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SYNTHESIS OF 5-ETHYLPICOLINE ACID

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Vestn.Mosk.Univ.Ser.Khim. 19, 6 (1964) 427-430
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PROCUREMENT EXECUTIVE, MINISTRY OF DEFENCE

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In the references there is plenty of data about the physiological activity of picoline acid and its derivatives. For example, picoline acid restrains the growth of dysentry bacterii[1], and also "Desulfovibriodesulfuricus"[2], its ethers reduce the growth of "Staphilococcus aureus"[3] and the development of nasturtium plants[4]. Picoline acid itself and 5-butylpicoline (fusarine) acid depresses the growth of many plants. Being the antivitamin of nicotine acid, picoline acid slows up the growth of cockroaches and their nymphs, and also removes the stimulating action of corresponding vitamins on the growth of tumours of Drosophila melanogaster[6].

During investigations in the field of substitutions, in particular of 5-alkylpicoline acids, we decided to check the applicability of different methods for the conversion of the a-methyl group of pyridine into the carboxyl group. As the model substance we choose 2-methyl-5-ethyl-pyridine[1], which we converted into 5-ethylpicoline acid by different methods (see diagram).

As methods of oxidation we chose (1) the reaction of Vilgerodt, (2) the conversion of 2-methyl-5-ethylpyridine by way of N-oxide into 2-oxymethyl-5-ethylpyridine with a subsequent gentle oxidation, (3) a condensation of the a-methyl group with benzaldehyde and oxidation of the stilbazole, (4) direct oxidation of the methyl group by selenium dioxide.

By analogy with the data in the references about the use of the reaction of Vilgerodt to α- and γ-picoline, we checked this reaction with 2-methyl-5-ethylpyridine and obtained thioanilid 5-ethylpicoline acid with a yield of 65%, which we then hydrolized with sulphuric acid and isolated 5-ethylpicoline acid with a yield of 84%.

Mainly following the work of Japanese authors[8-11], we converted 2-methyl-5-ethylpyridine into N-oxide, and, without isolating the intermediate products, obtained 2-oxymethyl-5-ethylpyridine with a yield of 83%. When conducting the

process stage by stage the yield was significantly lower. The spirit obtained was oxidized with concentrated nitric acid at room temperature to 5-ethylpicoline acid with a yield of 60%.

A method is described in a reference for the oxidation of 2-methyl-5-ethylpyridine with selenium dioxide with 58-65% yields depending on the conditions of the experiment[12,13]. Our data fully coincides with the references. Finally, by a fourth means it was necessary to obtain at first a styryl derivative. According to the data in reference[14] the yields fluctuate from 45 to 73%. We made a condensate of 2-methyl-5-ethylpyridine from benzaldehyde in a medium of acetic anhydride and obtained 5-ethyl-2-styrylpyridine with a yield of 83%, which was then oxidized by $KMnO_4$ in acetone to 5-athylpicoline acid (isolated in the form of a cupric salt) with a yield of 65%.

The identity of the substances obtained was established by chromatography on paper in a system of formic acid : butanol : water 15 : 70 : 10, and by a method of thin-layer chromatography in an unfixed layer of alumina. The first method gave better results.

Comparing these methods, it can be noted that the fastest is the oxidation of 2-methyl-5-ethylpyridine with selenium dioxide, but with this method it is difficult to cleanse the substance of colloidal selenium.

A convenient way is the synthesis by the reaction of Vilgerodt with a subsequent hydrolysis of thioanalid. The process is quick, it gives good yields, and the acid obtained is of good quality.

Getting it by way of N-oxide can be convenient when it is important to oxidize the CH_3-group gradually, leaving untouched the other substituents.

EXPERIMENTAL SECTION

Thioanalid of 5-ethylpicoline acid (II) 60 g of 2-methyl-5-ethylpyridine, 70.5 g of aniline and 48 g of sulphur were heated for 12 hours at 160°, the aniline and the substance which had not reacted was distilled off in a vacuum, the remains poured into boiling absolute methyl alcohol, cooled, filtered, the filtrate evaporated in a vacuum and the residue distilled in a vacuum. The yield was 69 g (65%); boiling point 254-250°/10 mm; flame temperature 40-52°; R_f* 0.9; ultra-violet spectrum λ_{max} 300 mmk (lgε 4.23). The percentages found were C 69.71; 69.57; H 5.94; 5.95; $C_{14}H_{14}N_2S$. The calculated percentages were: C 69.42; H 5.79.

*Everywhere that R_f is given it is obtained by a method of paper chromatography in a system of formic acid; butanol:water 15:70:10. The ultra-violet spectrum is photographed in mehylated spirit.

5-ethylpicoline acid (III) A mixture of 5 g of thianilid, 5-ethylpicoline acid and 65 ml of concentrated sulphuric acid was boiled for 4 hours, cooled, neutralized with a 25% water solution of ammonia, evaporated dry in a vacuum and the acid extracted from the residue by carbon tetrachloride in Soxhlets apparatus. The yield was 2.7 g (84%); flame temperature 110-112[13]; R_f 0.65. The total yield for the 2-methyl-5-ethylpyridine introduced into the reaction was 55%.

N-oxide 2-methyl-5-ethylpyridine (IV) A mixture of 60 g of 2-methyl-5-ethylpyridine, 50 ml of 33% hydrogen peroxide and 300 ml of iced acetic acid was heated in a water bath at 70-80° for 3 hours, then 35 ml of hydrogen peroxide was added and heated for another 9 hours. 100 ml of water was added and evaporated in a vacuum to 100 ml. The mixture was neutralized with soda, extracted with chloroform, dried with anhydrous sulphate of ammonia, the solvent distilled off and the residue distilled in vacuum. The yield was 58 g (86%); boiling point 140-145°/10 mm; n^{20}_D 1.5420; boiling point 144°/10 mm[10]; R_f 0.8.

2-acetoximethyl-5-ethylpyridine (V) To a weakly boiling acetic anhydride - 80 g mixed for 2 hours, 47 of N-oxide 2-methyl-5-ethylpyridine were added, boiled for a further 3 hours and distilled in a vacuum. The yield was 53.4 g (86%); boiling point 142°/18 mm; n^{20}_D 1.5000; boiling point 120-127°/5mm; n^{25}_D 1.5005[10]; R_f 0.8.

2-oxymethyl-5-ethylpyridine (VI). A A mixture of 8 g of (V), 50 ml of 10% sodium hydroxide and 20 ml of methanol was boiled for 5 hours, extracted with chloroform, the solvent distilled, and the residue distilled in a vacuum. The yield was 5.24 g (87%); boiling point 140-146°/18 mm; n^{20}_D 1.5522; 116-117.5° mm; n^{25}_D 1.5299; R_f 0.5. The total yield counting (I), 64%.

B A mixture of 60 g (I), 300 ml of iced acetic acid, and 50 ml of 33% hydrogen peroxide was heated at 70-80° for 3 hours; 35 ml of hydrogen peroxide was then added and the mixture heated for a further 9 hours. 100 ml of water were added and evaporated in a vacuum to 100 ml. 74 ml of acetic anhydride were added to the hot solution during the course of 1.5 hours, which was then boiled for 3 hours and evaporated in a vacuum to half the volume. 350 ml of a 10% solution of sodium hydroxide were then added, boiled for 7 hours, extracted with chloroform, the extract dried with anhydrous magnesium sulphate, the solvent distilled and the residue distilled in a vacuum. The yield was 55.6 g (83%); boiling point 140-142°/18 mm; n^{20}_D 1.5532; R_f 0.5.

Oxidation of 2-oxymethyl-5-ethylpyridine (VII) A mixture of 5.5 g of (VI), 31.5 ml of nitric acid with specific gravity of 1.42, and 6.3 ml of nitric acid with specific gravity of 1.5 was left for 72 hours at room temperature. During the second 24 hours the solution turned green. During intense cooling the solution was neutralized with a concentrated solution of ammonia, evaporated dry, and from the residue 5-ethylpicoline acid was extracted with carbon tetrachloride in Soxhlets apparatus. The yield was 3.6 g (60%); flame temperature 110-112°; R_f 0.65. The total yield of acid for the 2-methyl-5-ethylpyridine introduced into the reaction (method B) was 50%.

5-ethylpicoline acid A mixture of 30 g of (I) and 41.5 g of selenium dioxide in 250 ml of absolute pyridine was boiled during 2 hours of mixing, the selenium filtered off, the sediment washed with water and the filtrate distilled with steam. After distillation the residue was filtered off, the filtrate evaporated until dry, and from the residue 5-ethylpicoline acid was extracted with carbon tetrachloride in Soxhlets apparatus. The yield was 24.5 g (65%); flame temperature 110-112° (from cyclohexane); R_f 0.65.

5-ethyl-2-styrylpyridine A mixture of 23 g of (I), 46 g of benzaldehyde and 46 g of acetic anhydride was boiled for 66 hours. The solution was then acidified with 30 ml of hydrochloric acid 1:1, the surplus benzaldehyde was distilled with steam, neutralized with a 20% solution of sodium hydroxide and extracted with chloroform; the extract was evaporated and the residue distilled in a vacuum. The yield was 35 g (83%); boiling point 210-212°/12 mm; flame temperature 47-52°[14]; R_f 0.8; ultra-violet spectrum λ_{max} 310 mmk; lgε 4.45.

5-ethylpicoline acid To a solution of 5 g of (VII) in 110 ml of acetone, which was energetically mixed for 1 hour at a temperature from 0 to 5°, were added 8 g of $KMnO_4$, and the reacting mixture was left for 4 hours at room temperature. The sediment was filtered off and thrice extracted with boiling water (about 80 ml). The combined extract was acidified with 30 ml of hydrochloric acid 1:1, the evaporated benzoic acid filtered off, and to the boiling filtrate 2 g of copper carbonate were added. During cooling 5-ethylpicoline cuprate was obtained. The yield was 2.2 g (65%); flame temperature 317°; R_f 0.65.

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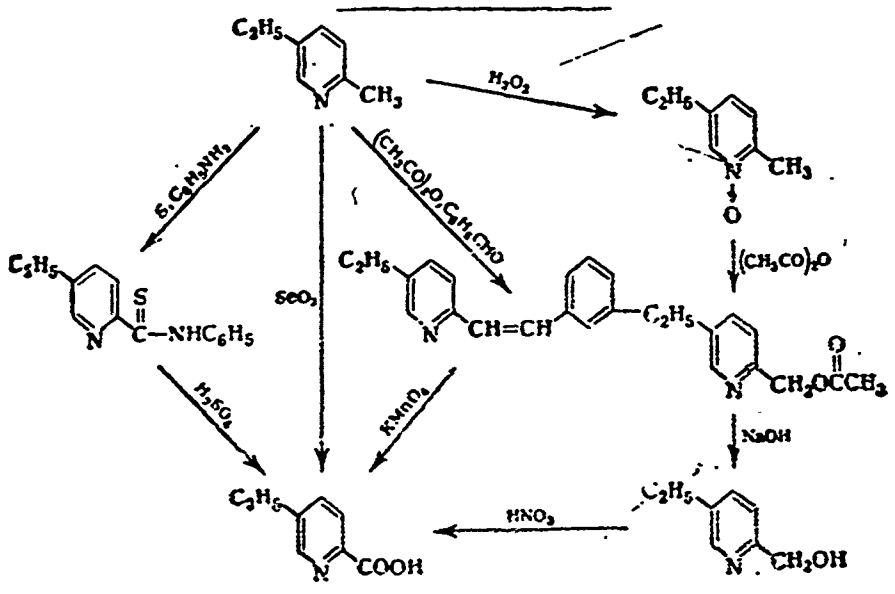
Translator's Notes

(1) Thioanilid appears several times in the Russian text (literal translation), whereas according to all the dictionaries one can have thioanalin but not thioanalid.

(2) On the second page of the Russian text, after minor headings, will be seen (II) and (III), but no (I); this is odd because later mixtures refer to, for example: "30 g of (I)", or "23 g of (I)".



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