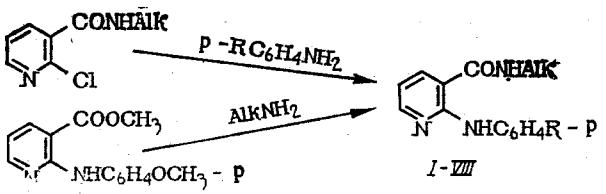
99. G. A. Porter, Mol. Pharmacol., 4, 224 (1968).
100. G. W. G. Sharp, C. L. Komack, and A. Leaf, J. Clin. Invest., 45, 450 (1966).
101. T. S. Herman, G. M. Fimognari, and I. S. Edelman, J. Biol. Chem., 243, 3949 (1968).
102. D. D. Fanestil, Biochem. Pharmacol., 17, 2240 (1968).
103. W. Sadée, Intra-Sci. Chem. Rep., 8, 133 (1974).
104. G. L. Gantt, Excerpta Med. Found. Int. Congr. Ser., 132, 591 (1966).
105. W. Sadée, S. Riegelmann, and S. C. Jones, J. Pharm. Sci., 61, 1129 (1972).
106. W. Sadée, M. Dagcioglu, and R. Schröder, in: Extrarenal Activity of Aldosterone and Its Antagonists, Nice (1970), pp. 40-43.
107. F. Gross, Experientia (Basel), 17, 57 (1961).
108. R. Schröder, V. P. Schuren, G. Biamino, et al., Klin. Wschr., 49, 1093 (1971).
109. K. R. Koczorek, et al., in E. S. Bucherl, F. Kruck, W. Ceppla et al. (editors), Postoperative Störungen des Elektrolyt- und Wasserhaushaltes, Stuttgart (1968), p. 177.
110. A. Baethmann, W. Land, K. R. Koczorek, et al., Eur. Surg. Res., 3, 40 (1971).
111. V. Hiemeyer and H. J. Kahler, Klin. Wschr., 40, 786 (1962).
112. H. Selye, Experientia (Basel), 27, 1445 (1971).
113. B. Solymoss, S. Toth, S. Varga, et al., Toxicol. Appl. Pharmacol., 18, 586 (1971).
114. S. Fukuchi, R. Shioji, and S. Abe, Tohoku J. Exp. Med., 76, 195 (1962).
115. C. E. Fisher, J. Woo, and R. Horton, Clin. Res., 20, 217 (1972).
116. E. H. Jenis and R. W. Hertzog, Arch. Pathol., 88, 530 (1969).
117. D. A. Davis and N. M. Medine, Am. J. Clin. Pathol., 54, 22 (1970).
118. G. Sel'e, Patol. Fiziol., No. 2, 3-18, (1971).
119. M. G. Kolpakov (editor), Corticosteroid Regulation of Water-Salt Homeostasis [in Russian], Novosibirsk (1967).

# SYNTHESIS AND BIOLOGICAL ACTIVITY OF SUBSTITUTED AMIDES OF 2-ARYLAMINONICOTINIC ACID

A. I. Mikhalev, V. K. Kudryashova,
V. S. Zalesov, V. P. Chesnokov,
and M. E. Konshin

UDC 615.213:547.826.1

Earlier we found that substituted amides of 2-chloro- and 2-aminonicotinic acid [1, 2] showed anticonvulsive activity. In the course of these investigations we synthesized alkylamides of 2-(p-toluidino)- and 2-(p-anisidino)nicotinic acids (I-IV and V-VIII).




I-VIII

Compounds I-IV, VII, VIII were obtained by replacing the halogen in alkylamides of 2-chloronicotinic acid by an arylamino group in boiling solutions of the starting materials in 50% acetic acid (method A). The results of the experiments show that by this method the products were obtained in yields of 63-86%. The reaction is evidently catalyzed by protons and appears to be an example of the acid catalysis of nucleophilic substitution of chlorine in α-chloropyridines [3].

The syntheses of amides V-VIII were also conducted by amidation of the methyl ester of 2-(p-anisidino)nicotinic acid by heating it with the amine in methanol (method B).

Compounds I-VIII (Table 1) are colorless crystalline substances, quite soluble in organic solvents and insoluble in water. Their composition and structure were confirmed by elemental analyses and by IR spectra in which the following absorption bands were observed: $\nu_{CO}$ 1640,

Perm Pharmaceutical Institute. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 11, No. 11, pp. 78-81, November, 1977. Original article submitted May 4, 1977.

 0091-150X/77/1111-1512$07.50 

TABLE 1. Alkylamides of 2-Arylaminonicotinic Acid

| Compound | R | Alk | Yield, % | | Melting point of base °C* | Melting point of hydrochloride, °C | Found, % | | | Empirical formula | Calculated, % | | | $LD_{50}$, mg/kg |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | method A | method B | | | C | H | N | | C | H | N | |
| I | $CH_3$ | $C_3H_7$ | 63 | — | 105—6 | 198—9 | 71,40 | 7,15 | 15,56 | $C_{16}H_{19}N_3O$ | 71,35 | 7,11 | 15,60 | 208 (163÷266) |
| II | $CH_3$ | $C_4H_9$ | 68 | — | 101—2 | 176—8 | 72,10 | 7,40 | 14,80 | $C_{17}H_{21}N_3O$ | 72,05 | 7,47 | 14,83 | 180 (157÷207) |
| III | $CH_3$ | изо-$C_5H_{11}$ | 64 | — | 85—6 | 164—5 | 76,85 | 8,20 | 14,95 | $C_{18}H_{23}N_3O$ | 76,83 | 8,24 | 14,93 | 240 (222÷259) |
| IV | $CH_3$ | $C_6H_5CH_2$ | 72 | — | 115—6 | 213—4 | 75,70 | 6,00 | 13,27 | $C_{20}H_{19}N_3O$ | 75,68 | 6,03 | 13,24 | 233 (203÷268) |
| V | $CH_3O$ | $CH_3$ | — | 32 | 108—10 | 169—71 | 65,20 | 5,80 | 16,40 | $C_{14}H_{15}N_3O_2$ | 65,35 | 5,88 | 16,33 | 288 (272÷306) |
| VI | $CH_3O$ | $C_2H_5$ | — | 29 | 83—5 | 165—7 | 66,16 | 6,35 | 15,72 | $C_{15}H_{17}N_3O_2$ | 66,40 | 6,32 | 15,49 | 200 (171÷264) |
| VII | $CH_3O$ | $C_3H_7$ | 78 | 69 | 68—70 | 168—70 | 67,30 | 7,00 | 14,63 | $C_{16}H_{19}N_3O_2$ | 67,35 | 6,71 | 14,73 | 150 (117÷192) |
| VIII | $CH_3O$ | $C_6H_5CH_2$ | 86 | 67 | 65—7 | 166—8 | 72,00 | 5,50 | 12,50 | $C_{20}H_{19}N_3O_2$ | 72,05 | 5,74 | 12,61 | 460 (418÷506) |

*All compounds crystallized from ethanol.

TABLE 2. Anticonvulsant Activity of Substituted Amides VII, VIII, IX, X Introduced Intraperitoneally

| Compound | Electroshock test | | $ED_{50}$ Corazole test, mg/kg | Operating ratio for pharmacological activity | |
|---|---|---|---|---|---|
| | $ED_{50}$, mg/kg | peak activity, min | | by electroshock test | by Corazole test |
| VII | 76 (68÷86) | 10 | 52 (42÷65) | 2,0 | 2,9 |
| VIII | 290 (260÷324) | 10 | 180 (153÷212) | 1,6 | 2,6 |
| IX* | 105 (80÷124) | 20 | 140 (131÷150) | 5,1 | 3,8 |
| X† | 145 (128÷165) | 5 | 110 (97÷126) | 5,4 | 7,1 |
| Chloracon | 94 (75÷118) | 15 | 143 (118÷173) | 7 | 4,5 |

*$LD_{50}$ equals 530(523-547) mg/kg.
†$LD_{50}$ equals 780(736-823) mg/kg.

$\nu_{NH}$ 3330, 3440 $cm^{-1}$. They have basic properties and form water-soluble hydrochlorides. In the UV spectra of amides I-VIII, two maxima were noted at 290 and 348 nm. They absorb intensely in the 220 nm region but we were unable to determine the absorption maximum for this band.

## EXPERIMENTAL

### Pharmacological

The pharmacological studies were conducted on mice of both sexes weighing 18-22 g. The substances were introduced intraperitoneally in a 2% starch suspension. We studied compounds I-VIII, as well as the isoamylamide and the benzylamide of 2-chloronicotinic acid (IX, X).

The experimental data were developed statistically for P = 0.05, according to Litchfield and Wilkinson [4].

The properties studied were acute toxicity [5], anticonvulsant activity by the maximum electroshock test [6] and by the Corazole test, antitremor activity by the nicotine and arecoline tests [7]. Depression and excitation effects were determined visually. In addition we determined the operating ratio for pharmacological activity ($LD_{50}/ED_{50}$). Antimicrobial activity was determined by the method of successive dilution in cultures of *staphylococcus aureus* and *Escherichia coli*. The effective dose was taken to be the minimum concentration which inhibited growth in the bacterial culture. The results are given in Tables 1 and 2.

Compounds VII and IX are most active, the difference in $ED_{50}$ between these compounds and the well-known anticonvulsant chloracon in the electroshock test being statistically insignificant. Compounds VIII and X are less active than chloracon by a factor of 1.5 to 3.

The dynamics of development of the anticonvulsant effect of compounds VII-X were investigated. Anticonvulsant activity reaches a maximum in 5-10 min. The effect was most prolonged (5 h) with VIII, the duration of the effect of the others being 1 h.

Anti-Corazole activity was observed for compounds VII-X. Compound VII was most active in the Corazole test ($ED_{50}$ was 52 (42-65) mg/kg), thus surpassing chloracon by a factor of 1.5 on the electroshock test and by a factor of 2.8 on the Corazole test.

Compounds VII-X in doses corresponding to the $ED_{50}$ in maximum electroshock test do not prevent or diminish nicotine and arecoline tremors, i.e., they do not exhibit m- or n-cholinolytic activity. Some compounds act as central nervous system depressants: VII and VIII at doses close to the $ED_{50}$ in maximal electroshock test, IX and X in doses close to the lethal value.

Acute toxicity exhibited by the anticonvulsant compounds decreases in the order VII, VIII, IX, X, with IX and X having about the same level of toxicity as chloracon, while VIII and VII have toxicities 1.4 and 4.3 times as high, respectively. The highest pharmacological ratio was found for compound X: 5.4 by the electroshock test, 7.1 by the Corazole test.

The compounds showed weak antimicrobial activity ranging from 1:4000 to 1:16,000 for *S. aureus*.

Thus the introduction of the D-tolyl radical into the amino group of substituted amides of 2-aminonicotinic acid leads to the disappearance of anticonvulsant activity independent of the radical in the amide group. In compounds V-VIII there appears to be a link between activity and the substituent in the amide part. Thus the methylamide (V) and the ethylamide (VI) showed no anticonvulsant activity in the maximal electroshock test; the propylamide (VII) exhibited a fairly high activity which was reduced when the aliphatic radical was replaced by benzyl (VIII).

These studies allow one to judge the prospects of searching for anticonvulsant substances among the derivatives of 2-arylamino and 2-chloronicotinic acids.

### Chemical

IR spectra were obtained for carbon tetrachloride solutions on the UR-20 apparatus. UV spectra were obtained for $2 \cdot 10^{-5}$ M solutions on a Spectro MOM-202 apparatus.

Alkylamides of 2-Arylaminonicotinic Acid (I-VIII). Method A. A solution of 0.01 mole of alkylamide of 2-chloronicotinic acid [1] and 0.01 mole of arylamine in 15 ml of 50% acetic

acid was boiled for 6 h, cooled, poured into water and neutralized with 10% aqueous sodium hydroxide. The resulting precipitate was filtered off and recrystallized from ethanol.

Method B. A solution of 0.01 mole of the methyl ester of 2-(p-anisidino)nicotinic acid and 0.015 mole of alkylamine* in methanol was boiled for 8 h. The solvent and excess amine were boiled off under vacuum. The residue was recrystallized. The hydrochlorides of compounds I-VIII were obtained by dissolving the bases in ethanolic hydrogen chloride and subsequent precipitation with ether.

Isoamylamide of 2-chloronicotinic acid (X). To 0.01 mole of 2-chloronicotinic acid was added 20 ml thionyl chloride and the solution was heated on a water bath for 3 h. Excess thionyl chloride was evaporated off under vacuum. To the residue was added 20 ml of benzene, 0.01 mole of isoamylamine and 3 ml of triethylamine. The reaction mass was kept at room temperature for 4 h. The precipitate of triethylamine hydrochloride was filtered off. Benzene and volatile impurities were evaporated off under vacuum. The residue was crystallized from hexane. Yield 60%; mp 69-70°C. Found, %: 15.3; N 10.52. $C_{11}H_{15}ClN_2O$. Calculated, %: Cl 15.4; N 10.46. The benzylamide of 2-chloronicotinic acid (X) was prepared analogously. Yield 67%; mp 116-117°C (from hexane). Found, %: Cl 14.43; N 11.72. $C_{13}H_{11}ClN_2O$. Calculated, %: Cl 14.4; N 11.70.

## LITERATURE CITED


1. A. I. Mikhalev, V. K. Kudryashova, M. E. Konshin et al., Khim.-Farm. Zh., 1975, 15-18.
2. V. P. Chesnokov, M. E. Konshin, V. S. Zalesov et al., Khim.-Farm. Zh., 1973, 20-23.
3. G. Mosher, in: Heterocyclic Compounds [in Russian], Vol. 1, Moscow (1953), pp. 311-479.
4. M. L. Belen'kii, Elements of Quantitative Assays in Pharmacological Effect [in Russian], Riga (1959), pp. 71-92.
5. G. N. Pershin, Methods of Experimental Chemotherapy [in Russian], Moscow (1959), pp. 109-117, 456-460.
6. K. S. Raevskii, Farmakol. Toksikol., 1961, 495-497.
7. V. S. Zalesov, Farmakol. Toksikol., 1963, 418-431.


*In preparing amides V and VI saturated methanolic solutions of the corresponding amines were used.