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# SYNTHESIS AND ANTISPASMODIC ACTIVITY OF 2-CHLORO- AND 2-ARYLAMINO-4,6-DIMETHYL-NICOTINIC ACID ALKYLAMIDES

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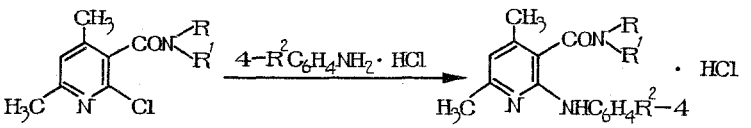
In order to further study the antispasmodic properties of 2-substituted nicotinic acid amides [5], we prepared new alkylamides of 4,6-dimethyl-2-chloronicotinic acid (Ia-i) and 4,6-dimethyl-2-arylaminonicotinic acid hydrochlorides (IIa-n) (Table 1).



*I* a-i *II* a-n

R = H(Ia-g, IIa-j), $R^1$ = Pr(Ia, IIa, IIb), n-Bu (Ib, IIc), t-Bu (Ic, IId, IIe), i-Am (Id, IIf, IIg), cyclohexyl (Ie, IIh, IIi), cyclopropyl (If), benzyl (Ig, IIj), $R^2$ = H (Ia, Ic, Id, If, Ih, Ij, Ik, Im), OMe (IIb, IIe, IIg, IIi, III, IIm), $NRR^1$ = piperidino (Ih, IIk, III), morpholino (Ii, IIm, IIn)

The syntheses of alkylamides Ia-i were carried out by the interaction of the corresponding acyl chloride with alkylamines in anhydrous benzene in the presence of $Et_3N$.

Upon reaction of arylamine hydrochlorides by heating in isopropanol, the amides Ia-i were transformed into the hydrochlorides of the alkylamides IIa-n. If the same compounds Ia-i were allowed to react with arylamine free bases, a prolonged heating of the reaction mixture was required, and the desired products were formed in low yields. It should be noted that the amides Ia-i react with more difficulty with arylamines than the analogous 2-chloro-6-methylnicotinic acid amides [6], which apparently is connected with the inductive effect of the $C_4$-methyl group, promoting the diminished mobility of the halogen. An additional essential contribution is the steric interference of this same methyl group with the conjugation of the amide function with the pyridine ring, weakening the influence of the latter on the mobility of the chlorine atom. This proposal is confirmed by the known literature fact of the decreased rate of nucleophilic substitution of halogen in 2,6-dimethyl-4-chloronitrobenzene by comparison with 2,6-dimethyl-4-chloropyridine as a result of the steric barrier to the conjugation of the nitro group with the benzene ring [2].

The structures of the compounds obtained were confirmed by IR and NMR spectroscopy.

## EXPERIMENTAL (CHEMICAL)

The IR spectra were recorded on an UR-20 instrument as pastes in mineral oil, and the NMR spectra were obtained on a RYa-2310 (60 MHz) instrument as 5% solutions in DMSO-$d_6$ (If) and in $CDCl_3$ (IIf base), with HMS as internal standard. TLC was carried out on Silufol UV-254 plates in the systems ethyl acetate–benzene (1:1) (for Ia-i) and benzene–acetic acid–water (1:1:1) (for IIa-n).

The elemental analysis data corresponded with the calculated values.

4,6-Dimethyl-2-chloronicotinic Acid Alkylamides (Ia-i). A solution of 0.06 mole of 4,6-dimethyl-2-chloronicotinoyl chloride in 50 ml of anhydrous benzene was added to a solution of 0.06 mole of alkylamine in 10 ml of anhydrous benzene. To the mixture was then added

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TABLE 1. Characteristics of the Synthesized Compounds

| Compound | Yield, % | T. mp, °C | $R_f$ | Empirical formula |
|---|---|---|---|---|
| Ia | 46 | 49—51 | 0,33 | $C_{11}H_{15}ClN_2O$ |
| Ib | 61 | 57—69 | 0,37 | $C_{12}H_{17}ClN_2O$ |
| Ic | 57 | 152—153 | 0,44 | $C_{12}H_{17}ClN_2O$ |
| Id | 65 | 96—98 | 0,38 | $C_{13}H_{19}ClN_2O$ |
| Ie | 48 | 168—169 | 0,40 | $C_{14}H_{19}ClN_2O$ |
| If | 47 | 56—58 | 0,29 | $C_{11}H_{13}ClN_2O$ |
| Ig | 35 | 101—103 | 0,46 | $C_{15}H_{15}ClN_2O$ |
| Ih | 66 | | 0,20 | $C_{13}H_{17}ClN_2O$ |
| Ii | 56 | 99—101 | 0,17 | $C_{12}H_{15}ClN_2O$ |
| Ia | 46 | 177—180 | 0,65 | $C_{17}H_{22}ClN_3O$ |
| IIb | 37 | 210—214 | 0,74 | $C_{18}H_{24}ClN_3O$ |
| IIc | 65 | 157—159 | 0,69 | $C_{18}H_{24}ClN_3O$ |
| IId | 67 | 232—234 | 0,63 | $C_{18}H_{24}ClN_3O$ |
| IIe | 34 | 229* | 0,66 | $C_{19}H_{26}ClN_3O_2$ |
| IIf | 45 | 170* | 0,70 | $C_{19}H_{26}ClN_3O$ |
| IIg | 54 | 178* | 0,73 | $C_{20}H_{28}ClN_3O_2$ |
| IIh | 40 | 175* | 0,65 | $C_{20}H_{26}ClN_3O$ |
| IIi | 30 | 208* | 0,72 | $C_{21}H_{28}ClN_3O_2$ |
| IIj | 53 | 222* | 0,70 | $C_{21}H_{22}ClN_3O$ |
| IIk | 60 | 194* | 0,69 | $C_{19}H_{24}ClN_3O$ |
| IIl | 35 | 220* | 0,61 | $C_{20}H_{26}ClN_3O_2$ |
| IIm | 45 | 226* | 0,54 | $C_{18}H_{22}ClN_3O_2$ |
| IIn | 49 | 188* | 0,53 | $C_{19}H_{24}ClN_3O_3$ |

*With decomposition.

TABLE 2. Antispasmodic Activity and Acute Toxicity of 4,6-Dimethylnicotinic Acid Alkylamides

| Compound | Antispasmodic Actiity by MES Test | | Acute Toxicity | |
|---|---|---|---|---|
| | dose, mg/kg | %protectn. of animals against | dose, mg/kg | % dead Animals |
| Id | 300 | 100 | 500 | 50 |
| If | 250 | 50 | 250 | 25 |
| Ig | 250 | 50 | 500 | 100 |
| IIc | 300 | 33 | — | — |
| IId | 300 | 33 | — | — |
| IIe | 300 | 33 | — | — |
| IIm | 300 | 33 | — | — |
| IIn | 300 | 66,6 | 1000 | 50 |

10 ml of $Et_3N$, and the mixture was boiled for 30 min in a water bath. After standing at room temperature for 12 h, the resulting precipitate was filtered off, and the filtrate was passed through a column of alumina. The benzene was distilled and the residue was crystallized from a mixture of benzene and hexane (2:1). IR spectrum, $\nu_{max}$, $cm^{-1}$: 1620-1630 (CO), 3075-3095 (=CH), 3225-3360 (NH). $^1H$ NMR spectrum of If, δ, ppm: 2.33 (d, 6H, $2CH_3$), 3.83-4.66 (t, 2H, $CH_2$), 5.03-5.37 (t, 2H, $=CH_2$), 5.60-6.00 (m, 1H, =CH), 7.00 (s, 1H from $C_5$ of pyridine).

2-Arylamino-4,6-dimethylnicotinic Acid Alkylamide Hydrochlorides (IIa-n). A solution of 0.01 mole of alkylamides Ia-i and 0.01 mole of arylamine hydrochloride in 20 ml of isopropanol was boiled for 8 h, the solvent was distilled, and the residue was crystallized from aqueous dioxane (IIb, i, h, n), a mixture of acetone–ethanol (IIa, c, d, e, j, m) or acetone–ether (IIf, g, k, l). IR spectra, $\nu_{max}$, $cm^{-1}$: 1610-1630 (CO), 3060-3150 (=CH), 3220-3380 (NH). $^1H$ NMR spectrum of IIf, free base, δ, ppm: 0.8 (d, 6H, $2CH_3$, Alk), 1.10-1.43 (m, 1H, CH), 2.20 (d, 6H, $2CH_3$, Pyr), 3.10-3.40 (m, 4H, $2CH_2$), 5.83 (s, 1H, CONH), 6.33 (s, 1H, CH, Pyr), 6.93-7.53 (m, 5H, Aryl), 7.83 (s, 1H, NH).

## EXPERIMENTAL (PHARMACOLOGICAL)

Compounds Ic-g, Ii, and IIa-k, IIm, and IIn were tested for antispasmodic activity. The studies were carried out by the maximal electroshock test (MES) [4] on non-hybrid white mice of both sexes weighing 18-25 g. The studied materials were introduced intraperitoneally in 2% starch slurries 30 min before application of the electric stimulation.

The studies showed that compounds Ic, e, i and IIf, h, i, j, k were not active in doses of 300 mg/kg, and that compounds IIa, b, g were inactive in doses of 100 mg/kg.

The acute toxicity was determined for compounds Id, f, g, and IIn [3].

The results of the studies are presented in Table 2, from which it can be seen that the most active according the MES test is the isoamylamide of 4,6-dimethyl-2-chloronicotinic acid IId and the salt of 2-(p-anisidino)-4,6-dimethylnicotinic acid morpholinoamide IIn. For compound IIn the $ED_{50}$ and the $LD_{50}$ were 280 (220.4-355.6) mg/kg and 1000 (746.2-1340.0) mg/kg, respectively. In addition, these same compounds were tested for antispasmodic activity by the corazole test upon intraperitoneal introduction of the compounds in doses of 300 mg/kg 30 min before introduction of corazole (pentylene tetrazole) in a dose of 100 mg/kg. In the control experiments, corazole was introduced at 100 mg/kg. It was established that compound IIn did not eliminate the corazole convulsions, which have a clonic-tonic character. But after introduction of the preparation the death of the animals occurred much later; the control animals died after 4.8 min, and the test animals died after 35.1 min.

On the basis of the above data, it can be said that the series of 4,6-dimethyl nicotinic acid alkyl amides contains compounds possessing antispasmodic activity which is weaker than that of the analogous unsubstituted amides [1].

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# SYNTHESIS AND ANTI-INFLAMMATORY ACTIVITY OF 2,3-DIMETHOXY- AND 2,3,4-TRIMETHOXY-SUBSTITUTED 3-DIMETHYLAMINOPROPIONYLBENZENE


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1-(3-Dimethylaminopropionyl)-3,4-dimethoxybenzene exhibits anti-inflammatory activity and low toxicity [3]. To study the relationship between chemical structure and pharmacological properties and also to search for new drugs, we have synthesized and studied new structural analogs (IIa, b) of this aminoketone.

The hydrochlorides of the aminoketones IIa and b were obtained by the Mannich reaction from the acetylamino derivatives Ia [6] and Ib [8], dimethylamine hydrochloride, and formaldehyde

$$ArCOCH_3 \rightarrow ArCOCH_2CH_2NMe_2 \cdot CH$$

Ia, b — IIa, b

$Ar = C_6H_2(OMe)_2$-2,3-R-4; R=H (a), OMe (b).

The structures of compounds IIa and b were confirmed by UV, IR, and PMR spectra. Elemental analysis data was in good agreement with calculated values.

In the UV, the trimethoxy derivative IIb absorbs at a lower frequency than the dimethyoxy analog IIa, indicating removal of the methoxy substituents from conjugation with the aromatic ring by rotation of the $C_{Ar}$–O bond in IIb [2]. In the infrared, the carbonyl group conjugated with the benzene ring absorbed at 1665 $cm^{-1}$ for both IIa and IIb.

## EXPERIMENTAL (CHEMICAL)

UV Spectra were taken on a Specord UV-Vis (Germany) using ethanol as solvent, IR spectra (in Jujol) on a UR-20 instrument (Germany), and PMR spectra on a Tesla-BS 487C (ChSFR, 80 MHz) in deuteromethanol with TMS as internal standard.

Hydrochlorides of Aminoketones (IIa and b). A mixture of ketone (Ia or b) (30 mmole), paraform (1.35 g, 45 mmol), $Me_2$–NH·HCl (2.9 g, 36 mmol), ethanol (20 ml), and concentrated HCl (0.2 ml) were refluxed for 10 hours, concentrated in vacuo to one quarter volume, and cooled to −10°C. The precipitated material was washed with ether and recrystallized.

Hydrochloride of 1-(3-dimethylaminopropionyl)-2,3-dimethoxybenzene (IIa), $C_{13}H_{19}NO_3 \cdot HCl$, yield 53%, mp 121-122°C (ethanol). UV spectrum, $\lambda_{max}$, nm (log ε): 218 (4.18), 255 (3.67), 314 (3.18). IR spectrum, $\nu_{max}$, $cm^{-1}$: 1665 (C=O). PMR spectrum, δ, ppm: 2.88 s (6H, $CH_3N$), 3.49 s (4H, $COCH_2CH_2N$), 3.83 s (3H, $CH_3O$), 3.88 s (3H, $CH_3O$), 7.17-7.21 m (3H, ArH).

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