SYNTHESIS AND BIOLOGICAL ACTIVITY OF ARYLAMIDES OF 2-METHYLNICOTINIC AND 2-PHENYLINDOLIZINE-8-CARBOXYLIC ACIDS

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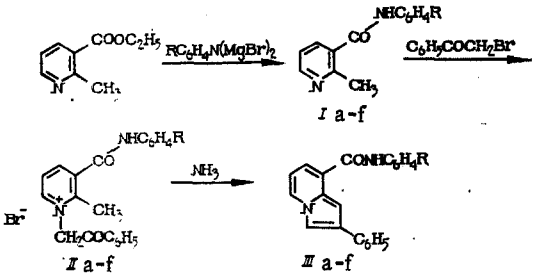
We have previously [7] found anticonvulsant activity in 2-methyl-6-phenylnicotinamide and some of its derivatives. This served as the starting point for further studies of the anticonvulsant activity of N-aryl-2-methylnicotinamides, and for the synthesis of the little-known indolizine amides obtained therefrom. The N-aryl-2-methylnicotinamides (Table 1, 1a-f) were obtained by reacting the ethyl ester of the acid with aryldimagnesylamines.



I — III: a — R = H; b — R = p-CH_3; c — R = m-CH_3; d — R = p-CH_3O; e — R = p-Cl; f — R = p-Br.

The arylamides (Ia-f) were colorless, crystalline solids, the IR spectra of which contained absorption at 1655-1670 cm^{-1} (C=O) and 3265-3436 cm^{-1} (NH). They display basic properties, and form water-soluble hydrochlorides.

Compounds (Ia-f) can be used as starting materials for the preparation of indolizines. Indolizines with substituents in the pyridine ring have received little attention; the corresponding nitro-compounds are known [3], and in the last decade the ethoxycarbonyl derivatives have been examined in detail [5]. It has been found that 8-ethoxycarbonylindolizines are not converted into amides when their solutions are kept with ammonia for three months, owing to the effect of the π-electron system of indolizine in increasing the electron density of the carboxyl carbon atom. For this reason, it was of interest to examine the possibility of synthesizing indolizines with an existing carboxamide function from the arylamides (Ia-f). With this in view, the latter were reacted with phenacyl bromide to give the 1-phenacyl-2-methyl-3-(N-arylcarbamoyl)pyridinium bromides (IIa-f), which on boiling with ammonia in aqueous solution underwent smooth cyclization to the N-aryl-2-phenylindolizine-8-carboxamides (IIIa-f). The compositions and structure of (IIIa-f) were confirmed by their elemental analyses, and their UV, IR, and PMR spectra.

The UV spectra of (IIIa-f) were similar to those of unsubstituted indolizine [8], exhibiting two absorption bands with maxima at 260-262 and 331-333 nm. A band was also seen at 220 nm, the maximum of which lay outside the resolving power of the apparatus. The IR spectra of these compounds showed absorption at 1655-1665 (C=O) and 3235-3240 cm^{-1} (NH). The PMR spectra contained chemical shift signals for protons at 6.35-6.66 (1H at C_6), a doublet centered on 7.93-8.33 (1H at C_8), and a multiplet centered on 7.33-7.5 ppm (aromatic ring H and H at C_1, C_3, and C_7 of the indolizine ring). Signals are also present at 9.26-10.42 ppm (1H, amide group).

EXPERIMENTAL CHEMICAL PART

IR spectra were obtained on a UR-20 instrument (East Germany) in vaseline oil, and PMR spectra on a RYa-2310 apparatus (USSR), operating frequency 60 MHz, internal standard hexa-

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TABLE 1. Properties of (Ia-f), (IIa-f), and (IIIa-f)

Compound	Yield, %	mp, °C	Found, %				Empirical formula	Calculated, %			
			C	H	Hal	N		C	H	Hal	N
Ia	30	113—4	73,79	5,87	—	13,47	$C_{13}H_{12}N_2O$	73,58	5,66	—	13,20
Ib	32	143—4	74,60	5,98	—	12,14	$C_{14}H_{14}N_2O$	74,33	6,19	—	12,39
Ic	31	132—3	74,51	6,38	—	12,61	$C_{14}H_{14}N_2O$	74,33	6,19	—	12,39
Id	34	151—3	69,70	5,96	—	11,32	$C_{14}H_{14}N_2O_2$	69,42	5,78	—	11,57
Ie	30	104—6	62,97	4,51	14,54	11,62	$C_{13}H_{11}ClN_2O$	63,20	4,46	14,40	11,36
If	30	137—9	53,49	4,02	27,63	9,39	$C_{13}H_{11}BrN_2O$	53,61	3,78	27,49	9,62
IIa	92	219—20	61,57	4,45	19,28	7,08	$C_{21}H_{19}BrN_2O_2$	61,31	4,62	19,46	6,81
IIb	80	156—7	62,34	5,17	19,01	6,66	$C_{22}H_{21}BrN_2O_2$	62,11	4,94	18,82	6,58
IIc	80	174—5	61,98	5,21	18,98	6,88	$C_{22}H_{21}BrN_2O_2$	62,11	4,94	18,82	6,58
IId	93	169—70	60,01	4,87	18,16	6,54	$C_{22}H_{21}BrN_2O_3$	59,86	4,76	17,95	6,34
IIe	93	186—7	56,75	4,23	...	5,99	$C_{21}H_{18}BrClN_2O_2$	56,56	4,04	...	6,28
IIf	95	202—4	51,19	3,88	32,88	5,92	$C_{21}H_{18}Br_2N_2O_2$	51,42	3,67	32,65	5,71
IIIa	80	178—80	80,54	4,98	—	9,06	$C_{21}H_{16}N_2O$	80,76	5,12	—	8,97
IIIb	70	210—11	80,73	5,71	—	8,63	$C_{22}H_{18}N_2O$	80,98	5,52	—	8,59
IIIc	80	181—3	80,65	5,63	—	8,88	$C_{22}H_{18}N_2O$	80,98	5,52	—	8,59
IIId	80	221—1,5	77,30	5,45	—	8,32	$C_{22}H_{18}N_2O_2$	77,19	5,26	—	8,18
IIIe	70	182—3	72,90	4,50	10,38	8,31	$C_{21}H_{15}ClN_2O$	72,72	4,32	10,24	8,08
IIIf	98	189—90	64,55	4,01	20,60	6,86	$C_{21}H_{15}BrN_2O$	64,45	3,83	20,46	7,16

TABLE 2. Anticonvulsant Activity and Toxicity of N-Aryl-2-methylinicotinamides (Ia-f)

Compound	ED_{50} in MET, mg/kg	Peak of activity, min	Anticorazole activity in a dose of 1/5 of the LD_{50}	LD_{50}, mg/kg	LD_{50}/ED_{50} for MET
Ia	133 (115—153)	5	—	820 (774—890)	6,2
Ib	138 (109—162)	5	—	830 (815—850)	6,0
Ic	297 (254—347)	15	60	890 (881—900)	3,0
Id	245 (211—281)	5	50	710 (659—861)	2,9
Ie	300 (240—375)	40	33	350 (282—434)	1,5
If	Inactive in a dose of 600	—	—	730 (695—766)	—
Hexamidine	90 (79—103)	240	—	340 (288—401)	3,8

methyldisiloxane. UV spectra were obtained on an SF-16 apparatus (USSR), in ethanol.

N-Aryl-2-methylnicotinamides (Ia-f). To the dimagnesylamine, obtained from 90 mmole of the appropriate arylamine and 180 mmole of ethylmagnesium bromide in dry ether, was added 60 mmole of ethyl 2-methylnicotinoate in 20 ml of dry ether. The mixture was heated for 30 min, decomposed with saturated ammonium chloride solution, and the ether layer separated. The solvent and volatile impurities were steam-distilled, and the residue crystallized from water.

1-Phenacyl-2-methyl-3-(N-arylcarbamoyl)pyridinium Bromides (IIa-f). A mixture of 6 mmole of (Ia-f) and 9 mmole of phenacyl bromide in 15 ml of acetone was boiled for 6 h. The solid which separated was filtered off, washed with acetone, and crystallized from ethanol.

N-Aryl-2-phenylindolizine-8-carboxamides (IIIa-f). A solution of 6 mmole of (IIa-f) in 50 ml of water was heated for 1 h, cooled, 25% ammonium hydroxide added until a solid separated, heated for a further 30 min, and the solid which separated was filtered off and recrystallized from ethanol. The physicochemical properties of (I-IIIa-f) are given in Table 1.

EXPERIMENTAL PHARMACOLOGICAL PART

Pharmacological studies of (Ia-f) and (IIIa-f) were carried out in mice of both sexes weighing 18-22 g. The compounds were administered intraperitoneally in 2% starch mucilage. The experimental data were treated statistically by the Litchfield and Wilocoxon method, P = 0.05 [1].

The anticonvulsant activity (ACA) of compounds (Ia-f) was determined by the maximum electroshock test (MET) [6] and the corazole test [2], and the acute toxicity as described in [4], the LD_{50} values being calculated. Depressant and excitatory effects were assessed visually. The ratios of the LD_{50} to the ED_{50} values were calculated as an arbitrary measure of the breadth of the pharmacological effect. Compounds (IIIa-f) were examined for ACA by the MET, but acute toxicities were not found.

Compounds (Ia-f) display anticonvulsant activity in the Met (Table 2). The highest activity was shown by (Ia) and (Ib), these being less active than hexamide by a factor of 1.5. Compounds (If) and (IIIa-f) showed no ACA at doses up to 600 mg/kg.

A study of the dynamics of the development of anticonvulsant activity in the N-aryl-2-methylnicotinamides showed that the anticonvulsant effect developed after 5-30 min, in contrast to hexamidine, the maximum ACA of which is reached after 240 min. The ACA of the test compounds lasted for 2-2.5 h.

Anticorazole activity was shown by (Ic), (Id), and (Ie). In a dose of 1/5 of the LD_{50}, (Ic) and (Id) prevented clonictonic convulsions in 50%, and (Ie) in 33% of the test animals. No ACA was shown by (Ia), (Ib), or (If) in the corazole test.

Compounds (Ia-f) are of low toxicity. In doses close to the lethal values, they have a depressant effect on the CNS.

The search for compounds with ACA amongst nicotinic acid derivatives must be regraded as promising.

LITERATURE CITED

1. M. L. Belen'kii, Fundamentals of the Quantitative Measurement of Pharmacological Activity [in Russian], Riga (1959), pp. 71-92.
2. V. S. Zalesov, Farmakol. Toksikol., No. 4, 418-431 (1963).
3. A. N. Kost, R. S. Sagitullin, and S. P. Gromov, Khim. Geterotsikl. Soedin., No. 7, 922 (1976).
4. G. N. Pershin (editor), Methods of Experimental Chemotherapy [in Russian], Moscow (1959), pp. 109-117, 456-460.
5. E. E. Mikhlina, A. D. Yanina, T. S. Loseva, et al., Khim. Geterotsikl. Soedin., No. 7, 977 (1974).
6. K. S. Raevskii, Farmakol. Toksikol., No. 4, 495-497 (1961).
7. V. I. Sigova, N. V. Semyakina, and V. S. Zalesov, paper deposited at VINITI (Nat. and Exact Sciences, Technol.), No. 11 (1984).
8. W. L. F. Armarego, J. Chem. Soc., 4226 (1964).

SYNTHESIS AND ANTIVIRAL ACTIVITY OF SALTS OF TRANSITION METALS WITH p-AMINOBENZENESULFONAMIDES

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It has previously been found that the sulfanilamide salt of silver, a metal with high bactericidal activity against both gram-positive and gram-negative microorganisms, is completely devoid of antiviral activity, whereas some sulfanilamide salts of cobalt display marked antiviral effects [5].

These findings provided the basis for systematic studies of the synthesis and examination of other salts of transition metals with p-aminobenzenesulfonamide derivatives as potential antiviral drugs.

This communication describes the synthesis of salts of Cr^{3+}, Mn^{2+}, Fe^{3+}, and Ni^{2+} with p-aminobenzenesulfonamide derivatives (Id, f, IIa-g, IIIa-g, and IVa-h)

$$(p\text{-}H_2NC_6H_4SO_2\bar{N}R)_nM^{n+}$$

(Id,f), (IIa-g), (IIa-g), and (IVa-h)

(Id,f): M = Cr^{3+}; (IIa-g); M = Mn^{2+}; (IIIa-g): M = Fe^{3+}; (IVa-h): M = Ni^{2+}; a): R = 4-thiazolyl; b) R = 2-methoxypyrimidin-6-yl; c) R = 2,4-dimethyl-pyrimidin-6-yl; d) R = 5-ethyl-1,3,4-thiadiazol-2-yl; e) R = 3-methoxypyridazin-6-yl; f) R = 3-methoxypyridin-2-yl; g) R = 2,4-dimethoxypyrimidin-6-yl; h) R = Ac.

EXPERIMENTAL CHEMICAL PART

The compositions of the compounds obtained were proved by elemental analysis as described in [4].

IR spectra were obtained on a UR-20 instrument in KBr disks, as described in [3].

The required compounds were obtained by ion exchange between the sodium forms of the benzenesulfonamides and water-soluble salts of Cr^{3+}, Mn^{2+}, Fe^{3+}, and Ni^{2+} in mineral acids. Equimolar amounts of the concentrated aqueous solutions of the starting materials were mixed with vigorous stirring, the metal salts of the mineral acids being added to the sodium sulfonamide solutions. The resulting solids were filtered off, washed with hot water until anions of the mineral acids were absent from the filtrate, and recrystallized from DMSO.

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