REACTION OF 3- AND 4-PYRIDINEALDEHYDES WITH INDOLE-2-CARBOXYLIC ACID

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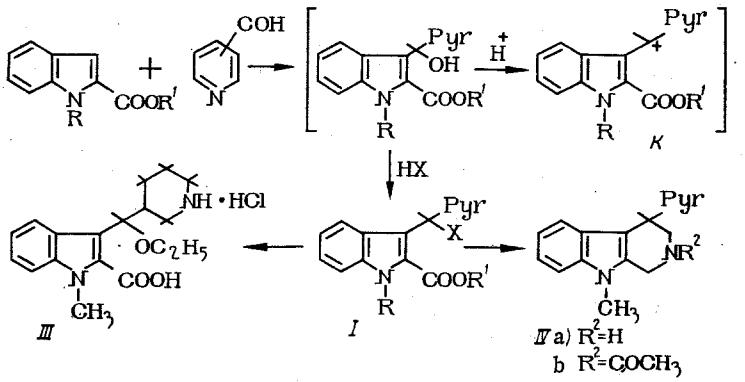
In the continuing search for medicinal substances among products of condensation of indoles with aldehydes [1], we turned to pyridinealdehyde, in view of the extensive participation of the pyridine ring in metabolism, and in anticipation of the ready availability of these compounds. The condensation reaction of pyridine 3-aldehyde with indole to form 3-indolidenepyrimidyl methane is described in the literature [2]. The addition product of indolyl magnesium bromide with 2-pyridinealdehyde at 25°C (3-indolyl-2^1-pyridylcarbinol) was formed in 50% yield [3]. Elevated temperatures resulted in the formation, predominantly, of di-(indolyl-3)pyridylmethane [3]. Aromatic aldehydes with indolyl-2-carboxylic acid under conditions of acid catalysis produce a high yield of the addition product — 2-carboxy-3-(α-halobenzyl)indoles [4]. In that reaction electron donor substituents in the aldehyde lead to di-(indolyl-3)phenylmethanes, while electron acceptor substituents produce structures, like I.



It is the purpose of the present work to compare and evaluate pyridinealdehyde with benzaldehydes in their reaction with indolyl-2-carboxylic acids, as well as the investigation of the anti-inflammatory activity of the reaction products.

Pyridine-3- and pyridine-4-aldehyde easily produced the intermediate 2-carboxy-3-indolylpyridylcarbinol in the reaction with the ethyl ester of indolyl-2-carboxylic acid (Iℓ) and its N-methyl derivatives (Ia, b, d, i, and g). Depending on the catalyst (acetyl chloride, acetyl bromide), we obtained chlorides Ia and Ii, bromide Ib; and when the reaction was conducted in alcohol saturated with hydrogen chloride, the products were the methoxy-(Ic) and ethoxy derivatives (Id and Ig) (See Table 1).

Pyridine-3-aldehyde formed hydrochloride Id, which was converted by the action of ammonia into the base Ie. The hydrochlorides of pyridine-4-aldehyde derivatives were unstable, and upon standing lost a molecule of hydrogen chloride. The halogen in compounds Ia, b, and e was exchanged by group X, with X = OH (in NaOH) or CH_3O (in methanol), or C_2H_5O (in ethanol), or CN (with NaCN in dimethylsulfoxide). The ability to substitute group X in 3-(α-X-pyridylmethyl)indoles I depends essentially on the change of the nitrogen atom in the pyridine ring. Group X in pyridine salts is rather unreactive, while in neutral or weakly alkaline media it can be as readily substituted as in 3-(α-X-benzyl)indoles. Thus, conversion of the neutral carbinol If into the ethoxy derivative Ie is accomplished by recrystallization of If from ethanol, while for the conversion of Ia into Ie it is necessary to reflux in ethanol for 1 h. The chloride Ia does not hydrolyze in aqueous solutions, in contrast with the bromide Ib which yields carbinol If.

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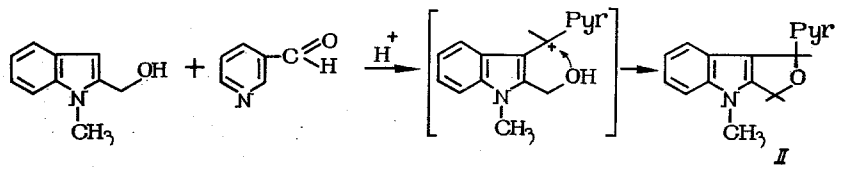
TABLE 1. Derivatives of 1-Alkyl-(pyridyl-X-methyl)-indolyl-2- Carboxylic Acids

Compound	R	R'	X	Pyridyl	Yield, %	Melting point, °C	Found				Molecular formula	Calculated			
							C	H	N	halogen		C	H	N	halogen
Ia	CH_3	OH	Cl	3-Pyr·HCl	85	186—8	56,5	3,6	8,3	21,0	$C_{16}H_{13}N_2O_2Cl \cdot HCl$	57,0	3,85	8,3	21,1
Ib	CH_3	OH	Br	3-Pyr·HBr	80	189—200	—	—	6,2	37,0	$C_{16}H_{13}N_2O_2Br \cdot HBr$	45,0	3,20	6,55	37,4
Ic	CH_3	OH	OCH_3	3-Pyr·HCl	93	187	60,8	4,7	8,3	10,4	$C_{17}H_{16}N_2O_3 \cdot HCl$	61,5	4,82	8,45	10,7
Id	CH_3	OH	OC_2H_5	3-Pyr·HCl	88	182	—	—	8,1	10,8	$C_{18}H_{18}N_2O_3 \cdot HCl$	61,5	5,20	8,10	10,3
Ie	CH_3	OH	OC_2H_5	3-Pyr	78	173	69,3	5,4	14,3	—	$C_{18}H_{18}N_2O_3$	69,6	5,80	9,0	—
If	CH_3	OH	OH	3-Pyr	75	184	68,2	7,0	14,0	—	$C_{16}H_{14}N_2O_3$	68,0	7,30	14,5	—
Ig	CH_3	OH	OC_2H_5	4-Pyr·HCl	50	215—220	60,8	4,7	9,9	9,9	$C_{18}H_{18}N_2O_3 \cdot HCl$	61,5	5,20	8,10	10,3
Ih	CH_3	OH	OC_2H_5	4-Pyr	45	215—218	—	—	8,8	—	$C_{18}H_{18}N_2O_3$	69,6	5,80	9,0	—
Ii	CH_3	OH	Cl	4-Pyr	60	210—3	63,7	6,5	8,8	12,2	$C_{16}H_{13}ClN_2O_2$	64,0	6,76	9,35	11,8
Ij	CH_3	OH	OC_2H_5	3-Pyr·CH_3I	69	175—7	47,7	3,6	6,3	27,8	$C_{18}H_{18}N_2O_3 \cdot CH_3I$	48,0	4,0	6,20	28,0
Ik	CH_3	OH	CN	3-Pyr	35	227—230	69,4	4,4	14,1	—	$C_{17}H_{13}N_3O_2$	70,7	4,46	14,4	—
Il	H	OC_2H_5	OC_2H_5	3-Pyr	54	100—3	74,0	6,3	9,10	—	$C_{19}H_{22}N_2O_2$	74,5	6,83	8,69	—
Im	$CH_2C_6H_5$	OCH_3	Cl	4-Pyr	61	255	69,6	4,4	7,22	9,0	$C_{24}H_{19}ClN_2O_2$	70,5	4,91	7,21	9,2
In	$CH_2C_6H_5$	OCH_3	Cl	3-Pyr	65	188	69,8	4,3	7,0	8,7	$C_{23}H_{19}ClN_2O_2$	70,5	4,91	7,21	9,2
III	CH_3	OH	OC_2H_5	2-Piperidyl·HCl	72	155—7	61,0	6,5	7,4	9,5	$C_{18}H_{24}N_2O_3 \cdot HCl$	61,3	6,8	7,96	10,0

An important characteristic of the reaction producing structures I is the absence among the products of di-(2-carboxyindolyl-3)pyridylmethanes. The formation of the latter should be the result of electrophilic attack by carbonation K on chloride Ia [5]. In a strongly acidic medium chloride Ia exists in the form of a pyridinium salt, and therefore the formation of a doubly-charged cation K as well as its interaction with the pyridyl cation Ia, is quite unlikely.

The proof of the formation of a carbonium center at the α-carbon of the side chain comes from research on molecules in which the carbon center is intramolecularly attacked by the nucleophilic reagent — the CH_2OH group — with the formation of 1-(pyridyl-3)-4-methyldihydrofuro[3,4-b]indole (II).



II

The role of the carboxyl group in the original indolecarboxylic-2-acids consists of weakening the nucleophilicity of position 3 in indole, so that under the conditions leading to the formation of compounds Ia, b, and g, 2-methylindole reacts with pyridine-3-aldehyde to form di-(2-methylindolyl-3)pyridyl-3'-methane (VI).

All the compounds Ia - Ik are colorless crystalline substances, soluble in acidic and basic aqueous solution, but precipitating at pH 6.0 - 8.0. The acids Ia - Ik have high melting points (170 - 230°C), while the ester Il (Iℓ) melts at 100 - 103°C.

The structures of compounds Ia - Ig are confirmed by UV- IR- and NMR-spectral data. The NMR-spectra of chlorides Im and In (in deuterochloroform, 90 MHz) show a group of signals due to aromatic protons centered at 7.4 ppm (13H), $N{=}CH_2$ (s, 5.86 in component Io and s, 5.91 ppm in Im, 2H), OCH_3 (s, 3.9 ppm, 3H), and a characteristic singlet of an isolated proton of the CHCl group (s, 6.70 ppm, 1H). The methoxy- and ethoxy derivatives Ic and Id differ in the NMR spectrum only in the signal of the alkoxy group: in Ic — OCH_3 (s, 4.2 ppm, 3H), in Id — OC_2H_5 (q, 4.5 ppm, 2H; t, 1.35 ppm, 3H). The other groups show the corresponding signal interpretations: $N\text{-}CH_3$ (s, 4.0 ppm, 3H), CH (s, 7.4 ppm, 1H), aromatic protons (7.7 ppm, 8H). The IR-spectra of carboxylic acid derivatives Ia - Ik contained bands at 1700 - 1710 cm^{-1}, the esters Iℓ - In at 1740 - 1750 cm^{-1}, the cyano group in the nitrile Ik — 2380 cm^{-1}. The UV spectra of compounds Ia - Id showed the same absorption maximum (λ_{max} 296 nm, log ε 4.2 - 4.4) as 1-methylindolecarboxylic acid (λ_{max} 295 nm, log ε 4.2), which proves the preservation of the indole chromophore and the absence of its conjugation with the pyridine ring.

In order to increase the structural similarity of compounds I with natural compounds, substances Id and Ik were converted into homotryptamine III and tetrahydrocarboline IV, respectively. By contrast with compound Ig, Id easily transformed the pyridine ring into piperidine (III), while the fragment $C{-}OC_2H_5$ survived. This is characteristic of N-alkylated indolyl-3-carbinols [5]. Nitrile Ik was treated with lithium aluminum hydride after the cyclization to form tetrahydro-β-carboline IV, which was isolated in the form of the base IVa and the N-acyl derivative IVb.

Compounds Ic, d, and g, in contrast with the derivatives of benzaldehydes [1], show no anti-inflammatory activity and are toxic (LD_{50} 100 mg/kg, rats).

EXPERIMENTAL

1-Methyl-2-carboxy-3-(pyridyl-3-chloromethyl)indole Hydrochloride (Ia). We mixed 1.5 g (8.5 mmole) of 1-methylindole-2-carboxylic acid and 1.5 ml (14 mmole) of 3-pyridinaldehyde in 15 ml of a acetic acid—acetylchloride mixture (1:1). The reaction mixture was heated to boiling, kept hot for 2 - 3 min, then cooled to room temperature. Crystals of compound Ia precipitate (see Table 1) in a 2.4 g yield (85%). Compounds Ig, m, and o are obtained in the same way, but are isolated in the form of bases by neutralizing the aqueous solutions of their salts with pyridine. To obtain compound Ib we added to the reaction mixture acetic acid—bromide (3:1) at room temperature.

1-Methyl-2-carboxy-3-(3-pyridyloxymethyl)indole (If). This compound was obtained by treating 15 ml of an aqueous solution of 0.55 g (2 mmole) of Ib with pyridine until a precipitate formed (0.4 g, 75%), which was recrystallized from acetonitrile. Recrystallization from ethanol yielded the ethoxy derivative Ie.

1-Methyl-2-carboxy-3-(3-pyridylethoxymethyl)indole Hydrochloride (Id). We boiled 2.4 g (7.2 mmole) of compound Ia in 15 ml of ethyl alcohol for 1 h. Upon cooling we obtained 2.2 g (93%) of compound Id.* The base Ie was obtained by neutralizing the aqueous solution of Id with pyridine. The methyl iodide of compound Ie was obtained by the action of methyl iodide on a benzene solution of Ie, by refluxing for 15 min. Upon cooling we isolated the methyl iodide compound Ij.

1-Methyl-2-carboxy-3-(4-pyridylethoxymethyl)indole Hydrochloride (Ig). Method A. We boiled for 2 h 1.5 g (8.5 mmole) of 1-methylindole-2-carboxylic acid with 1.5 ml (14 mmole) of 4-pyridinaldehyde in 20 ml of absolute ethanol saturated with hydrogen chloride. Upon cooling, the crystals of Ig separated.

Method B. We refluxed compound Ii in ethanol for 2 h. Compound Ig is converted into the base Ih by neutralizing the aqueous solution with pyridine.

1-Methyl-2-carboxy-3-(3-pyridylcyanomethyl)indole (Ik). We heated 1.0 g (3 mmole) of compound Ia and 0.3 g (6 mmole) of NaCN in 20 ml of dimethylsulfoxide at 100°C for 2 h. The cooled solution was diluted threefold with water, extracted with ether (50 ml), and the ether extract was centrifuged [it contained 0.05 g (5%) of 1-methyl-2-cyano-3-(3-pyridylmethyl) indole, mp 78°C]. The aqueous layer was acidified with acetic acid to a pH of 6.0 - 7.0 and extracted with ether (2 × 100 ml). The ether extract was washed with water, dried over sodium sulfate, and then distilled. The crystals of substance Ik which were obtained were purified from acetonitrile. The yield was 0.33 g (35%).

2-Acetyl-4-(3-pyridyl)-9-methyl-1,2,3,4-tetrahydro-β-carboline (IV). To a suspension of 0.3 g of lithium aluminum hydride in 50 ml of ether we added dropwise an ether solution of 0.33 g (1.1 mmole) of compound Ik and refluxed for 2 h. The excess of lithium aluminum hydride was decomposed with water, the inorganic salts were fitered off, and the ether filtrate was dried over sodium sulfate, then evaporated to dryness. We obtained the crude 4-(3-pyridyl)-9-methyltetrahydro-β-carboline, which was purified prior to analysis by treatment with acetic anhydride (boiled with it for 2 min, then diluted with acetic acid and water). Compound IVb separated as an oily substance which crystallized on grinding and was purified from alcohol. The yield was 0.14 g (40%). mp 147 - 149°C. Elemental analysis, found %: C 74.0; H 6.85; N 13.3. $C_{19}H_{19}N_3O$. Calculated, %: C 74.6; H 6.25, N 13.5.

1-(3-Pyridyl)-4-methyldehydrofuro[3,4-b]indole (II). We boiled for 2 h 1.61 g (10 mmole) of 1-methyl-2-oxymethylindole and 1.2 g (1 mmole) of 3-pyridinealdehyde in 20 ml of ethanol saturated with hydrogen chloride. The mixture was cooled, diluted with water, and neutralized with ammonia solution to a pH of 9.0 - 10.0. A precipitate of compound II formed, which was reprecipitated from 2% acetic acid by treatment with pyridine. We obtained 1.25 g (50%), mp 215 - 218°C. Elemental analysis, found %: C 76.4; H 5.5; N 10.91. $C_{16}H_{15}N_2O$. Calculated, %: C 76.5; H 6.0; N 11.2.

1-Methyl-2-carboxy-3-(3-piperidylethoxymethyl)indole Hydrochloride (III). An alcohol solution (10 ml) of compound Id (0.70 g, 2 mmole) and 0.05 g PdO_2 on carbon were placed in a conical flask of 50 ml capacity, with a magnetic stirrer, and attached to an apparatus for hydrogenation under normal pressure. A volume of 128 ml of hydrogen (theoretical delivery 132 ml) was absorbed in 30 min. The catalyst was filtered off and the filtrate evaporated till crystallization started. The product was purified in alcohol. Yield 0.48 g (72%).

Di(2-methylindolyl-3)pyridyl-3-methane (VI). A mixture of 1.31 g (10 mmole) of 2-methylindole and 1.08 g (10 mmole) of 3-pyridinaldehyde in 15 ml of an acetic acid—acetyl chloride mixture (1:1) was boiled for 2 min. Upon cooling the crystals of compound VI separated. They were then filtered and purified by recrystallization from alcohol; yield 1.46 g (75%), mp 310°C. Elemental analysis, found %: C 73.9; H 5.62; N 10.5; Cl 9.0; $C_{24}H_{22}N_3 \cdot HCl$. Calculated, %: C 74.7; H 5.7; N 10.8; Cl 9.1%.

*Compound Ic was obtained in a similar way with methanol.

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SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF FUSARIC ACID AND ITS DERIVATIVES

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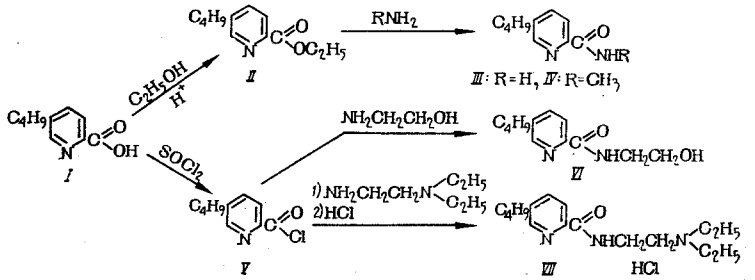
Recently there has been considerable interest in studying pharmacologically active compounds formed as products of microbial activity. Fusaric (5-butylpicolinic) acid (I) was first isolated [1] in 1934 from liquid cultures of the fungus *Fusarium heterosporum* and later found in a number of other fungi [2]. A recent method for its chemical synthesis [3] gives a low yield of the final product. We utilized microbial synthesis by *Fusarium oxysporum*, which yielded 1.6 g/liter of fusaric acid [4]. Isolation was carried out by extraction and crystallization [5]. The derivatives of fusaric acid were obtained by chemical synthesis.



The amide (III) and N-methylamide (IV) of fusaric acid were produced by reaction of the corresponding amine with the ethyl ester of fusaric acid (II). The chloranhydride of fusaric acid (V), after condensation with monoethanolamine, produced the N-ethanolamine of fusaric acid (VI), and with β-(N,N-diethylamino)ethanolamine, the N,N-diethylaminoethylamide of fusaric acid, which was isolated as the hydrochloride (VII).

PHARMACOLOGICAL PROPERTIES OF FUSARIC ACID AND ITS DERIVATIVES

Investigation of the activity of fusaric acid and its analogs were conducted using male mice (18-28 g), male rats (180-200 g), and isolated organs of cold-blooded and warm-blooded animals. The LD_{50} of fusaric acid of one intraperitoneal injection in mice was 94.4 mg/kg and this agrees with published data of 100 mg/kg [6] and 88 mg/kg [7]. Fusaric acid did not have a cumulative effect and daily injection of mice for 7 days in doses of $^1/_2$, $^1/_3$, and $^1/_4$ fo the LD_{50} did not produce detectable changes.

Hidaka [8] has shown that fusaric acid inhibited dopamine-β-hydroxylase *in vivo* and *in vitro*. On this is based the recommendation for the clinical use of fusaric acid during Parkinson's disease [9] and hypertonic disorders. In 1972 it was reported [10] that introduction of halogen in the side chain decreased the hypotensive effect and the toxicity.

In our investigation, low and medium doses of fusaric acid had no effect on the apprehensive or aggressive behavior of mice. Only in doses of $^1/_4$ to $^1/_2$ LD_{50} was the emotional

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