SYNTHESIS OF 2,3-POLYMETHYLENEPYRIDINES
FROM 3-AMINOACROLEIN AND CYCLIC KETONES

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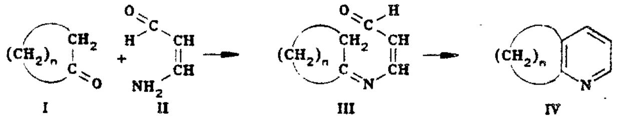
It is shown that the reaction of 3-aminoacrolein with cyclic ketones of medium size can be used to synthesize inaccessible 2,3-polymethylenepyridines with polymethylene chains of 5, 6, 10, and 12 carbon atoms.

It has been demonstrated in [1] that polymethylenepyridines IV can be obtained by condensation of cyclic ketones I with 3-aminoacrolein II at 120°C using a mixture of triethylamine and piperidine acetate as catalyst in yields of 60% for n = 3 and 30% for n = 5.

We have repeated the condensation of aminoacrolein II with cyclooctanone (n = 6) under the reported condition but obtained 2,3-hexamethylenepyridine in only very low yield. The basic product of the reaction appeared to be derived from polymerization of aminoacrolein.

The mechanism of the formation of IV apparently includes the formation of an intermediate Schiff base III followed by a Knoevenagel condensation to form IV. The first stage is catalyzed by the tertiary amine and the second by the piperidene salt.



On the basis of this proposed mechanism we have optimized the reaction conditions for the yield of IV. Raising the temperature from 120 to 150°C did not increase this yield. It was found that the ketone was not completely converted so the ratio of reactants was changed to 1.5 mole of aminoacrolein (II) to 1 mole of ketone. Under these conditions, the yield of IV could not be increased since the extent of polymerization of II became more significant. Evidently this polymerization occurred more rapidly than its reaction with the ketone. A satisfactory yield of IV was, in fact, achieved by variation of the amount of catalyst. A tenfold increase in the catalyst led to a 4.5-fold increase in yield (see Table 1).

Chromatography of the reaction mixture has shown that the reaction takes place with formation of a fairly large number of side products. It was not possible to separate polymethylenepyridine from starting ketone by distillation and a chromatographic separation based on an aluminum oxide column was used.

Analogous conditions were used to carry out the reaction of II with cycloheptanone, cyclododecanone, and cyclotetradecanone.

It can be seen that the smallest amount of ketone was recovered from the reaction product in the case of cycloheptanone and the most for cyclododecanone. An analogy with aliphatic ketones occurs here. It is known that increase in length of the hydrocarbon chain decreases the susceptibility of the ketone toward nucleophilic addition reactions [3]. Apparently the tendency of ketones to participate in the described condensation reactions also decreases as the ring size increases.

The polymethylenepyridines IV were identified using PMR and mass spectra (Table 2).

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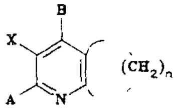
TABLE 1. Dependence of the Yield of Polymethylenepyridines on Reaction Conditions

Time, h	Reaction temperature, °C	Quantity of piperidine acetate (mole) to 0,1 mole of aminoacrolein	Yield of 2,3-hexamethylenepyridine, %
22	120	0,0007	7
23	130—140	0,0014	15
24	120	0,0035	30
27	120—130	0,0070	32

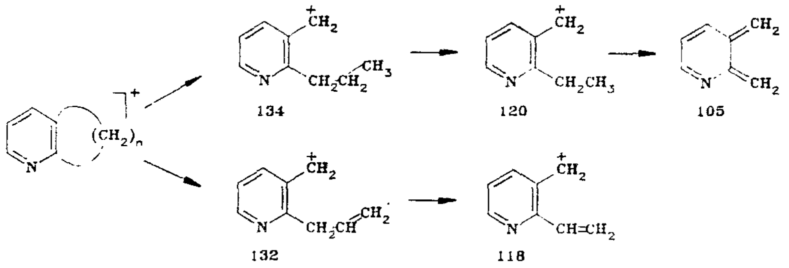
TABLE 2. Spectral Parameters and Yields of Polymethylenepyridines

Starting ketone	M⁺	PMR spectrum in CCl_4, ppm			Ketone converted in reaction, %	Yield of polymethylenepyridine, % (based on reacting ketone)
		A—H	B—H	X—H		
Cycloheptanone	147	8,2—8,4	6,9—7,1	7,2—7,5	75	40
Cyclooctanone	161	—	—	—	50	40
Cyclododecanone	217	9,5—9,7	7,1—7,4	8,4—8,7	7	30
Cyclotetradecanone	245	—	—	—	21	10

The aromatic proton signals for these compounds were found in the region 7.0-9.5 ppm. The A—H proton signals were at lower field (due to their proximity to the electronegative nitrogen atom) than those for X—H and B—H protons. The methylene protons gave rise to a complex multiplet between 1.1 and 3.5 ppm.



Mass spectroscopy* showed the presence of molecular ion peaks (M⁺, Table 2) corresponding to the molecular weights of the polymethylenepyridines. Based on this data, it was proposed that the initial step was a β-dissociation corresponding to the homologous series of the polymethylene chain. The most stable ions formed on dissociation (with m/z 134, 132, 120, 118, 105) probably have the following structures:



Thus, cyclic ketones of intermediate size (with 7, 8, 12, and 14 carbon atoms in the ring) will react with 3-aminoacrolein to form 2,3-polymethylenepyridines.

EXPERIMENTAL

PMR Spectra were recorded on Varian T-60 and XL-100 instruments (internal standard TMS) and mass spectra on Spectra-System MAT-166 and MX-1303 instruments with an ionization intensity of 50 eV. GLC analysis was carried out using an LKM-8MD with 3-m column, a Chromaton acid washed phase loaded with 5% SE-30, and nitrogen gas carrier with velocity of 20

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*The authors sincerely thank P. B. Terentéva for recording and discussion of the mass spectral data.

cm^3/min. Monitoring of the reaction course and the purity of materials was carried out on Silufol UV-254 plates. The chromatographic separation was effected on a neutral alumina column with benzene:acetone (1:1) as elutent.

3-Aminoacrolein (II). A solution of propargyl aldehyde (10.8 g, 0.2 mole) in benzene (120 ml) was added over 1 h at 25-30°C with stirring to a solution of N-methylpiperidine (0.6 g, 0.005 mole) in a mixture of absolute ethanol (35 ml) and benzene (60 ml). The mixture was stirred for 1 h and gaseous ammonia passed through until the increase in temperature (to 35°C) ceased. The solution was treated with carbon and the solvent evaporated to give the product (7.9 g, 60%) with mp 104-105°C (methanol). PMR spectrum (D_2O): 11.0 (1H, s, CHO), 7.6-7.2 and 6.4-6.0 (2H, dd, CH=CH), 4.4-3.8 ppm (2H, m, NH_2). From the literature: mp [3], 103-104°C.

Polymethylenepyridines (IV). A mixture of II (0.01 mole), the cycloalkanone (0.012 mole), triethylamine (0.5 ml), and piperidine acetate (0.05 g) were sealed in an ampul at 120°C for 24 h. The reaction mixture was poured into water which had been acidified to pH 2-3, extracted several times with ether, the aqueous layer separated and basified to pH 9-10, and then extracted again with ether. The ether extracts were separately dried ($MgSO_4$). Evaporation of the ether extract from the acid solution gave unreacted ketone. After evaporation of the ether extract from the basified solution, the residue was chromatographed on an aluminum oxide column using benzene:acetone (1:1) eluent and monitored by TLC. The yields and mass and PMR spectroscopic data for IV are given in Table 2.

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N-GLYCOSIDES.

7.* SYNTHESIS OF 4,5'-ANHYDRO-3-(2',2'-O-ISOPROPYLIDENE-β-D-RIBOFURANOSYL)-4-HYDROXYHEXAHYDROPYRIMIDINE-2-THIONES

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Reaction of 2,3-O-isopropylideneribofuranosylamine p-toluene-sulfonate with β-isothiocyantoaldehydes in the presence of bases leads to the formation of 4,5'-anhydro-3-(2',3'-O-isopropylidene-β-D-ribofuranosyl)-4-hydroxyhexahydropyrimidine-2-thiones, whose steric structure was established by PMR spectroscopy.

The reaction of β-isothiocyantocarbonyl compounds with ammonia or primary amines is a convenient method for the synthesis of substituted 4-hydroxyhexahydropyrimidine-2-thiones [2, 3]. In order to enlarge the scope of this reaction and the synthesis of N-glycosides of hydrogenated pyrimidines, we studied the reaction of 2,3-O-isopropylideneribofuranosylamine p-toluenesulfonate (I) with β-isothiocyantocarbonyl compounds in the presence of bases We have already shown [4] that the reaction of compound I with 4-isothiocyanato-4-methyl-2-pentanone in pyridine leads to a mixture of isomeric 3-(2',3'-O-isopropylidene-β-D-ribofuran

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*For Communication 6, see [1].

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