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# PREPARATION OF A SERIES OF N-PHENYLAMIDES OF 5-BROMO-6-CHLORONICOTINIC ACID AND 5-BROMO-2-CHLORONICOTINIC ACID

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## ABSTRACT

A series of N-phenylamides of 5-bromo-6-chloronicotinic acid and 5-bromo-2-chloronicotinic acid were synthesized by treatment of their freshly prepared acid chlorides with the appropriately ring-substituted anilines. Thirty new compounds were prepared, and their structures were ascertained by elemental analyses and spectroscopic techniques. Spectroscopic trends in the infrared spectra of the two series were examined in an attempt to correlate structural and electronic effects to hydrogen bonding tendencies.

## INTRODUCTION

In connection with our continuing search for dihalonicotinic acid derivatives with potential pesticidal, herbicidal, and fungicidal activity (Setliff *et al.*, 1989), we have prepared a series of N-phenylamides of 5-bromo-6-chloronicotinic acid (I) and 5-bromo-2-chloronicotinic acid (II) (Setliff, 1970). These compounds, with the dihalopyridine moiety on the carbonyl side of the amide function, exhibit a reversal of the amide linkage in comparison to previously reported benzamide and phenylurea halopyridine derivatives (Setliff and Palmer, 1987; Setliff and Rankin, 1988; Setliff *et al.*, 1989).

Thirty new N-phenylnicotinamides were synthesized with a variety of electron releasing groups and electron withdrawing groups present on the benzene ring. Having available two such closely related series of compounds, we also sought to look for any trends in their infrared spectra which could be related to the electronic effects of the benzene ring substituents.

## MATERIALS AND METHODS

Acids I and II were prepared as previously reported (Setliff, 1970). The substituted anilines employed were fresh practical grade samples from either Aldrich Chemical Company or Eastman Organic Chemicals. All liquid anilines were freshly distilled. All solid anilines were used without further purification with the exception of 4-chloroaniline and 4-methoxyaniline which were recrystallized from methylcyclohexane.

Melting points are uncorrected and were determined using a Mel-Temp II capillary melting apparatus. Infrared spectra were obtained on samples prepared as potassium bromide disks using a Perkin-Elmer 1430 spectrophotometer equipped with a Model 7300 data station. Proton nuclear magnetic resonance spectra were obtained using an AC-F Bruker 200 MHz FT spectrometer with deuterated dimethyl sulfoxide as the solvent and tetramethylsilane as the internal standard. All elemental analyses were performed by Desert Analytics Organic Microanalysis, Tucson, Arizona.

The N-phenyl-5-bromo-6-chloronicotinamide compound series (III) and N-phenyl-5-bromo-2-chloronicotinamide compound series (IV) were obtained by heating a chloroform solution of the freshly prepared acid chlorides with an excess amount of the appropriately substituted anilines. The reaction sequence is depicted in Figure 1. Dihalooacid I or II (0.50 g; 0.0021 mol) was stirred and heated under reflux with thionyl chloride (3.0 mL) for 30 minutes then cooled to room temperature. The acids completely dissolved to yield a transparent yellow solution. Excess thionyl chloride was removed from this solution under reduced pressure on a rotary evaporator (oil bath 50-60 °C). The residual viscous acid chloride was taken up in chloroform (2.0 mL) and to this mixture was added a solution of the appropriately substituted aniline (0.0050 mol) in chloro-

form (10.0 mL). A solid precipitate formed, and the resulting reaction mixture was heated under reflux for one hour and 30 minutes then cooled to room temperature. The solid precipitate was collected by vacuum filtration, dried and weighed, and the chloroform filtrate was saved.

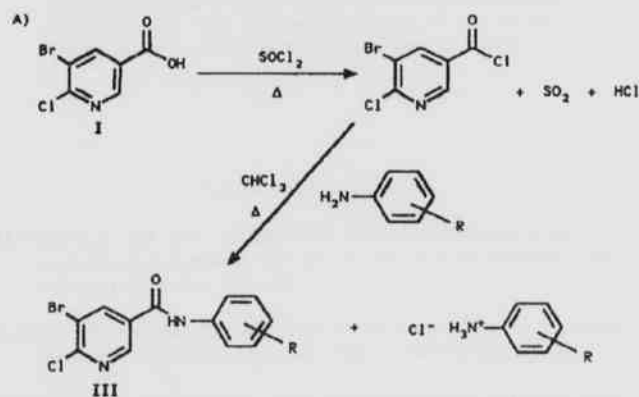


Figure 1. A) Preparation of the 5-bromo-6-chloronicotinamides and B) the 5-bromo-2-chloronicotinamides

Isolation and purification of the amide products varied according to their chloroform solubilities. Some of the amides were extremely chloroform-soluble as evidenced by the weight and water solubility of the amine hydrochloride isolated from the reaction mixture. In these instances, purification procedure A was employed as follows: The chloroform filtrate from the reaction mixture was washed with water (2 x 10 mL) followed by 10% hydrochloric acid (2 x 10 mL) and then evaporated to yield the crude amide product, which was subsequently recrystallized from aqueous ethanol.

Several amide products were insoluble in chloroform and precipitated together with the amine hydrochlorides. These compounds were purified by procedure B as follows: The precipitate from the reaction mixture was stirred magnetically in water (150 mL) to dissolve the amine hydrochloride. The residual crude amide was collected by filtration and recrystallized from aqueous ethanol.

In a few instances, the amide product was partially soluble in chloroform and was distributed between the precipitated solid and the chloroform filtrate. Purification procedure C was employed in these cases as follows: The reaction mixture precipitate was stirred magnetically in water (150 mL), and the undissolved amide product was collected by filtration. The original chloroform filtrate was washed with water (2 x 10

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mL) followed by 10% hydrochloric acid (2 x 10 mL) and then evaporated to yield an additional amount of amide. The two portions of the crude amide were combined and recrystallized from aqueous ethanol.

Summaries of melting points, percentage yields, and purification procedures employed appear in Table 1 (series III amides) and Table 2 (series IV amides.)

Table 1. Percentage Yields, Melting Points, and Purification Procedures of the N-(Substituted phenyl)-5-bromo-6-chloronicotinamides.

Compound	R	Yield (%)	mp (°C)	Purification Proce
IVa	4-CH <sub>3</sub>	89.7	158.5	A
IVb	4-Br	87.0	176	A
IVc	H	90.1	140-140.5	A
IVd	4-Cl	93.2	161-162	A
IVe	4-OCH <sub>3</sub>	97.2	163.5-164	A
IVf	3-CH <sub>3</sub>	89.7	156-156.5	A <sup>a</sup>
IVg	4-OCH <sub>2</sub> CH <sub>3</sub>	92.0	185.5-186	C
IVh	2-CH <sub>3</sub>	89.7	213-214	C <sup>a</sup>
IVi	2,4-diCH <sub>3</sub>	80.0	189-189.5	A
IVj	2-Cl	93.2	176.5-177	A
IVk	4-I	84.8	201.5-202	C
IVl	4-F	87.0	155.5-156.5	A
IVm	2-F	92.8	141-141.5	A
IVn	4-NO <sub>2</sub>	80.0	221.5-222	B <sup>b</sup>
IVo	4-COCH <sub>3</sub>	78.0	212-216	A

a...

Table 2. Percentage Yields, Melting Points, and Purification Procedures of the N-(Substituted phenyl)-5-bromo-2-chloronicotinamides.

Compound	R	Yield (%)	mp (°C)	Purification Proce
IIIa	4-CH <sub>3</sub>	86.7	182-183	A
IIIb	4-Br	75.6	229-231	B
IIIc	H	89.2	166-166.5	A
IIId	4-Cl	75.3	212-212.5	C
IIIe	4-OCH <sub>3</sub>	80.6	181.5-182	C
IIIf	3-CH <sub>3</sub>	91.2	155-156	A <sup>a</sup>
IIIg	4-OCH <sub>2</sub> CH <sub>3</sub>	88.0	177	C
IIIh	2-CH <sub>3</sub>	70.6	206.5-207	B
IIIi	2,4-diCH <sub>3</sub>	88.0	185	A
IIIj	2-Cl	80.3	184-184.5	A
IIIk	4-I	76.1	256.5-257.5	B
IIIl	4-F	82.6	175.5-176	A
IIIm	2-F	85.5	178.5-179	A
IIIn	4-NO <sub>2</sub>	65.0	229.5-230	B <sup>b</sup>
IIIo	4-COCH <sub>3</sub>	59.5	237-238	C

## RESULTS AND DISCUSSION

Thirty new amides, 15 from each series, were synthesized in excellent yields (usually greater than 80%). Elemental analysis of these compounds showed agreement to within 0.4% of the calculated percent compositions. Infrared spectra revealed the expected absorption bands for both the carbonyl group and amide proton frequencies. Tables 3 (series III amides) and 4 (series IV amides) summarize these infrared absorption frequencies and elemental analysis results.

Table 3. Infrared Spectral Data and Elemental Analysis Results of the N-(Substituted phenyl)-5-bromo-6-chloronicotinamides.

Compound	R	IR, (cm <sup>-1</sup> )		Elemental Anal., Calc'd % (Found %)		
		N-H	C=O	C	H	N
IIIa	4-CH <sub>3</sub>	3314	1680	47.94(48.08)	3.07(3.11)	8.61(8.47)
IIIb	4-Br	3340	1678	36.90(37.03)	1.79(1.72)	7.17(7.14)
IIIc	H	3280	1642	46.24(45.94)	2.57(2.62)	8.99(8.75)
IIId	4-Cl	3354	1683	41.63(41.41)	2.02(1.87)	8.10(8.01)
IIIe	4-OCH <sub>3</sub>	3328	1669	45.69(45.46)	2.93(2.92)	8.20(8.13)
IIIf	3-CH <sub>3</sub>	3277	1649	47.94(47.82)	3.07(2.88)	8.61(8.49)
IIIg	4-OCH <sub>2</sub> CH <sub>3</sub>	3349	1667	47.27(47.02)	3.38(3.24)	7.88(7.66)
IIIh	2-CH <sub>3</sub>	3281	1643	47.94(47.53)	3.07(3.01)	8.61(8.47)
IIIi	2,4-diCH <sub>3</sub>	3262	1638	49.48(49.44)	3.54(3.49)	8.25(8.16)
IIIj	2-Cl	3285	1649	41.63(41.74)	2.02(1.81)	8.10(7.97)
IIIk	4-I	3332	1676	32.93(32.51)	1.60(1.59)	6.40(6.18)
IIIl	4-F	3273	1644	43.72(43.82)	2.13(1.98)	8.50(8.40)
IIIm	2-F	3287	1649	43.72(43.61)	2.13(2.02)	8.50(8.39)
IIIn	4-NO <sub>2</sub>	3326	1685	40.42(40.26)	1.98(1.82)	11.79(11.64)
IIIo	4-COCH <sub>3</sub>	3313	1674	47.55(47.81)	2.86(2.77)	7.92(7.85)

Table 4. Infrared Spectral Data and Elemental Analysis Results of the N-(Substituted phenyl)-5-bromo-2-chloronicotinamides.

Compound	R	IR, (cm <sup>-1</sup> )		Elemental Anal., Calc'd % (Found %)		
		N-H	C=O	C	H	N
IVa	4-CH <sub>3</sub>	3248	1655	47.94(47.72)	3.07(3.11)	8.61(8.50)
IVb	4-Br	3240	1656	36.90(36.81)	1.79(1.76)	7.17(7.03)
IVc	H	3274	1658	46.24(46.03)	2.57(2.51)	8.99(8.72)
IVd	4-Cl	3293	1663	41.63(41.42)	2.02(2.00)	8.10(8.01)
IVe	4-OCH <sub>3</sub>	3245	1649	45.69(45.43)	2.93(2.90)	8.20(8.06)
IVf	3-CH <sub>3</sub>	3247	1657	47.94(48.05)	3.07(2.83)	8.61(8.50)
IVg	4-OCH <sub>2</sub> CH <sub>3</sub>	3253	1649	47.27(47.10)	3.38(3.29)	7.88(7.70)
IVh	2-CH <sub>3</sub>	3239	1654	47.94(47.70)	3.07(2.94)	8.61(8.40)
IVi	2,4-diCH <sub>3</sub>	3241	1652	49.48(49.10)	3.54(3.44)	8.25(8.18)
IVj	2-Cl	3237	1659	41.63(41.88)	2.02(1.86)	8.10(8.34)
IVk	4-I	3263	1649	32.93(32.81)	1.60(1.52)	6.40(6.20)
IVl	4-F	3292	1658	43.72(43.85)	2.13(2.05)	8.50(8.41)
IVm	2-F	3245	1665	43.72(43.70)	2.13(2.02)	8.50(8.41)
IVn	4-NO <sub>2</sub>	3235	1649	40.42(40.32)	1.98(1.72)	11.79(11.64)
IVo	4-COCH <sub>3</sub>	3269	1670	47.55(47.30)	2.86(2.70)	7.92(7.79)

## Preparation of a Series of N-Phenylamides of 5-Bromo-6-Chloronicotinic Acid

Having available such a closely related series of compounds, we sought to look for any trends in their spectra which could be related to the electronic effects of the R group within the amide series III or series IV. In addition, trends which could be related to the position of the chlorine on the pyridine ring (6 position in series III vs. 2 position in series IV) for a common R substituent were also sought. We chose to compare the N-H and carbonyl stretching frequencies of crystalline samples prepared as KBr disks, since comparisons of these absorption frequencies might reveal the degree of hydrogen bonding which might be occurring in the solid state (Silverstein *et al.*, 1981).

An obvious trend noted was that the series III amides exhibited N-H stretching bands ranging from 3354  $\text{cm}^{-1}$  (III<sub>d</sub>) to 3262  $\text{cm}^{-1}$  (III<sub>i</sub>), while the amides in series IV showed a significantly lower range of absorption frequencies (3293  $\text{cm}^{-1}$  for IV<sub>d</sub> to 3235  $\text{cm}^{-1}$  for IV<sub>n</sub>). The differences in frequencies between the two series for a given R substituent ranged from 100  $\text{cm}^{-1}$  (III<sub>b</sub> > IV<sub>b</sub>) to 6  $\text{cm}^{-1}$  (III<sub>c</sub> > IV<sub>c</sub>). The only discrepancy in the cross-series trend was the 4-fluoro substituent where IV<sub>1</sub> > III<sub>1</sub> by a margin of 19  $\text{cm}^{-1}$ .

Since the change in frequencies between the two series was smallest for R = H (6  $\text{cm}^{-1}$ ), it was attractive to speculate that the presence of a substituent on the benzene ring does appreciably affect the magnitude of the N-H stretching frequency. However, attempts to correlate the N-H stretching frequencies within each series with electronic effects of the R substituent were unrewarding. A Hammett plot of these N-H frequencies versus the 3 and 4 position R substituent constants (Exner, 1988) showed no linearity in either amide series. It is noteworthy that since N-H stretching frequencies are influenced by other factors such as vibrational coupling and Fermi resonance, localized substituent effects on the N-H bond are difficult to measure (Exner, 1988). This complication may be responsible in part for our poor correlations.

Observations of various carbonyl stretching frequencies revealed that the series III amides as a group exhibited a broader range of frequencies (1685  $\text{cm}^{-1}$  to 1638  $\text{cm}^{-1}$ ) than did the series IV amides (1679  $\text{cm}^{-1}$  to 1649  $\text{cm}^{-1}$ ), but there was no clear trend in the cross-series comparisons. In fact, in seven of the 15 cases the series III compounds showed a lower carbonyl stretching frequency than the series IV compounds. In addition, there was no apparent correlation of these frequencies with Hammett substituent constants within either series.

One attractive conclusion of the observed spectral trends is that the overall lower N-H stretching frequencies in the series IV amides suggest stronger solid state hydrogen bonding in this series than in the series III amides. The inconsistencies in the carbonyl stretching frequencies could be explained by the fact that several other proton acceptor sites are available for hydrogen bonding in these compounds. However, intermolecular forces other than hydrogen bonding are present in solid state molecular crystals, and these forces, which influence crystal structure, may also be responsible for the observed spectral trends (Williams, 1981).

Proton nuclear magnetic resonance spectra of all amides were obtained in deuterated dimethyl sulfoxide and were consistent with the expected structures. Correlations of certain nuclear magnetic resonance spectral characteristics with Hammett substituent constants will be the subject of a future communication.

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