethynylpyridine with bp 80°–85° C (20 mm).

| R | $R_1$ | Yield*, % | Bp, °C (mm) | $n_D^{20}$ | Mp of the picrate (from alcohol), °C | $R_f$ |
|---|---|---|---|---|---|---|
| $C_2H_5C\equiv C$ | $CH_3$ | 70 (22) | 112 (7) | 1.5500 | 160—161 | 0.57 |
| $C_4H_9C\equiv C$ | $CH_3$ | 76 (41) | 136 - 138 (6) | 1.5365 | 144—146 | 0.60 |
| iso-$C_4H_9C\equiv C$ | $CH_3$ | 70 | 112 (5) | 1.5381 | 166—168 | 0.60 |
| n-$C_4H_9$ | $CH_3$ | 87 | 95 (10) | 1.4950 | 133—134 [4] | 0.40 |
| n-$C_6H_{13}$ | $CH_3$ | 83 | 130—132 (15) | 1.4929 | 120—121 [9] | 0.47 |
| n-$C_4H_9$ | COOH | 40 | Mp 98—100 [4] | — | — | 0.83 |
| n-$C_6H_{13}$ | COOH | 32 | Mp 101—102 [9] | — | — | 0.87 |

*Yield of the substances in the first three experiments was obtained by method A on the basis of the 2-methyl-5-ethynylpyridine that had reacted. The yields of method B are given in brackets.

B. With stirring, 0.05 mole of 2-methyl-5-ethynylpyridine was added slowly to 0.05 g-at of sodium shavings in 20 ml of boiling absolute xylene, after which 0.05 mole of the appropriate ester of p-toluenesulfonic acid was added over 10 min at 70° C. Stirring was continued at 80° C for 3 hr, after which the mixture was cooled, decomposed with water, extracted with ether, and worked up as described above.

The previously unreported 2-methyl-5-alkynylpyridines were characterized in the form of their picrates.

2-Methyl-5-butynylpyridine picrate.

Found, %: N 14.94, 15.03. Calculated for $C_{16}H_{14}N_4O_7$, %: N 14.96.

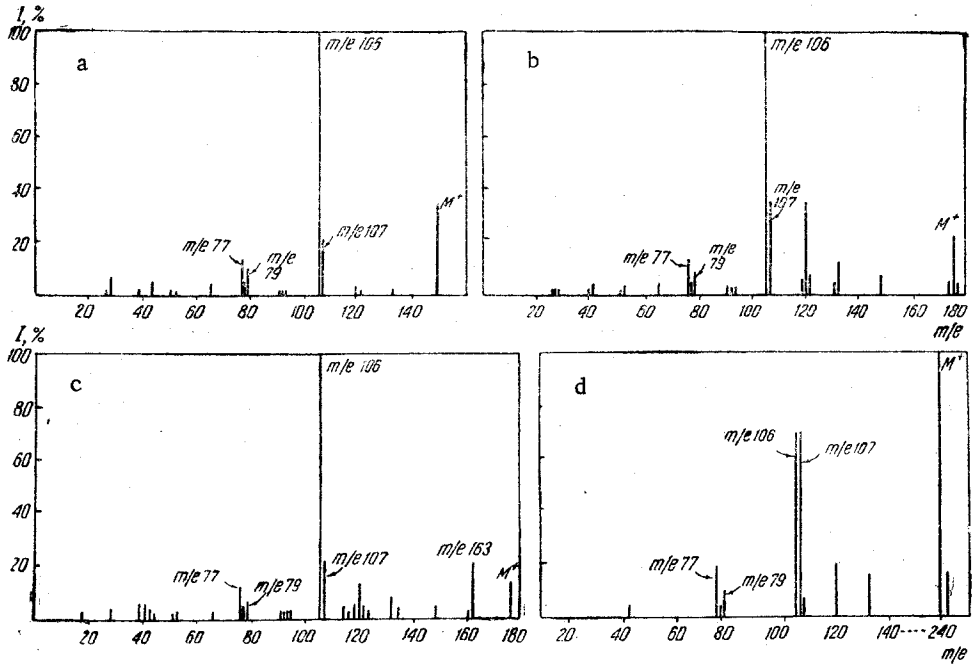
2-Methyl-5-hexynylpyridine picrate.

Found, %: C 53.59, 53.61; H 4.58, 4.62. Calculated for $C_{18}H_{18}N_4O_7$, %: C 53.73; H 4.58.

2- Methyl-5-isohexynylpyridine picrate.

Found, %: N 13.94, 13.73. Calculated for $C_{18}H_{18}N_4O_7$, %: N 13.93.

Synthesis of the 2-methyl-5-alkylpyridines. A Ni/Al alloy was added in portions to 0.01 mole of a 2-methyl-5-alkylpyridine in 30 ml of 20% caustic soda solution at 90° C with vigorous stirring throughout the experiment. After the vigorous evolution of hydrogen had ceased, another 1 g of aluminum–nickel alloy and 5 ml of 20% caustic soda solution were added and the experiment was continued for another 0.5 hr. The hot solution was filtered, the precipitate was washed with water, and the filtrate was extracted with ether. The ethereal extract was dried, the solvent was distilled off, and the residue was vacuum-distilled.




Synthesis of 5-alkylpicolinic acids. A suspension of 0.08 mole of a 2-methyl-5-alkylpyridine and 0.12 mole of selenium dioxide in 100 ml of pyridine was boiled with stirring for 2 hr. Then the mixture was filtered, the residue was washed with water, the pyridine was steam-distilled, the residual solution was filtered, and the filtrate was evaporated to dryness in vacuum. The residue was extracted with a boiling mixture of carbon tetrachloride and cyclohexane. The solvent was evaporated and the acid was crystallized from heptane.

Synthesis of 1,4-bis(6-carboxypyrid-3-yl)butane. This was obtained similarly from 3.6 g of 1,4-bis(6-methylpyrid-3-yl) butane and 4.9 g of selenium dioxide. Reaction time 4 hr. Yield 1.4 g (36%), mp 256°–258° C [dioxane–water (1:1)].

Rf on paper 0.13 in the butan-1-ol–acetic acid–water (75:15:10) system.

Found, %: C 63.36, 63.30; H 5.68, 5.63. Calculated for $C_{16}H_{16}N_2O_4$, %: C 63.98; H 5.36.

## Summary

1. A new method for synthesizing fusaric acid and its analogs has been proposed which starts from 2-methyl-5-ethynylpyridine; this is alkylated and the hydrogenated 2-methyl-5-alkynylpyridines are oxidized to the corresponding 5-alkylpicolinic acids.

2. The mass-spectroscopic behavior of the 2-methyl-5-alkylpyridines has been studied.

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