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SYNTHESIS AND EFFECTS ON THE CENTRAL NERVOUS SYSTEM OF SALTS OF 3-HYDROXYMETHYLPYRIDINE

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Most syntheses of 3-hydroxymethylpyridine (I) involve the reduction of nicotinic acid derivatives [1-3]. Methods have also been described for the synthesis of (I) by the reduction of 3-pyridinaldehyde (II) with sodium borohydride [4] or with hydrogen in the presence of nickel and palladium catalysts [5, 6]. We here describe a method for the reduction of (II) to (I) using thiourea dioxide, which has been used with success for the reduction of both aliphatic and aromatic ketones [7].

The reduction of (II) with thiourea dioxide was studied with initial concentrations of aldehyde and dioxide of 0.3-2.3 mole/liter in aqueous and aqueous-alcoholic media (Table 1). The reaction rates increase considerably in the presence of NaOH.

The yield of (I) dependes on the type of solvent, increasing with increasing dielectric constant from isopropyl alcohol (ε = 26) to water (ε = 80). The optimum initial concentration of (II) was 0.9 mole/liter, further increases in concentration resulting in a decrease in the

TABLE 1. Reduction of 3-Pyridinaldehyde (II) with Thiourea Dioxide at 90°C

Solvent	Initial concentration, mole/liter			Reaction time, h	Yield of (I),* %
	II	thiourea dioxide	NaOH		
Water	0,30	0,30	—	3	17,0
»	0,30	0,30	0,6	3	64,3
»	0,91	0,91	1,8	3	80,0
»	1,52	1,52	3,0	3	62,7
»	2,30	2,30	4,6	3	30,2
»	0,91	0,91	0,3	5	33,7
»	0,91	0,45	0,9	5	5,8
Isopropyl alcohol–water (1.5:1) (1,5 : 1)	0,91	0,91	1,8	5	58,1
Isopropyl alcohol	0,91	0,91	1,8	5	45,1
Ethyl alcohol– water (1,5 : 1)	0,91	0,91	1,8	5	27,5

*Yield determined by GLC.

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TABLE 2. Properties of 3-Hydroxymethylpyridine (I) Salts

Salt of (I)	mp, °C	Found, %			Empirical formula	Calculated, %		
		C	H	N		C	H	N
Oxalate	143—145	44,21	5,10	6,44	$C_8H_9NO_5 \cdot H_2O$	44,65	4,82	6,58
Maleate	69—71	51,39	4,96	5,99	$C_{10}H_{11}NO_5 \cdot 0{,}5H_2O$	51,34	5,13	5,65
Tartrate	147—148	46,40	5,08	5,33	$C_{10}H_{13}NO_7$	46,72	5,05	5,40

yield of product, apparently as a result of side reactions of the aldehyde. When the ratio of (II), reductant, and NaOH was 1:1:2, the yield of (I) reached 80.6%, with 90% selectivity.

The compound (I) forms crystalline salts with oxalic, tartaric, and maleic acids.

Ronikol (I tartrate) is used in arteriosclerosis, disturbances of peripheral and cerebral circulation, and fatty degeneration of the liver [8, 9].

We now present the results of a study of the effects of (I) oxalate, maleate, and tartrate on the central nervous system, and their toxicities.

EXPERIMENTAL CHEMISTRY

GLC and liquid chromatography were used to analyze the reaction mixtures and to determine the composition and degree of purity of the salts of (I). GLC was carried out on 2.4 m × 3 mm columns with a stationary phase consisting of 2.5% phenyldiethanolamine succinate on Chromosorb WAW DMCS (45/60 mesh), thermostat temperature 150°C, carrier gas helium, 50 ml/min, internal standard quinaldine. Liquid chromatography was carried out with a 100 × 4.6 mm column with Silasorb 600 (particle size 5 μ), rate of addition of eluent (50% $CHCl_3$ and 50% alcohol) 2 ml/min, pressure 5 MPa.

IR spectra were obtained on a Perkin-Elmer 580 B instrument in Nujol. Melting points were determined on a Boëtius microblock.

3-Hydroxymethylpyridine (I). A solution of 20.14 g (0.2 mole) of (II) (obtained by catalytic oxidation, as described in [10]), 21.16 g (0.2 mole) of thiourea dioxide, and 16 g (0.4 mole) of NaOH in 200 ml of water was heated at 90°C for 3 h, cooled, and extracted with 4 × 100 ml of a mixture of chloroform and isopentanol (9:1). The extract was dried over anhydrous Na_2SO4, filtered, the solvent distilled off, and the still residue fractionated *in vacuo* to give 8.2 g (40%) of a colorless oily liquid boiling at 135°C/10 hPa (lit. bp 140-141°C/17 hPa [2]), n_D^{20} 1,5390 (lit. n_D^{20} 5410 [2]). Found. %: N 12.68. C_6H_7NO. Calculated, %: N 12.84. IR spectrum, cm^{-1}: 3400-3050 (ν_{OH}), 1600, 1560, 1430 ($\nu_{C=C}$, $C=N$)

Salts of (I). A solution of 8.2 g (0.064 mole) of (I) and 0.096 mole of the acid (14.4, 11.1, and 8.6 g, respectively, of d-tartaric, maleic, or anhydrous oxalic acid) in 150 ml of isopropyl alcohol was stirred at ambient temperature for 15 min, the solid which separated filtered off, and air-dried to give colorless crystalline solids in 93-97% yields. The tartrate and oxalate were recrystallized from 75% ethyl alcohol (1:5 and 1:4), and the maleate from acetone (1:6) with activated charcoal (grade A).

The physicochemical properties of the salts are given in Table 2.

EXPERIMENTAL PHARMACOLOGY

Studies were carried out in mice of the BALB/c strain, of both sexes, weighing 18-25 g, and in female mongrel white rats weighing 200-250 g. The test compounds were administered intraperitoneally in doses of 0.5, 5, and 50 mg/kg as the aqueous solution, 30, 60, 120, 180, and 240 min before the appropriate test was carried out. The controls were treated with distilled water.

The experimental results were evaluated statistically, and the median effective (ED_{50}) and median lethal (LD_{50}) doese were calculated by the method of Lichfield and Wilcoxon, together with the mean arithmetic values and standard deviations of these means (M ± m). The Student t-test was used to assess the significance of the differences in the mean values. These differences were considered to be significant at the probability level $P \leqslant 0.05$.

The effects of the salts of (I) on the central nervous system were assessed by the following tests:

TABLE 3. Acute Toxicities of Salt of (I) and Nicotinic Acid by the Intraperitoneal Route in BALB/c Male Mice Weighing 18-22 g

Compound	LD_{50} (limiting values)
(I) Tartrate	1410 (680—2020)
(I) Maleate	708 (430—1019)
(I) Oxalate	1120 (84—1794)
Nicotinic acid	1120 (790—1474)

TABLE 4. Effects of Salts of (I) and Nicotinic Acid on the Duration of Narcosis Induced by Hexobarbital, Barbital-Sodium, and Chloral Hydrate, in Experiments on BALB/c Male Mice Weighing 18-22 g (t = 22°C)

Salt of (I)	Dose, mg/kg	Mean duration of narcosis, min					
		hexobarbital		barbital-sodium		chloral hydrate	
		$M \pm m$	%	$M \pm m$	%	$M \pm m$	%
Control	0	55,0±6,3	100	23,3±2,5	100	31,6±2,7	100
Tartrate	0,5	50,0±6,4	90,9	54,1±13,3*	232,2	46,7±6,9	147,8
	5	78,3±3,0	142,4	125,0±15,7*	536,5	45,8±4,1*	144,9
	50	88,3±16,1	160,5	123,3±8,4*	529,2	52,5±9,2*	166,1
Maleate	0,5	55,8±7,7	101,4	113,3±5,9*	486,3	72,5±11,3*	229,4
	5	53,3±14,3	96,9	100,8±16,0*	432,6	80,0±6,7*	253,2
	50	72,5±4,3	131,8	126,7±8,0*	543,8	72,5±8,9*	229,4
Oxalate	0,5	68,7±4,5	124,9	130,8±24,5*	561,4	35,8±11,9	113,3
	5	78,3±7,5*	142,4	95,0±17,3*	407,7	29,2±4,3	92,4
	50	81,7±7,6*	148,5	52,5±21,5	225,3	47,5±8,0*	150,3
Tartrate	0	47,5±2,9	100	24,5±1,3	100	32,0±2,7	100,0
Nicotinic acid	0,5	52,0±2,5	109,5	21,2±2,5	86,5	55,5±3,7*	173,4
	5	53,5±4,4	112,6	23,3±4,5	95,1	57,0±3,7*	178,1
	50	77,5±9,6	163,1	23,4±5,3	95,5	56,0±5,2*	175,0

*Difference from controls statistically significant at $P \leq 0.05$.

1. Effect on motor coordination and muscle tone were studied in the rotating rod test (using a Natsume Sizake apparatus, model KN-75, frequency of rotation 8 rpm for 2 min), and in tube test (using a glass tube of dimensions 30 × 2.5 cm, 30 sec).

2. Effects on motor activity (vertical and horizontal) and the exploratory reaction were studied in the 'open field' test.

3. Effects on the duration of narcotic activity were measured from the moment of loss of the turnover reflex to its return. Hexobarbital was administered intravenously in a dose of 70 mg/kg, barbital-sodium in a dose of 175 mg/kg, and chloral hydrate in a dose of 300 mg/kg intraperitoneally 30 min after the solution of the test compound had been introduced into the peritoneum.

4. Effects on the convulsive effects of an electrical current (maximum electroshock, alternating current, 50 mA, frequency 50 cycles/sec, duration of stimulus 0.2 sec) and of the convulsant drugs corazole (1% solution) and strychnine (0.01% solution), administered intravenously at a rate of 0.01 ml/sec, were studied.

5. Analgesic effects were determined by the hot plate method.

6. Effects on the central adrenergic and dopaminergic processes were studied in the 'amphetamine stereotypy' test (the amphetamine was administered subcutaneously in a dose of 10 mg/kg 30 min after injection of the test compounds).

7. Acute toxicities were determined in male mice.

TABLE 5. Effects of Salts of (I) and Nicotinic Acid on the Duration of Amphetamine Stereotypy in Mongrel White Female Rats Weighing 220-250 g

Salt of (I)	Dose, mg/kg	Mean duration of stereotypy, min	
		$M \pm m$	%
Control	0	36,6±4,8	100,0
Tartrate	0,5	24,5±5,0	66,9
	5	57,5±4,9	157,1
	50	109,2±17,9*	289,4
Maleate	0,5	38,6±9,3	105,7
	5	58,3±5,4*	159,3
	50	75,8±6,7*	207,1
Oxalate	0,5	54,2±3,7	148,1
	5	59,2±8,4*	161,7
	50	102,5±13,2*	280,1
Control	0	73,3±20,9	100,0
Nicotinic acid	0,5	66,6±11,3	90,8
	5	160,8±14,1*	219,4
	50	187,5±8,7*	255,8

*Difference from controls statistically significant at $P \leqslant 0.05$.

RESULTS AND DISCUSSION

It has been found that (I) is present in the body in equilibrium with nicotinic acid, and some workers have suggested that nicotinic acid itself is the active form of ronicol [8, 11]. For this reason, the effects of the salts of (I) on the central nervous system were compared with those of nicotinic acid. The tartrate was not significantly different in its toxicity from nicotinic acid (Table 3).

The maleate and oxalate were more toxic, evidently as a result of the effects of the acid component.

Treatment of the animals with these salts of (I) in subtoxic doses (500 mg/kg) resulted in inhibition of the central nervous system, manifested in disturbances of motor coordination, weakening of the skeletal musculature, reduction in motor activity, and other depressant effects.

In doses of 0.5-50 mg/kg, the salts of (I) had no appreciable effects on motor coordination and muscle tone. It was, however, found that in low doses (0.5-5 mg/kg) the compounds exerted a stimulant effect on the central nervous system for the first 30-60 min, increasing horizontal motor activity by 25-55%, and intensifying the exploratory reaction of the mice. In parallel experiments, nicotinic acid inhibited both the exploratory reaction and the horizontal and vertical components of motor activity.

It follows from the results given in Table 4 that the salts of (I) substantially increased the duration of narcosis induced by barbital-sodium. This demonstrates the true neurotropic activity of (I), since barbital-sodium does not undergo metabolic changes in the body. At the same time, nicotinic acid has no significant effect on the duration of narcosis induced by barbital-sodium. All the salts of (I), together with nicotinic acid, extended chloral hydrate narcosis in mice, but they had scarcely any effect on hexobarbital-induced narcosis.

The salts of (I) had no analgesic or anticonvulsant effects in electroshock convulsions. They did, however, show some protectant effects (increasing the dose of the convulsant drug by 30-60%) in strychnine-induced convulsions (clonic phase) and corazole-induced convulsions (tonic phase).

In doses beginning at 5 mg/kg, the (I) salts significantly increased (by 57-189%) the stimulant effects of amphetamine (Table 5). Nicotinic acid had a similar effect.

Thus, these salts of (I) differ from nicotinic acid in their stimulant effects on the exploratory reaction and vertical motor activity of the animals, and in their effect on the

duration of narcosis induced by barbital-sodium, showing that (I) has independent psychotropic activity, which is a substantial argument against the theory that the physiological activity of (I) is due to its conversion in the body to nicotinic acid. As regards the potentiation of the stimulant activity of amphetamine and the increased duration of chloral hydrate narcosis, there is no difference between the effects of (I) and nicotinic acid, and in this instance the possible occurrence of carbinol ⇄ nicotinic acid interconversion, as suggested previously [8, 11], cannot be excluded.

These studies have shown that the psychotropic activity of salts of (I) as assessed by the above tests is virtually independent of the nature of the acid.

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SYNTHESIS AND ANTIVIRUS ACTIVITY OF UNPROTONATED COMPLEX SALTS OF AMINO ACIDS WITH NICKEL AND COBALT

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It is known that heavy metals in trace amounts are necessary for all forms of life. They penetrate the living cell in the form of cations, and their absorption is strictly regulated, since many heavy metals are toxic in large amounts [1, 2].

It is also known that disruption of the ratio of amino acids in the cell gives rise to a deficiency of specific components of the cell membrane and has a retarding effect on microbiological systems, which is expressed, for example, in disruption of the synthesis of the membrane of a bacterial cell [3].

The literature contains data on the biological activity of complexes of some amino acids. Thus their antimicrobial activity is higher than that of the corresponding amino acids [4].

Some natural amino acids have antivirus activity. Arginine, lysine, and ornithine have a virostatic effect on influenza and epidemic parotities viruses in cell cultures of the chorioallantois membrane of chicken embryos [5].

Proceeding from the infromation set forth above, we synthesized neutral complexes of some amino acids with Ni and Co in the form of dihydrates (Ia-k) and studied their antivirus activity. $2AA + Me(NO_3)_2 \cdot 6H_2O = A_2Me \cdot 2H_2O + 2KNO_3 + 4H_2O$ Ia, b: A = (here and subsequently, and amino acid residue) DL-β-phenyl-α-alanine; Ic: A = DL-leucine; Id: A = DL-valine; Ie: A = DL-threonine; If, g: A = glycine; Ih: A = L-aspartic acid; Ii: A = DL-methionine; Ij, k: A = β-alanine; Ia, c-f, h-j: Me = Ni(2+); Ib, g, k: Me = Co(2+).

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