SYNTHESIS AND ANTIINFLAMMATORY PROPERTIES OF CARBOXYPHENYLAMIDES OF NICOTINIC AND ISONICOTINIC ACID 1-OXIDES

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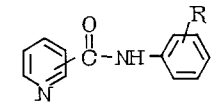
Nicotinic acid and its amide have a broad spectrum of physiological activity [1].

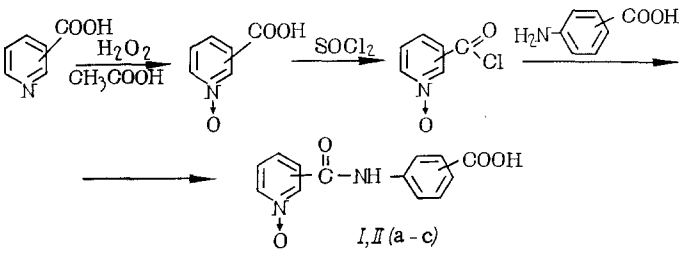
N-Arylamides of nicotinic and isonicotinic acids have been described in the literature. They include compounds with antiinflammatory, antipyretic, analgesic [2-5], bactericidal [6, 7], tuberculostatic [8-12], and therapeutic activity against protozoal diseases [13].

Our intention in the work described here was to synthesize and examine the physiological activity of new carboxyphenylamides of nicotinic (Ia)-(Ic) and isonicotinic (IIa)-(IIc) acid 1-oxides with the general formula



I,II a) R=*o*-COOH, b) m-COOH, c) *n*-COOH

We prepared these carboxyphenylamides of nicotinic and isonicotinic acid 1-oxides by condensing the appropriate pyridinecarbonyl chloride 1-oxide with o-, m-, or p-aminobenzoic acid in the presence of a hydrogen chloride acceptor (triethylamine) in anhydrous DMF. The reaction sequence was



I,II (a-c)

Carboxyphenylamides (Ia)-(Ic) and (IIa)-(IIc) are yellowish crystalline substances, soluble in DMF and dilute acids; their properties are summarized in Table 1. For identification we prepared the picrates (IIIb), (IIIc), (IVb), and (IVc); their properties are summarized in Table 2.

We checked the purity of compounds (Ia)-(Ic) and (IIa)-(IIc) by thin-layer chromatography on Silufol UV-254 plates (Czechoslovakia) in system A: n-butanol—5% aqueous ammonia—glacial acetic acid—water (6:1:1:2); and system B: ethyl alcohol—25% aqueous ammonia (10:1). We characterized N-carboxyphenylamides (Ia)-(Ic) by their IR spectra (Table 1).

We examined the toxicity and the antiexudative, analgesic, and antipyretic activities of the N-carboxyphenylamides of nicotinic (Ia)-(Ic) and isonicotinic (IIa)-(IIc) acid 1 oxides. Our results are summarized in Table 3. We evaluated the acute toxicity in white

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TABLE 1. Carboxyphenylamides of Nicotinic (Ia)-(Ic) and Isonicotinic (IIa) Acid I-Oxides

Compound	Yield, %	Melting point °C (solvent)	Found, % N	Formula	Calculated, % N	R_f in system		IR spectrum, , cm^{-1}					
						A	B	C—OH	C=O	NH (deformation)	NH (free)	intramolecular hydrogen bond	dimers (hydrogen bond)
I a	47,7	206 (chloroform)	10,85 10,78	$C_{13}H_{10}N_2O_4$	10,85	0,81	0,83	1410	1670	1530	3360	3460	—
I b	43,6	264 (water)	11,02 11,14	$C_{13}H_{10}N_2O_4$	10,85	0,69	0,73	1410	1660	1540	3280	—	3290
I c	43,5	295 (water)	10,78 10,94	$C_{13}H_{10}N_2O_4$	10,85	0,57	0,60	1400	1660	1520	3380	—	3290
II a	50,2	258 (water)	10,84 10,97	$C_{13}H_{10}N_2O_4$	10,85	0,68	0,76	—	—	—	—	—	—
II b	48,2	272 (water)	10,52 10,81	$C_{13}H_{10}N_2O_4$	10,85	0,67	0,68	—	—	—	—	—	—
II c	40,5	300—301 (water)	10,92 11,06	$C_{13}H_{10}N_2O_4$	10,85	0,59	0,72	—	—	—	—	—	—

TABLE. 2. Picrates of Carboxyphenylamides of Nicotinic (IIIb), (IIIc) and Isonicotinic (IVb), (IVc) Acid-1-Oxides

Compound	Melting point, °C	Found, % N	Formula	Calculated, % N
IIIb	255—256	14,08; 14,12	$C_{19}H_{13}N_5O_{11}$	14,38
IIIc	214—216	13,94; 13,98	$C_{19}H_{13}N_5O_{11}$	14,38
IVb	218—219	14,24; 14,30	$C_{19}H_{13}N_5O_{11}$	14,38
IVc	254—255	14,52; 14,68	$C_{19}H_{13}N_5O_{11}$	14,38

TABLE 3. Some Pharmacological Properties of Carboxyphenylamides of Nicotinic and Isonicotinic Acid 1-Oxides (M ± m)

Compound	Toxicity (LD_{50}), mg/kg	Inhibition of edema, %		Analgesia (with thermal stimulation), %	Antipyretic effect (reduction in rectal body temperature of rats with lactic fever °C)
		kaolin	formalin		
Ia	765	12,9±6,4	30,9±6,0	50,6±2,2	0,60±0,19
Ib	1120	4,2±1,0	21,5±7,2	40,2±9,8	0,70±0,23
Ic	1720	36,9±3,0	25,8±5,9	47,1±8,7	0,70±0,34
IIa	1180	24,0±3,6	28,4±0,9	58,9±4,9	1,60±0,10
IIb	1630	34,2±6,4	25,2±7,2	59,8±8,6	1,10±0,18
IIc	2000	26,2±3,9	41,4±5,0	85,9±4,1	0,60±0,11

mice by intraperitoneal administration. We assayed the antiexudative activity in rats, in which edema of the rear paw was induced by subplantar injection of 10% kaolin suspension (0.1 ml) or 2% formalin solution (0.1 ml). The test compounds were administered intraperitoneally in a dose of 1/10 LD_{50} 30 min before administration of the inflammation-induced substance. The size of the paw was measured plethysmographically 4 h after administration of the phlogogen. We assayed the antipyretic activity of the preparations in tests on rats with lactic fever. Milk was administered intramuscularly in the basis of 1 ml per 100 g weight. The test compounds were administered in a dose of 1/10 LD_{50} at the peak of the fever. The antipyretic effect was monitored over a period of 3 h. We examined the analgesic activity in white mice by the method of [14].

These carboxyphenylamides of nicotinic and isonicotinic acids are relatively nontoxic (LD_{50} from 765 to 2000 mg/kg). Their toxic properties show some correlation with structure; for derivatives of both nicotinic and isonicotinic acids the compound in which the carboxyl group is in the ortho position in the phenyl ring is more toxic than those with the meta-or para-carboxyl.

All the synthetic compounds have some antiexudative activity. The p-substituted derivatives are more active. They also have analgesic activity, which is greatest in N-(carboxyphenyl)isonicotinamide 1-oxide. These compounds have an antipyretic effect, reducing the rectal body temperature of rats with lactic fever, although the correlation of this effect with chemical structure is not clear.

EXPERIMENTAL

N-(2-Carboxyphenyl)nicotinamide 1-Oxide (Ia). A mixture of nicotinic acid 1-oxide (13.9 g, 0.1 mole) and thionyl chloride (30 ml) was refluxed for 2 h. Excess thionyl chloride was stripped off and the residue was dissolved in a mixture of anhydrous DMF (50 ml) and triethylamine (20.2 g, 0.2 mole). To the resulting solution at 0°C with stirring was added dropwise over 1 h a solution of anthranilic acid (13.7 g, 0.1 mole) in DMF (50 ml). The mixture was left overnight at room temperature, the solvent was stripped off under vacuum, and the residue was crystallized.

Compounds (Ib), (Ic), and (IIa)-(IIc) were prepared in the same way.

N-(3-Carboxyphenyl)nicotinamide 1-Oxide Picrate (IIIb). To a solution of amide (Ib) (0.5 g, 0.002 mole) in DMF (20 ml) was added a solution of picric acid (0.25 g, 0.025 mole) in DMF (10 ml). The mixture was cooled and the resulting precipitate was separated.

Picrates (IIIc), (IVb), and (IVc) were prepared in the same way.

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SYNTHESIS AND ANTIVIRAL ACTIVITY OF BIS(DIETHYLAMINOETHYL) ESTERS OF 2-METHYL-3-CARBOXYBENZINDOL-5-YLOXYACETIC ACIDS

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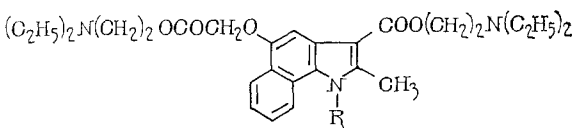
In conjunction with the interest in the preparation tilorone and its analogs, which have antiviral properties [1], we have synthesized and examined the antiviral activity of the hitherto unknown bis(diethylaminoethyl) esters of 2-methyl-3-carboxybenzindol-5-yloxyacetic acids (Ia)-(Ic).



Ia-c

R = a) CH_3, b) C_6H_5, c) o-$CH_3C_6H_4$

The starting compounds for the synthesis were 2-methyl-3-(ethoxycarbonyl)benzindol-5-yloxyacetic acids (IIa)-(IIc) [2], prepared from the 2-methyl-3-(ethoxycarbonyl)-5-hydroxybenzindoles [3]. Hydrolysis with alcoholic alkali converted (IIa)-(IIc) to the 2-methyl-3-carboxybenzindol-5-yloxyacetic acids (IIIa)-(IIIc).

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