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THE SYNTHESIS OF THE FUSARINIC ACID, ITS ISOMERS AND HOMOLOGUES

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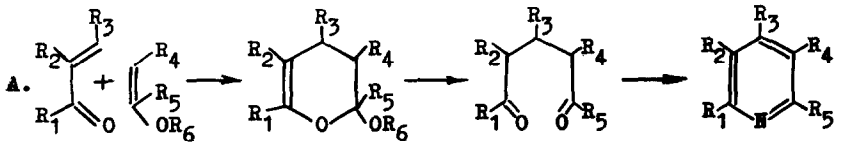
The most elaborate method of the synthesis of the fusarinic acid proceeds from 2-methyl-5-ethylpyridine (1). The method is a multistaged one and the resulting yield of the product is small. The new method of the synthesis of this anthibiotic recently published is based on the Nesmeyanov-Kochetkov's reaction and allows to get a better yield in a simpler way (2). The shortcoming of both of the methods is the impossibility of obtaining the fusarinic acid's isomers with different relative location of n.butyl and carboxyl groups in the pyridine ring.

We have found that the best way of the pyridine ring formation with the location of two alkyl substitutes planned in advance includes a dien condensation of α,β-unsaturated aldehydes and ketones and vinyl ethers. The substituted 2-alkoxy-3,4-dihydro-1,2-pyrans thus obtained are easy to hydrolyze into 1,5-dicarbonyl compounds which react with hydroxylamine to yield substituted pyridines (scheme A).

A.

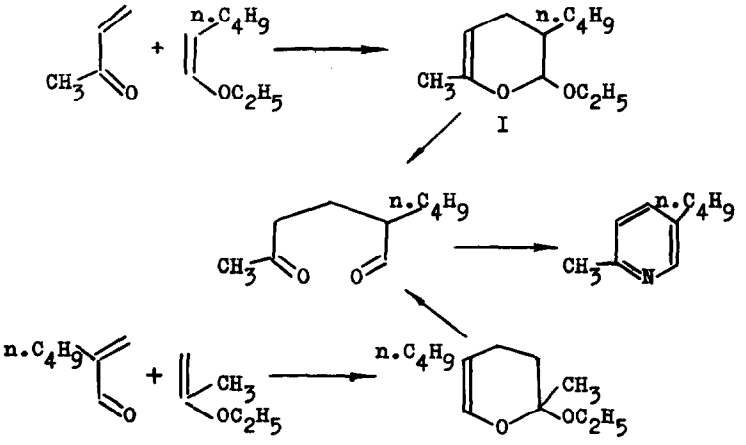


+In the experiment Mrs. S.A. Vereschagina has taken part.

A similar scheme was first used by Reppe and his collaborators[+] in a few patents on the synthesis of the simplest substituted pyridines, namely isomeric methylpyridines (3). It seems strange that this most convinient method of synthesis of mono- and polyalkylpyridines, including the rarest 2,5-, 3,5- and 3,4-dialkylpyridines, have not been practicaly used so far by those working with pyridine compounds, although it is the most direct way to such derivatives[++].

Considering the general scheme A one can see that when a molecule of a synthesized pyridine is asymmetric there are two possible ways of preparing the same pyridine base, since the two isomeric substituted 2-alkoxy-3,4-dihydro-1,2-pyrans will give the same 1,5-dicarbonyl compound when hydrolyzed (scheme B).

B.



[+]Before Reppe and his collaborators the possibility of converting glutaraldehyde to pyridine was shown by Shaw (4).

[++]Besides dialkylpyridines mentioned in this paper we have synthesized according to the similar scheme a number of compounds, namely 3-ethylpyridine, 2,5-, 3,5- and 3,4-dimethylpyridines, 3,5-diethylpyridine etc.

We have used the both ways of the synthesis in application to 2-methyl-5-n.butylpyridine. The dien condensation of n.hexen-1-ylethyl ether and methyl vinyl ketone was carried out as usual i.e. by heating the initial materials in the equimolar ratio in the presence of 0.1% of hydroquinone (the similar syntheses cf. (6,7). 2-Alkoxy-3-n.butyl-6-methyl-3,4-dihydro-1,2-pyran (I) thus obtained was isolated from the reaction mixture by fractional distillation in vacuum to separate a by-product formed by cyclodimerisation of methyl vinyl ketone (scheme C). The yield of (I) was 47% (b.p.$_{18}$ 106-107°,

C. 

n_D^{20}1.4462, d_4^{20}0.9165). Found: C, 72.62, 72.87; H, 10.97, 11.00 $C_{12}H_{22}O_2$ requires: C, 72.84; H, 11.11 %. The saponification of (I) was accomplished by heating for 0.5 hr. in a mixture with acetic acid. The 1,5-dicarbonyl derivative formed not isolated from the reaction mixture was added to hydroxylamine. Unlike the process described by Reppe and his collaborators the reaction with hydroxylamine was carried out by gradual addition of acetic acid solution of 1,5-dicarbonyl compound to the stirring refluxing suspension of hydroxylamine in glacial acetic acid. 2-Methyl-5-n.butylpyridine (II) after usual treatment was fractionated in vacuum to yield 37.5% of pure product, b.p.$_{19}$ 105-1[illegible] b.p.$_{750}$ 220-221°, n_D^{20}1.4911, d_4^{20}0.9068, the picrate [illegible] a recristallisation from ethanol melted at 137-138°(corr) Found: C, 79.88, 79.61; H, 10.24, 10.41; N, 8.90, 8.82. Calculated for $C_{10}H_{15}N$: C, 80.48; H, 10.13; N, 9.38 %. Besides 2-methyl-5-n.butylpyridine a small amount of a nitrogen contain-

ing compound was obtained, b.p.$_{19}$ 130-131°, n_D^{20}1.4322, d_4^{20} 0.9463. Found: C, 79.96, 80.01; H, 10.19, 10.26; N, 8.83, 9.04 %. It was not investigated in details.

3-n.Butyl-4-methylpyridine (III) and 2-methyl-5-n.hexylpyridine (IV) were synthesized in a similar way. From crotonaldehyde and n.hexen-1-ylethyl ether 2-ethoxy-3-n.butyl-4-methyl-3,4-dihydro-1,2-pyran was obtained (3 2.8% yield), b.p.$_{17}$ 112-114°, n_D^{20}1.4478, d_4^{20}0.9080. The latter was converted to yield 80.5% of 3-n.butyl-4-methylpyridine (III), b.p.$_{23}$119-120°, n_D^{20}1.4986, d_4^{20}0.9199, picrate m.p. 124.5-125°(corr.). Found: N, 14.74, 15.06. Calculated for $C_{16}H_{18}N_4O_7$: N, 14.81 %. Correspondingly from methyl vinyl ketone and n.octen-1-ylethyl ether 2-ethoxy-3-n.hexyl-6-methyl-3,4-dihydro-1,2-pyran was obtained, the yield 39.8%, b.p.$_{20}$ 80-83°, n_D^{20}1.4343. Found: C, 73.84, 73.73; H, 11.81, 11.80. $C_{14}H_{26}O_2$ requires: C, 74.35; H, 11.48 %. The latter was added to hydroxylamine to give 2-methyl-5-n.hexylpyridine (IV). The yield 42.3%, b.p.$_{22}$ 140-142°, n_D^{20}1.4868, d_4^{20}0.8870, picrate m.p. 123-124°(corr.). Found: N, 13.60, 13.69. $C_{18}H_{22}N_4O_7$ requires: N, 13.78 %.

2-Methyl-5-n.butylpyridine was oxidated by selenium dioxide in pyridine to 5-n.butyl-2-pyridine carboxylic (fusarinic) acid (V) according to the procedure similar to that reported by Jerchel (8) for oxydation of 2-methyl-5-ethylpyridine to 5-ethyl-2-pyridine carboxylic acid. In the same manner 3-n.butyl-4-pyridine carboxylic acid (VI) was obtained. Found: C, 67.08, 66.97; H, 7.41, 7.51; N, 8.13, 7.79. $C_{10}H_{13}O_2N$ requires: C, 67.01; H, 7.31; N, 7.81 %. 2-Methyl-5-n.hexyl-

TABLE I

Melting Points and Characteristic I.R. Frequencies [+]

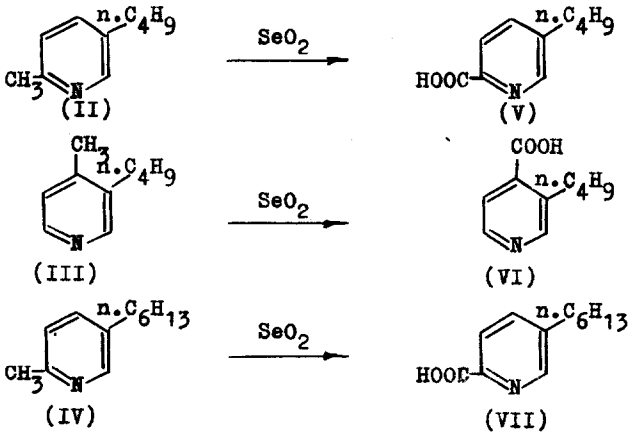
Compound	m.p. °C	Band position[++] (cm^{-1})				
		Alkyl substitutes	Disubstituted pyridines	2-Substituted pyridines	3-Substituted pyridines	4-Substituted pyridines
V	100-101	2952 s 2930 s 2686 m 2856 m 1465 s 1375 w 733 m	1313 s 1131 s 1105 m 1035 s 850 s 820 w	1595 m 1576 s 1435 w 1275 m 1156 s 995 w	1595 m 1576 s 1480 w 1103 w 1038 s 765 m 775 s	
VI	197-197,5	2950 s 2928 m 2868 m 2856 m 1469 m 1378 w 728 m	1315 s 1109 w 742 w		1595 m 1378 w 1315 s 1108 w 805 s 779 s	1605 m 1556 w 1380 w 1070 s 870 s
VII	100,5-101	2950 s 2920 s 2855 m 1470 m 728 m	1305 s 1028 s 850 s 816 m	1585 s 1475 m 1435 w 1152 s	1585 s 1475 m 1132 s 775 m	

[+]The samples analyzed were pressed with potassium iodide.

[++]I.R. Spectra of isomeric substituted pyridines cf. (9,10).

pyridine was oxidated to give 5- n.hexyl-2-pyridine carboxylic acid (VII). Found: C, 69.30, 6931; H, 8.47, 8.37, N, 6.74, 6.81. $C_{12}H_{17}O_2N$ requires: C, 69.53; H, 8.26; N, 6.76 %. (Scheme D).

D.



The structures of the pyridine carboxylic acids were confirmed by IR-spectra (Table I).

We did not aim to get maximum yields at separate stages and apparently they may be increased essentialy. As initial α,β-unsaturated aldehydes (ketones) and vinyl ethers are not difficult to prepare by usual methods, the proposed synthesis of the fusarinic acid, its isomers and homologues should be considered as the most universal and convinient among those known.

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