Thus, procurement of the rhizomes of *Dioscorea nipponica* can be organized in the Jewish Autonomous Province, primarily on slopes of coniform hills and along ravines in the basin of the Amur River and coniform hills on ridges of the Central Amur Plain.

For systematic collection of raw material that does not exhaust the reserves of *Dioscorea*, it is necessary to take into account our recommended annual procurement volume, which comprises 5-6 tons on clarified commercial tracts.

On the other hand, if tracts of wild *Dioscorea* are counted on for short-term use with subsequent transition to procurement of cultivated raw material, then the volume of procurement can be increased two- to threefold.

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THE OXIDATION OF 2,6-LUTIDINE BY POTASSIUM PERMANGANATE. KINETICS OF FORMATION OF DIPICOLINIC, 6-METHYLPICOLINIC, AND OXALIC ACIDS

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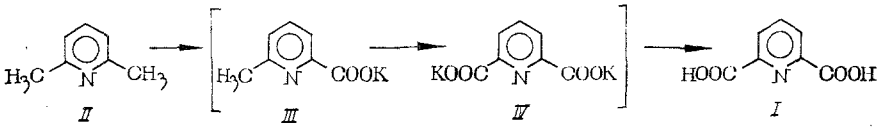
Dipicolinic acid (I) (pyridine-2,6-dicarboxylic acid), which is normally prepared by oxidation of 2,6-lutidine (II), is the major intermediate in the synthesis of the antisclerotic preparation parmidine [2,6-bis(hydroxymethyl)pyridine bis-N-methylcarbamic ester] [1].

Selenium dioxide [2] and its complexes [3] or nitrogen oxides in the presence of selenium dioxide [4] can be used as oxidants of 2,6-lutidine. However, the most accessible, relatively nontoxic oxidant that also gives the highest yields of dipicolinic acid is potassium permanganate [5, 6].

The oxidation of 2,6-lutidine by potassium permanganate is known to involve a stage of formation of potassium 6-methylpicolinate (III), which is then converted to dipotassium dipicolinate (IV). Since the oxidation is exothermal, potassium permanganate is added portionwise to the aqueous solution of 2,6-lutidine. Half the total quantity of the oxidant, which is thought to be consumed in the oxidation of (II) to (III), is added at 70-75°C and the other portions, which are considered to be responsible for the conversion of (III) to (IV), are added at 85-90°C. Increase in the amount of potassium permanganate over the stoichiometry based on 2,6-lutidine (4.0 mole) by 30% (to 5.3 mole) was empirically found [5] to raise the yield of dipicolinic acid by a factor of more than 1.5. However, we have found no explanation for these empirical features of the course of the reaction.



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Oxidation of 2,6-lutidine with potassium permanganate in aqueous solution forms a solution containing the dipotassium salt (IV) and potassium hydroxide. The free acid [1] is precipitated from this solution by addition of hydrochloric acid.

Our work has shown that this requires roughly a 38% excess of hydrochloric acid over the theoretical (based on the amount of potassium permanganate used). In this case the solution pH fluctuates from −0.2 to −0.25 and dipicolinic acid, which is more than 99% pure and contains no incombustible residue, can be isolated in 60% yield. When the theoretical amount of hydrochloric acid is used the solution pH is 0.05-0.1 and the dipicolinic acid isolated in 60% yield is more than 99% pure by titration but contains traces of its monopotassium salt (0.14% incombustible residue). Use of even less hydrochloric acid causes a further increase in the ash content of the product as a result of contamination by monopotassium dipicolinate.

We sought to raise the yield of (I) and to examine the reaction byproducts by evaporating the aqueous mother liquor after separating the dipicolinic acid and esterifying the residue with butanol in the presence of KU-2-8 cation exchange resin by the method we described earlier [7]. Gas–liquid chromatography (GLC) of the products revealed the presence of dibutyl dipicolinate, butyl 6-methylpicolinate, and a large quantity of another compound. We isolated this compound by fractional distillation of the mixture of esterification products and identified it by elemental analysis, IR and PMR spectroscopy, and mass spectrometry as dibutyl oxalate, which was identical to a sample prepared by independent synthesis.

The formation of oxalic acid (V) as its dipotassium salt in the oxidationof 2,6-lutidine by potassium permanganate as a result of cleavage of the pyridine ring has not been described hitherto and was unexpected.

For more detailed information we made a kinetic study of the oxidation of (I) with potassium permanganate in which we followed the concentrations of 2,6-lutidine and the potassium salts of 6-methylpicolinic, dipicolinic, and oxalic acids in the solution.

We determined 2,6-lutidine in samples removed from the reaction mixture by steam distillation and titration of the distillate. We determined oxalic acid by permanganatometric titration after acidification of the sample with sulfuric acid. We followed the formation of dipicolinic and 6-methylpiconlinic acids polarographically. We found that all three acids formed in the oxidation of 2,6-lutidine — dipicolinic, 6-methylpicolinic, and oxalic — are polarographically active. However, oxalic acid could not be determined polarographically, since in neutral solution its wave merges with those of the other two acids while in alkaline solution, where the pyridinecarboxylic acids are not reducible, oxalic acid also gives no reduction wave. In acidic solution with 0.1 N sulfuric acid as supporting electrolyte, oxalic acid does not interfere with the determination of the other two acids, since its wave is submerged by the background discharge. Under these conditions dipicolinic acid is reduced in two stages ($E_{1/2}$ — 0.77 V and −1.03 V) and 6-methylpicolinic acid in one stage ($E_{1/2}$ −0.90 V). Because of this difference in their half-wave potentials these two acids can be quantitatively determined separately when they are simultaneously present in the solution.

We examined the reaction kinetics by adding potassium permanganate in ten portions to a 4% aqueous solution of 2,6-lutidine. Each successive portion of the oxidant was added after the complete decoloration of its predecessor; the total quantity of potassium permanganate was 130% of the theoretical and the reaction temperature 70-75°C.

Figure 1 shows our kinetic measurements, which indicate that 2,6-lutidine is oxidized quite rapidly and is almost undetectable only 6 h after the start of the reaction. The quantity of intermediate 6-methylpicolinic acid reaches a maximum 3 h after the start of the reaction (i.e., after the addition of ~40% of the total quantity of the oxidant). However, even in its earliest stages the reaction proceeds further, forming dipicolinic and oxalic acids, and as a result at the moment when the oxidation of (II) is complete the reaction solution contains roughly equal amounts of dipicolinic and 6-methylpicolinic acids. Subsequently, the content of 6-methylpicolinic acid in the reaction products continues to fall, being 0.32 g per 100 ml at the moment when the tenth portion of potassium permanganate is decolorized (i.e., 23.5 h after the start of the reaction); after a further 5 h it is almost absent from the reaction mixture. The dipicolinic acid concentration reaches a maximum (4.2 g per 100 ml) after the decoloration of the tenth portion of potassium permanganate and the addition of more oxidant (more than 30% excess over the theoretical) forces the reaction toward reduction in the concentration of dipicolinic acid, which is 3.7 g per 100 ml 34 h after the start of

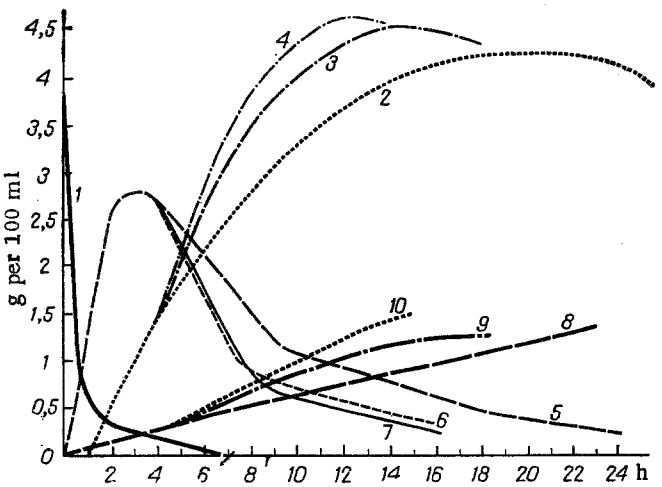

Fig. 1. Kinetics of the oxidation of 2,6-lutidine: 1) concentration of 2,6-lutidine; concentration of (I) at 2) 70-75°C; 3) 80-85°C; 4) 85-90°C; concentration of (III) at 5) 70-75°C; 6) 80-85°C; 7) 85-90°C; concentration of (V) at 8) 70-75°C; 9) 80-95°C; and 10) 85-90°C.

oxidation (282 g of the oxidant or a 50% excess over the theoretical) 3.0 g per 100 ml and after 55 h (352.5 g of the oxidant or a 95% excess over the theoretical).

Oxalic acid (V) appears in the reaction mixture unexpectedly early. Even 30 min after the start of the reaction, i.e., after the decoloration of the first portion of potassium permanganate, the mixture contains 0.06 g per 100 ml, which increases to 0.16 g per 100 ml after 3 h. Subsequently, the oxalic acid concentration continues to increase, being 1.36 g per 100 ml after 23.5 h (the time at which the content of dipicolinic acid in the solution is a maximum). After 34 h the quantity of oxalic acid reaches a maximum (2.05 g per 100 ml); subsequently addition of more oxidant causes the conversion of oxalic acid to carbonates and its content in the solution after 55 h is 1.8 g per 100 ml. These general features of the oxidation also persist at slightly different reaction temperatures. Increase in the reaction temperature to 80-85°C during decoloration of the sixth to tenth portions of potassium permanganate also accelerates the reaction and, as Fig. 1 shows, correspondingly displaces the maxima of all the product concentrations.

A run in which pure dipotassium dipicolinate was oxidized by potassium permanganate while samples were removed and analyzed confirmed the formation of oxalic acid by cleavage of the pyridine ring during the oxidation of dipicolinic acid. The kinetics of this process are shown in Fig. 2.

The appearance of oxalic acid (V) in addition to dipicolinic acid (I) during the oxidation of 2,6-lutidine demanded a more detailed examination of the method used to isolate free dipicolinic acid from their mixed potassium salts. For this we prepared synthetic mixtures of dipicolinic and oxalic acids containing 17, 23, 28, and 55% of the latter. The mixtures were dissolved in the calculated quantity of titrated alkali solution and then acidified with the calculated amount of 36% hydrochloric acid (the final solution pH was −0.15 to −0.2). We recrystallized the precipitate from the same solution and determined the content of oxalic acid in it. We found that if the content of oxalic acid in the original mixture does not exceed 23%, the resulting dipicolinic acid is not contaminated by oxalic acid. When the original mixture contains 28% oxalic acid, the product contains 12% oxalic acid as the monopotassium salt. In the case of a 55% content of oxalic acid in the original mixture, the product derived by precipitation consists mainly of monopotassium oxalate contaminated by coprecipitated dipicolinic acid. The dipicolinic acid was purified from the accompanying monopotassium oxalate by recrystallization from 5 N hydrochloric acid in 90% yield.

Our study of the kinetics of the oxidation of 2,6-lutidine by potassium permanganate thus enables us to account for the distinctive features of the course of this reaction and the empirical parameters reported earlier and to establish the effect of various factors (reactant ratio, temperature, reaction time, etc.) on the oxidation process and on the quality of the isolated dipicolinic acid.

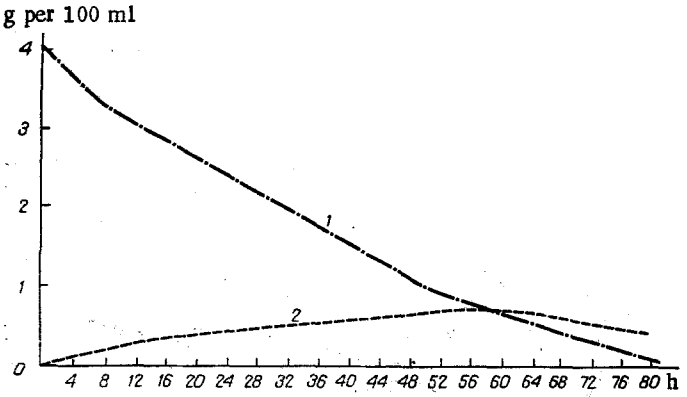

Fig. 2. Kinetics of the oxidation of dipicolinic acid (I) by potassium permanganate at 85°C. Concentration of 1) compund (I) and 2) compound (V).

EXPERIMENTAL

Oxidation of 2,6-Lutidine (II) by Potassium Permanganate. To 40.2% 2,6-lutidine [76.3 g; 30.6 g of 100% (II)] dissolved in water (690 ml) were added at 70-75°C with vigorous stirring ten portions of potassium permanganate (up to 23.5 g). Each successive portion was added after the complete decoloration of its predecessor (a sample of the reaction mixture was dabbed onto filter paper to check the absence of the characteristic color of aqueous potassium permanganate). The temperature of the reaction mixture was maintained between 70 and 75°C. After the complete decoloration of each portion of potassium permanganate, a sample (5 ml) was removed from the reaction mixture for analytical control. After the end of the reaction the precipitated manganese dioxide was filtered off at 70-75°C and washed on the filter with hot water (water temperature 80°C; 3 × 50 ml). The combined filtrates were evaporated to a volume of 600 ml and 35% hydrochloric acid (170 ml) was added. To secure complete conversion of monopotassium dipicolinate to the free diacid the initial precipitate was dissolved by heating of the reaction mixture to 90°C. The solution (pH −0.2 to −0.25) was then cooled to 12-15°C over a period of 1 h and kept at 10-12°C for 1 h. The precipitated dipicolinic acid was filtered off, dried to constant weight, and the content of dipicolinic acid was determined by titration with sodium hydroxide against phenophthalein and by polarographic titration by the method described below. Both methods gave a content of (I) of not less than 98%. The absence of oxalic acid was then determined by permanganatometric titration by the method described below and the absence of any incombustible residue (contamination by monopotassium dipicolinate and oxalate) was also verified. The yield of dipicolinic acid was 29 g (60%), mp 243-244°C (with decomposition).

The same method was used for runs in which the first five portions of potassium permanganate were added at 70-75°C and the other portions at 80-85 or 85-90°C. The yields of dipicolinic acid were respectively 29.6 (61%) and 30.1 g (62.2%). The kinetic curves were plotted on the basis of four series of runs (the data from parallel experiments were almost identical). Special runs were also made in which further portions (23.5 g each) of potassium permanganate were added. In these runs dipicolinic acid was not isolated preparatively at the end of the run, and only the analyses of samples of the reaction mixture were used (Fig. 1).

The acidic aqueous mother liquor after the removal of 29 g of dipicolinic acid as described above was evaporated to dryness. Residual water was removed by azeotropic distillation with benzene (100 ml) in a Dean-Stark trap, butanol (180 ml) and KU-2-8 cation-exchange resin (H^+ form; 20 g) were added, and the mixture was refluxed for 12 h with vigorous stirring with removal of the water liberated during the reaction by distillation. The cation-exchange resin and insoluble inorganic salts were filtered off and washed with hot butanol (3 × 20 ml). The combined butanol filtrates were evaporated. The residue contained (GLC) dibutyl dipicolinate (24.7%), butyl 6-methylpicolinate (2.9%), and dibutyl oxalate (72.4%). Fractional distillation of the resulting mixed esters under vacuum gave a fraction (15.5 g) with bp 88-92°C (4 mm). The colorless mobile liquid had n_D^{20} 1.4220. Found, %: C 59.20; H 8.85. $C_{10}H_{18}O_4$. Calculated, %: C 59.38; H 8.97. The compound was identical to a sample of dibutyl oxalate [8] prepared independently by esterification of oxalic acid with butanol in the presence of KU-2-8 cation-exchange resin by a procedure like that described above.

TABLE 1.

$f=m-2$	a	b	S	n_j	$\bar{x}$	P	$t(p,f)$	$\Delta\bar{x}$, g/liter	Relative $\Delta\bar{x}$, %
15	1,28	8408,26	1,727	2	0,01085	0,95	2,13	0,0025	2,3

Oxidation of Dipicolinic Acid with Potassium Permanganate. Dipicolinic acid (32 g) (purity 100%), potassium hydroxide (10.8 g), and potassium permanganate (25 g) were dissolved in water (768 ml) with heating and stirred at 85°C until complete decoloration of the potassium permanganate. A sample (5 ml) was removed for analysis and a fresh portion of potassium permanganate (25 g) was added. In all, ten portions of the oxidant (250 g) were added over a period of 80 h. The results are shown in Fig. 2.

GLC Analysis of the Mixed Butyl Esters of Dipicolinic, 6-Methylpicolinic, and Oxalic Acids. The analysis was carried out on a JEOL-810 chromatograph with a flame-ionization detector, stainless-steel column (length 1 m, inner diameter 3 mm), stationary phase Chromosorb W-HMDS with 4% XE-60, carrier gas helium (40 cm^3/min), with temperature programming from 105-160°C at 18°C/min. Contents were calculated by normalization of peak areas without use of correction coefficients.

Procedure for Determining Oxalic Acid in the Reaction Mixture. The reaction solution (2 ml) was transferred by pipette to a 50 ml conical flask containing water (30 ml), acidified with concentrated sulfuric acid (5 ml), and heated to 80°C. The hot solution was titrated with 0.1N potassium permanganate until the pink coloration persisted; 1 ml of 0.1 N potassium permanganate corresponded to 0.004501 g of anhydrous oxalic acid.

Runs with synthetic mixtures of the pure products demonstrated that 2,6-lutidine, 6-methylpicolinic acid, and dipicolinic acid when simultaneously present did not interfere with the quantitative determination of oxalic acid by this method.

Polarographic Determination of Dipicolinic and 6-Methylpicolinic Acids in the Reaction Mixture. This was carried out in a thermostatted cell at 25 ± 0.1°C. The dropping mercury electrode with forced detachment of drops with a blade had the parameters m = 1.06 mg/sec, t = 0.305 sec, and $m^{2/3}t^{1/6}$ = 0.85 in 1N potassium chloride with open circuit. Oxygen was purged from the solutions with a stream of purified nitrogen. The anode was a remote saturated calomel electrode. The polarograms were recorded on a Radiometer (Denmark) PO-4 polarograph. Pure samples of dipicolinic and 6-methylpicolinic acids were used to construct the calibration curve. To evaluate the method used to construct the calibration curve the results were processed by regression analysis [9]. Least squares and comparison of the dispersions by the Fisher test showed that, as exemplified by dipicolinic acid, the calibration curve can be fitted to the equation $Y = a + bx$, where y is the height of the polarographic wave (mm) and x is the concentration of dipicolinic acid in the solution (g/liter). The results of the statistical treatment of the calibration curve are summarized in Table 1 (with conventional notation).

Analytical Procedure. A sample of the reaction mixture (1 ml) was transferred by pipette to a 25 or 50 ml graduated flask and diluted to the mark with distilled water; 1 or 2 ml of of the resulting solution were transferred to a 10 ml graduated flask, 1 ml of 1N sulfuric acid was added, and the solution was diluted to the mark with distilled water. The solution was transferred to the polarographic cell, dissolved oxygen was purged with a stream of nitrogen, and the polarogram was recorded between −0.5 and −1.1 V. The wave heights of dipicolinic acid ($E_{1/2}$ − 0.77 V) and 6-methylpicolinic acid ($E_{1/2}$ −0.90 V) were measured and their concentrations were derived from the calibration curves.

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N-ACETYL-ε-AMINOCAPROIC ACID. III. IMPROVED SYNTHESIS OF N-ACETYL-ε-AMINOCAPROIC ACID

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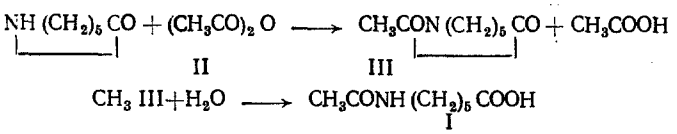
We have reported earlier [1] that the preparation Acemin, which is based on N-acetyl-ε-aminocaproic acid [1], is an effective stimulator of the reparative processes involved in wound healing and knitting of bones.

The literature describes a method for the synthesis of (I) [2]



Reaction of ε-caprolactam (II) with acetic anhydride gives N-acetyl-ε-caprolactam (III), which is hydrolyzed in aqueous solution with acetic acid as catalyst. Water and acetic acid are then distilled off from the reaction medium, acetone is added to the residue, and the solution is left for (I) to crystallize. The resulting crude product is recrystallized from acetone. The yield of (I) is 15% of the theoretical, based on the starting (II).

The purpose of our work was to develop an efficient method for the preparation of (I) that would give a higher yield.

Published figures [2, 3] for the quantity of the acetylating agent, temperature, and reaction time for the acetylation of (II) are conflicting. Thus, these sources specify the quantity of acetic anhydride as one and six moles per mole of (II), the reaction time as 1 and 4 h, and the acetylation temperature as 100 and 140°C. The yield of (III) is about 80% of the theoretical.

Detailed studies revealed that the acetylation of (II) is accompanied by side reactions of polymerization, which reduce the yield of the major product. Polymerization is accelerated by increase in temperature, reduction in the excess of acetic anhydride, and increase in the reaction time. We established that the optimum yield of (III) (up to 96% of the theoretical) is given by molar reactant ratios of 1:1.2 to 1:1.5, temperatures of 110-130°C, and acetylation times of not more than 2 h.

Following [2] we hydrolyzed (III) with 3% acetic acid with a (III)/hydrolyzing mixture weight ratio of 1:3 at 100°C over a period of 6 h. We isolated (I) by the published method; recrystallization from acetone resulted in a yield of about 18% of the theoretical based on starting (III).

Seeking the causes of so low a yield of (I) we found that the hydrolysis of (III) proceeds simultaneously by two pathways and further that reactions A and B have comparable rates [4]:

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