SYNTHESIS OF AMIDES OF 2-ARYLAMINO-4,6-DIMETHYLNICOTINIC ACID

L. M. Demina, M. Yu. Gavrilov, S. N. Shurov, and M. E. Konshin

The amides of 2-arylamino-4,6-dimethyl-2-chloronicotinic acid have been prepared. It has been shown that on account of steric hindrance on the part of the methyl group on the $C_{(4)}$ atom the conjugation of the amide function with the pyridine ring is broken and its influence on the mobility of the halogen is weakened, and the compound enters into a given reaction with more difficulty than its 6-monomethyl homolog.

It has been shown previously that the amides of 2-arylaminonicotinic acids are of interest as antispasmodics [1] and also as starting materials for the preparation of 2-acetonyl derivatives of 4-oxo-1,4-dihydropyridino[2,3-d]pyrimidines [2].

In the present work we have undertaken a synthesis of the previously known amides of 2-arylamino-4,6-dimethylnicontinic acids (Ia-e, Table 1) and we have studied their biological activity.

II Ia-e

Ia R = H; Ib R = 3-Me; Ic R = 4-Me; Id R = 3-Cl; Ie R = 4-Br

It has been established that the amides Ia-e can be prepared by boiling the amide of 4,6-dimethyl-2-chloronicotinic acid (II) and arylamines in 50% acetic acid. However, comparison of the results of experiments on the synthesis of amides Ia-e with those for the amides of 2-arylamino-6-methylnicotinic acid [1] shows that for preparing the former it is necessary to react at boiling point for 12 h whereas in the second case 6 h is sufficient and the desired products are obtained in high yields.

The low reactivity of the amide of 4,6-dimethyl-2-chloronicotinic acid in comparison with the amide of 6-methyl-2-chloronicotinic acid (III) is apparently connected with the inductive effect on the reaction center of the methyl group at $C_{(4)}$ together with steric hindrance of this group to the conjugation of the amide function with the pyridine ring which weakens its influence on the mobility of the chlorine.

To confirm the latter assumption and to determine the optimal spatial arrangement of the amide group relative to the plane of the pyridine ring, calculations were carried out on the molecules of the amides of 2-chloro-6-methyl- (III) and 2-chloro-4,6-dimethylnicotinic acid II in the MM_2 approximation (Tables 2 and 3). The calculations showed (Table 3) that in the amide III the carbamoyl group is unfolded relative to the plane of the ring by 15.7°, apparently on the strength of repulsion by the oxygen and chlorine atoms. Introduction of a methyl group into position 4 of the pyridine unfolds the carbamoyl group to a still greater extent (to 34.0°) relative to the plane of the ring.

The greater unfolding of the carbamoyl fragment reduces its conjugation with the pyridine ring and possibly lowers the electron-acceptor action, facilitating the nucleophilic replacement of the halogen. On the other hand, unfolding of the amide group creates steric hindrance to attack by a nucleophile on the $C_{(2)}$ atom and to the formation of a Meisenheimer transition complex. This would seem to explain the difficulty in replacing halogen in the amide II.

Perm Pharmaceutical Institute, Perm 614600. Perm M. Gorkii State University, Perm 614600. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1506-1508, November, 1992. Original article submitted March 20, 1992.

 0009-3122/92/2811-1286$12.50

TABLE 1. Amides of 2-Arylamino-4,6-dimethylnicotinic Acids

Compound	Empirical formula	mp, °C	R_f	mp (dec.) of hydro.	Yield, %
Ia	$C_{14}H_{15}N_3O$	128...130 [3]	0,58	—	54
Ib	$C_{15}H_{17}N_3O$	138...140	0,61	132	36
Ic	$C_{15}H_{17}N_3O$	136...138	0,65	180	43
Id	$C_{14}H_{14}ClN_3O$	177...178	0,51	210	30
Ie	$C_{14}H_{14}BrN_3O$	234...236	0,47	203	56

TABLE 2. Bond Lengths and Valence Angles of Amides II

Bond length, Å			Valence angle, ω°		
bond	compound		bond	compound	
	II	III		II	III
$N_{(1)}—C_{(2)}$	1,351	1,351	$N_{(1)}—C_{(2)}—C_{(3)}$	120,7	120,5
$C_{(2)}—Cl$	1,751	1,752	$Cl—C_{(2)}—C_{(3)}$	121,7	121,8
$C_{(2)}—C_{(3)}$	1,402	1,402	$C_{(2)}—C_{(3)}—C_{(4)}$	117,7	117,5
$C_{(3)}—C_{(4)}$	1,402	1,400	$C_{(3)}—C_{(O)}—O$	119,6	119,5
$C_{(3)}—C_{(O)}$	1,516	1,516	$C_{(3)}—C_{(O)}—N$	120,4	120.7
$C_{(O)}—O$	1,200	1,220	$O—C_{(O)}—N$	119,7	119,8
$C_{(O)}—N$	1,347	1,348	$C_{(O)}—N—H$	119,5	118,7
N—H	1,000	1,000	$C_{(O)}—C_{(3)}—C_{(4)}$	121,2	120,3
$C_{(4)}—H$	—	1,082	$C_{(3)}—C_{(4)}—H$	—	120,6
$C_{(4)}—C_{(H)}$	1,526	—	$C_{(3)}—C_{(4)}—C_{(H)}$	122,6	—
$C_{(H)}—H$	1,100	—	$C_{(4)}—C_{(H)}—H$	109,3	—
$C_{(4)}—C_{(5)}$	1,399	1,357	$C_{(3)}—C_{(4)}—C_{(5)}$	119,6	120,6
$C_{(5)}—H$	1,084	1,083	$C_{(4)}—C_{(5)}—C_{(6)}$	119,2	118,9
$C_{(5)}—C_{(6)}$	1,397	1,397	$C_{(4)}—C_{(5)}—H$	120,5	120,4
$C_{(6)}—N_{(1)}$	1,350	1,350	$C_{(5)}—C_{(6)}—N_{(1)}$	119,9	119,6
$C_{(4)}—C_{(H)}$	1,524	1,526	$C_{(6)}—N_{(1)}—C_{(2)}$	121,6	122,2
$C_{(H)}—H$	1,099	1,000	$C_{(6)}—C_{(H)}—H$	110,1	110,5

TABLE 3. Torsion Angles of Amides II and III

Bond	Torsion angle, τ°	
	II	III
$H—N—C_{(O)}—O$	178,3	179,1
$N—C_{(O)}—C_{(3)}—C_{(4)}$	- 34,0	15,7
$O—C_{(O)}—C_{(3)}—C_{(2)}$	33,5	15,4
$C_{(O)}—C_{(3)}—C_{(4)}—C_{(5)}$	163,0	172,5
$Cl—C_{(2)}—C_{(3)}—C_{(4)}$	9,1	9,8

The assumption about the reduction in conjugation of amide group and ring in this compound is further supported by the UV spectra of amides II and III. In the UV spectrum of 4,6-dimethyl-2-chloronicotin-amide the long-wave maximum at 268 nm has a smaller intensity and is shifted hypochromically by 3 nm in comparison with that of amide III.

The hydrochlorides of amides Ib-e were prepared by reacting the corresponding base with HCl in alcohol solution.

The structure of compounds Ia-e was confirmed by their IR and NMR spectra. In the IR spectra there were bands at 1625-1650 cm^{-1} (CO), 3125-3200 and 3290-3440 cm^{-1} (NH). The NMR spectra showed singlets at 1.90-2.57 ppm (6H, $2CH_3$), a broad signal at 5.90-6.17 ppm (1H, NH), a singlet at 6.30-6.50 ppm (1H, pyridine), a multiplet at 6.33-7.77 ppm (arom. protons), and a singlet at 8.13-9.60 ppm (2H, NH_2CO).

The antispasmodic activity of the amides Ia-e was studied* by the electric shock test [4]. The studies showed that high activity is inherent in the hydrochlorides of amides Ib-e which protect from electrospasm 50% of mice at doses of 55-95 mg/kg with a toxicity (LD_{50}) of 344-390 mg/kg. The activity of the hydrochlorides Ib-e falls along the series Id > Ic > Ie > Ib.

EXPERIMENTAL

IR spectra were run on a UR-20 instrument in mineral oil, PMR spectra on a RYa-2310 (60 MHz) spectrometer for 5% solutions in $CDCl_3$ with HMDS internal standard. UV spectra were recorded on an SF-26 instrument for solutions in ethanol ($c = 1 \cdot 10^{-4}$ mole/liter). TLC was carried out on Silufol UV-254 plates in 1:1 benzene–ethyl acetate; R_f values are given in Table 1. Calculations were carried out by the method of atom–atom potentials (molecular mechanics) [5].

The results of elemental analysis for C, H, N in compounds Ia-e and for Cl and Br in Id and Ie respectively were in agreement with calculations.

Amides of 2-Arylamino-4,6-dimethylnicotinic Acid (Ia-e). A solution of 1.8 g (0.01 mole) amide II and 0.01 mole arylamine in 50 ml 50% acetic acid was heated 12 h at bp, diluted with water and neutralized with 10% NaOH. The amide of 2-arylamino-4,6-dimethylnicotinic acid which separated was recrystallized from toluene.

Hydrochlorides of 2-Arylamino-4,6-dimethylnicotinamides. The appropriate amide Ib-e (0.01 mole) was dissolved in 20 ml 10% HCl in alcohol and part of the alcohol distilled off and the hydrochloride precipitated with ether.

REFERENCES

1. N. I. Shramm, N. A. Podushkina, V. S. Zalesov, M. E. Konshin, and A. A. Pulin, Dept. in TsBNTI (Central Office of Scientific and Technical Information); Khim.-farm. Prom., No. 61 (1981).
2. N. I. Shramm and M. E. Konshin, Khim. Geterotsikl. Soedin., No. 1, 114 (1985).
3. H. Jahine, H. A. Zaher, M. Seada, and M. F. Ishak, Indian J. Chem., **17**, No. 2, 134 (1979).
4. K. S. Raevskii, Toksikol. Farmakol., No. 4, 495 (1961).
5. U. Burkert and N. L. Allinger, Molecular Mechanics, ACS Monograph No. 177, Am. Chem. Soc., Washington, DC (1982).

*The tests were carried out by V. K. Danilov, L. P. Drovosekova, and V. É. Koll to whom the authors extend their thanks.