SYNTHESIS, PROPERTIES, AND BIOLOGICAL ACTION OF 5-ISOALKYLPICOLINIC ACIDS

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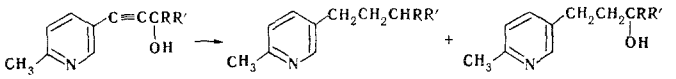
Reduction of (6-methyl-3-pyridyl)ethynylcarbinols with hydriodic acid gave a series of 2-methyl-5-isoalkylpyridines, oxidation of which with selenium dioxide gave a number of 5-isoalkylpicolinic acids. The antimicrobial activity of the latter is higher than that of fusaric acid, especially in the case of compounds with an unbranched alkyl chain.

Of the isomeric alkylpicolinic acids and their esters, 5-alkylpicolinic acids display the greatest bactericidal action, and this action increases as the length of the alkyl chain increases [1]. This sort of effect is probably associated with the increase in the hydrophobic character of the molecule and, correspondingly, with the ready lipoid solubility and increase in the ability of the compound to penetrate into the protoplast.

We have previously described the synthesis of 5-butylpicolinic (fusaric) acid and its homologs from 2-methyl-5-ethynylpyridine [2], but the possibilities of the synthesis, via this method, of compounds with longer or more branched groups were limited. To obtain such compounds we used 2-methyl-5-ethynylcarbinols containing tertiary and secondary alcohol groups [3].

We have previously shown that a triple bond conjugated with the pyridine ring is smoothly reduced with an aluminum–nickel alloy in alkaline media [4], but the hydroxyl group was not reduced in the process. It is known that hydriodic acid readily reduces olefins and acetylenes [5], as well as alcohols [8], to the corresponding hydrocarbons, but this reduction does not always proceed smoothly.

We have used this reagent for the simultaneous reduction of the triple bond and the hydroxyl group in pyridylethynylcarbinols by heating them with an excess of red phosphorus and iodine in glacial acetic acid for 8-10 h. It was found that the reduction does not go to completion and that the reaction products contain a considerable amount of halogen; a mixture of both 2-methyl-5-alkylpyridines (I) and 2-[(6-methyl-3-pyridyl)ethyl]carbinols (II) was obtained by additional reduction of them with a nickel–aluminum alloy in alkaline media [4]:



I a-e II b-e

a R=H, R′=C_8H_{17}; b R=R′=CH_3; c R+R′=$(CH_2)_5$; d R=CH_3, R′=t-C_4H_9; e R=CH_3, R′=C_6H_5

An increase in the reaction time to 30 h made it possible to increase the yield of I, but a small amount of II was nevertheless formed in a number of cases. This is apparently explained by the fact that the acetylene grouping is reduced considerably more readily by hydriodic acid than a tertiary alcohol group, the reduction of which does not always proceed quantitatively [6]. The properties of the newly synthesized alkylpyridines (I) are presented in Table 1. In the reduction with hydriodic acid, one might have expected isomerization of the hydrocarbon skeleton in the 5 position of the pyridine ring, but analysis of the mass spectra of I (Table 2) showed that this did not occur. As with other 2-methyl-5-alkylpyridines [7], the principal process in the disintegration of I under the influence of electron impact consisted of the dissocia-

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TABLE 1. 2-Methyl-5-alkylpyridines (I)

Compound	bp, °C (mm)	n_D^{20}	Yield, %	UV spectrum		Picrate					
				λ_{max}, nm	lg ε	mp, °C (alcohol)	empirical formula	found, %		calc., %	
								C	H	C	H
Ia	137—140 (1)	1,4875	58	268	3,61	127—129	$C_{17}H_{26}N \cdot C_6H_3N_3O_7$	58,1	6,7	58,2	6,4
Ib	120—121 (23)	1,4909	30[a]	267	3,63	153—155	$C_{11}H_{17}N \cdot C_6H_3N_3O_7$	52,3	5,2	52,0	6,4
Ic	138—139 (10)	1,5121	44[b]	267	3,59	105—108	$C_{14}H_{21}N \cdot C_6H_3N_3O_7$	55,4	5,5	55,5	5,6
Id	130—131 (7)	1,5020	50[c]	267	3,66	111—113	$C_{14}H_{23}N \cdot C_6H_3N_3O_7$	55,4	6,1	55,3	6,0
Ie	120—123 (0,6)	1,5540	44[c]	268	3,66	122—123	$C_{16}H_{19}N \cdot C_6H_3N_3O_7$	58,1	4,9	58,1	4,9

[a]Compound IIb was simultaneously isolated in 6% yield. [b]Traces of carbinol IIc were detected. [c]Compound IIe was also isolated in 23% yield. The picrate had mp 145-147° (from alcohol). Found: N 11.6%. $C_{16}H_{19}NO \cdot C_6H_3N_3O_7$. Calculated: N 11.9%.

TABLE 2. Mass Spectra of Alkylpyridines Ia-d and 5-Alkylpicolinic Acids IIIb-d, f

Compound	Mass spectrum[a]
Ia	M^+ 247 (12), 176 (12), 162 (12), 134 (21), 120 (100), 107 (93), 106 (69), 77 (24), 55 (13), 43 (15), 41 (29)
Ib	M^+ 169 (40), 148 (4), 120 (20), 107 (70), 106 (100), 79 (15), 78 (14), 77 (33), 65 (8), 57 (14), 41 (19)
Ic	M^+ 203 (26), 120 (22), 107 (100), 106 (46), 95 (16), 83 (9), 79 (16), 77 (22), 67 (14), 55 (35), 41 (19)
Id	M^+ 205 (10), 190 (5), 149 (12), 120 (24), 107 (100), 106 (72), 77 (23), 57 (23), 55 (22), 43 (25), 41 (42)
IIIf	M^+ 235 (8), 191 (8), 150 (82), 137 (56), 119 (41), 106 (86), 93 (100), 92 (58), 91 (30), 65 (55), 57 (68)
IIIb	M^+ 193 (1), 149 (100), 136 (7), 119 (21), 93 (11), 92 (10), 91 (17), 57 (21), 45 (8), 43 (13), 41 (23); *m** 115,0, 103,5, 69,5
IIIc	M^+ 233 (16), 189 (36), 137 (8), 119 (10), 106 (29), 97 (18), 93 (95), 92 (37), 83 (11), 65 (30), 56 (100)
IIId	M^+ 235 (1), 220 (6), 191 (7), 180 (6), 150 (10), 137 (91), 136 (9), 119 (28), 92 (6), 91 (6), 57 (100); *m** 185,5, 103,5

[a]The M^+ and m/e values of the most intense peaks and, in parentheses, the relative intensities (%) are presented.

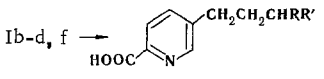
TABLE 3. 5-Alkylpicolinic Acids (III)

Compound	mp, °C[a]	Empirical formula	Found, %		Calc., %		UV spectrum		Yield, %
			C	H	C	H	λ_{max}, nm	lg ε	
IIIb	119—120	$C_{11}H_{15}NO_2$	68,3	8,0	68,4	7,8	270	3,77	20
IIIc	138—140	$C_{14}H_{19}NO_2$	72,5	8,3	72,1	8,2	270	3,57	29
IIId	123—125	$C_{14}H_{21}NO_2$	71,6	9,2	72,3	9,0	270	3,71	38
IIIf	104—106[b]	$C_{14}H_{21}NO_2$	72,3	8,8	72,3	9,0	270	3,57	30

[a]From heptane. [b]According to [8], mp 105-106°.

tion of the benzyl C—C bond to give an intense ion peak with m/e 106 and a rearranged ion with m/e 107. The presence in the investigated compounds of characteristic groupings (for example, tert-butyl or cyclohexyl residues) was characterized by the presence in the mass spectra of ions with m/e 57 and 83, respectively. Cleavage of the γ-C—C bond (with respect to the ring) of the alkyl chain to give an ion peak with m/e 120 is also characteristic for all I; for 2-methyl-5-undecylpyridine, this path is apparently energetically favorable, since the peak with m/e 120 is a maximum in the spectrum. In addition, the mass spectrum of this compound also contains characteristic peaks of lower intensity (m/e 134, 148, 162, etc.) that are specific for alkylpyridines.

The series of 2-methyl-5-alkylpyridines obtained in this manner were oxidized selectively with selenium dioxide to the corresponding 5-alkylpicolinic acids (Table 3).



IIIb-d, f

b $R=R'=CH_3$; c $R-R'=(CH_2)_5$; d $R=CH_3$, $R'=t\text{-}C_4H_9$; f $R=H$, $R'=C_6H_{13}$

TABLE 4. Antibacterial Activity of 5-Alkylpicolinic Acids

Microorganism[a]	Concn. at which the given compound inhibits growth					
	R=C_4H_9	R=C_6H_{13}	IIIb	IIIc	IIId	IIIe
Staphylococcus aureus	1 : 4000	1 : 30000	1 : 4000	1 : 30000	1 : 16000	1 : 30000
Hemolytic streptococcus	1 : 4000	1 : 16000	1 : 4000	1 : 16000	1 : 8000	1 : 30000
Diphtheria bacillus, PW_3 strain	1 : 8000	1 : 30000	1 : 8000	1 : 30000	1 : 16000	1 : 60000
Human tuberculosis bacillus	1 : 8000	1 : 60000	1 : 8000	1 : 250000	1 : 60000	1 : 500000
Acid-resistant saprophyte B_5	1 : 4000	1 : 16000	1 : 8000	1 : 30000	1 : 8000	1 : 120000
Actinomycete	1 : 8000	1 : 60000	1 : 8000	1 : 60000	1 : 120000	1 : 120000

[a]In addition, the investigated compounds proved to be active relative to Escherichia coli, Salmonella typhosa, the Flexner dysentery bacillus, anthracnose spores, avian tubercle bacillus, microsporon. Trichophyton, Achorion, and the yeast fungus Candida albicans.

Compounds III give the red-orange coloration with ferrous sulfate that is characteristic for picolinic acid, and frequencies of the C = O stretching vibrations of an un-ionized carboxyl group were observed in their IR spectra at 1700-1715 cm^{-1}. The structure of acids III was also confirmed by their disintegration under the influence of electron impact (Table 2). The dissociative ionization of acids III has characteristic peculiarities consisting of the fact that the mass spectra contain, in addition to relatively intense molecular-ion peaks,* groups of peaks of ions that characterize the presence in the molecule of both a carboxyl group and an alkyl radical. Thus intense $(M-CO_2)^+$ ion peaks are present in the mass spectra of acids III. On the other hand, the peaks of the ions of fragments formed by γ- or β-disintegration of the alkyl chain in the molecular ion with rearrangement or without rearrangement – ions with m/e 150, 137, and 136 (similar to ions with m/e 120, 107, and 106 in the mass spectra of I) – are also intense. They then undergo decarboxylation to give fragment ions with m/e 106, 93, and 92. One would especially note the rather intense peak of the ion with m/e 119. The presence of a metastable ion with m/e 103.5 proves that the ion with m/e 119 is formed by loss of a molecule of water by the rearranged ion with m/e 137. The mechanism of this process requires additional investigation.

According to the data of the division of chemotherapy of S. Ordzhonikidze All-Union Scientific-Research Pharmaceutical-Chemistry Institute, acids III, including those obtained in [3], inhibit the growth of a number of microorganisms (Table 4), and, as expected, the activity increases as the length of the alkyl chain increases. In some cases, 5-octylpicolinic acid (IIIf) proved to be more active (by factors of 30 and even 60) than 5-butylpicolinic (fusaric) acid. However, branching of the alkyl chains did not substantially affect the antibacterial properties of the investigated compounds. It can be assumed that the effect of bulky substituents is exerted on the permeability of the compounds through the cell membranes, and the further search for antibacterial preparations in the 5-isoalkylpicolinic acids is of little promise. At the same time, an increase in the hydrocarbon chain in the case of 5-n-alkylpicolinic acids may lead to an increase in the antibacterial activity. All of the new acids proved to be more active than natural fusaric (5-butylpicolinic) acid.

EXPERIMENTAL

The individuality of the synthesized compounds was verified by means of thin-layer chromatography (TLC) on activity-II aluminum oxide in benzene–methanol (25 : 1, system A) and benzene–acetone (5 : 1, system B) and, in the case of alkylpicolinic acids, by means of chromatography on "Leningrad medium" paper in ethanol–ammonia–water (20 : 1 : 4) and isopropyl alcohol–ammonia–water (10 : 1 : 1). The UV spectra of methanol solutions were recorded with an SF-4 spectrophotometer. The IR spectra were recorded with an IKS-14 spectrometer. The mass spectra were recorded with an MKh-1303 spectrometer with injection of the liquid compounds through the inlet cylinder and injection of the acids directly into the ion source at an ionizing electron energy of 50 eV.

2-Methyl-5-(1-octynyl)pyridine. A. A 46.4-g (0.4 mole) sample of 2-methyl-5-ethynylpyridine was added with stirring and cooling in the course of an hour to a solution of freshly prepared sodium amide [from 9.2 g (0.4 g-atom) of sodium in 600 ml of liquid ammonia], 3 h after which 6.6 g (0.4 mole) of hexyl bromide was added by drops. The mixture was stirred for 6 h, and the ammonia was evaporated. Water

*The intensity of the molecular ion does not exceed 0.5% of the maximum ion only in the case of acid IIId, which contains a very branched grouping.

(700 ml) was added to the residue, and the aqueous mixture was extracted with ether. The ether extracts were washed with water and dried with anhydrous potassium carbonate. The ether was evaporated, and the residue was vacuum-distilled to give 12.5 g (60% based on the converted 2-methyl-5-ethynylpyridine) of a product with bp 126-128° (2 mm), n_D^{20} 1.5235, and d_4^{20} 0.9215. The picrate had mp 121-122° (from alcohol). Found: C 55.9; H 5.1%. $C_{14}H_{19}N \cdot C_6H_3N_3O_7$. Calculated: C 55.8; H 5.2%. The product had an R_f value of 0.73 (system A). UV spectrum: λ_{max} 242-243, 247-248, 283-284 nm (log ε 4.24, 4.24, 3.68).

B. A 5.8-g (0.05 mole) sample of 2-methyl-5-ethynylpyridine was added with stirring in the course of 10 min to 1.15 g (0.05 g-atom) of sodium in 20 ml of refluxing absolute toluene, after which 12.8 g (0.05 mole) of hexyl p-toluenesulfonate was added rapidly in the course of 10 min at 70°. The mixture was stirred at 80° for another 3 h, after which it was cooled, decomposed with water, and extracted with ether. The organic layer was separated, washed with water, and dried with anhydrous potassium carbonate. The solvent was removed by vacuum distillation, and the residue was distilled to give 2.5 g (28%) of a product with bp 126-128° (2 mm) and n_D^{20} 1.5235.

2-Methyl-5-octylpyridine. A solution of 7.3 g (0.036 mole) of 2-methyl-5-(1-octynyl)pyridine in 30 ml of absolute ethanol was shaken in a hydrogenating device in the presence of 1.1 g of Raney nickel catalyst at 20° and normal pressure. After 1.6 liter of hydrogen (an equimolecular amount) had been absorbed, the catalyst was removed by filtration, the alcohol was removed by distillation, and the residue was vacuum-distilled to give 6.0 g (81%) of a product with bp 148-150° (11 mm) and n_D^{20} 1.4845. The picrate had mp 123-124° (from alcohol). Found: C 55.6; H 6.2%. $C_{14}H_{23}N \cdot C_6H_3N_3O_7$. Calculated: C 55.3; H 6.0%. The product had an R_f value of 0.66 (system A). UV spectrum: λ_{max} 267 nm (log ε 3.63).

2-Methyl-5-(3-hydroxy-1-undecynyl)pyridine. A solution of 11.7 g (0.1 mole) of 2-methyl-5-ethynylpyridine in 30 ml of absolute tetrahydrofuran was added by drops with stirring to a solution of butylmagnesium bromide [from 2.4 g (0.1 g-atom) of magnesium and 13.7 g (0.1 mole) of butyl bromide] in 250 ml of absolute tetrahydrofuran at room temperature in the course of 20 min. When butane evolution had ceased, the mixture was cooled to 0°, and 17.3 ml (0.1 mole) of freshly distilled nonanal was added by drops in the course of 15 min. The solution was stirred at room temperature for 2 h, heated to 100° in the course of 15 min, cooled to 0°, and treated with 100 ml of a saturated ammonium chloride solution. The resulting oil was extracted with ether, and the extract was dried with anhydrous magnesium sulfate. The ether was removed by vacuum distillation, and the residue was recrystallized from petroluem ether at −30 to −40° to give 14 g (54%) of a product with mp 33-34°. The picrate had mp 109-112° (from alcohol). Found: C 56.8; H 5.9%. $C_{17}H_{25}NO \cdot C_6H_3N_3O_7$. Calculated: C 56.6; H 5.8%. The product had an R_f value of 0.18 (system B).

2-Methyl-5-isoalkylpyridines. A mixture of 0.08 g-atom of red phosphorus, 0.5 mole of iodine, and 300 ml of glacial acetic acid was stirred for 20 min, after which a solution of 0.1 mole of [(6-methyl-3-pyridyl)ethynyl]carbinol in 50 ml of glacial acetic acid and 18 ml of water were added by drops successively. The mixture was refluxed with vigorous stirring for 8-30 h and cooled. The unchanged red phosphorus was removed by filtration, and the filtrate was treated with sodium bisulfite solution until it was decolorized. The colorless filtrate was made alkaline with concentrated ammonium hydroxide solution, and the resulting oil was extracted with ether. The ether extract was dried with anhydrous magnesium sulfate, and the ether was removed in vacuo. The residue was treated with 450 ml of 10% sodium hydroxide, and 40 g of nickel–aluminum alloy (1 : 1) was added in portions at 90° with continuous stirring. The mixture was stirred at 90° for another 3 h, and the hot solution was filtered. The solid material was washed with water, and the filtrate was extracted with ether. The extract was dried with anhydrous magnesium sulfate, and the ether was removed in vacuo. In the case of the formation of a mixture of I and II, the residue was separated preparatively with a column filled with aluminum oxide (2.5 by 10 cm). In this case, I was eluted with benzene, the eluate was evaporated, and the residue was vacuum-distilled. Subsequent elution with ethyl acetate gave II.

5-Alkylpicolinic Acids. A suspension of 0.014 mole of 2-methyl-5-alkylpyridine and 0.02 mole of selenium dioxide in 50 ml of β-picoline was heated with stirring at 125-130° for 2 h. The selenium was removed by filtration, and the filtrate was steam-distilled. The residue was vacuum-evaporated to dryness and crystallized three times from heptane. The light colorless crystals were vacuum-sublimed twice at 120-130° and 10 mm.

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