Journal of the Arkansas Academy of Science

Volume 46 Article 10

1992

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Recommended Citation

Setliff, Frank L. and Soman, Nikhil G. (1992) "4-Substituted Anilides of 2,6- and 5,6- Dichlorolicotinic Acid. Potential Agricultural Agents," *Journal of the Arkansas Academy of Science*: Vol. 46, Article 10.
Available at: https://scholarworks.uark.edu/jaas/vol46/iss1/10

4 - SUBSTITUTED ANILIDES OF 2,6 - AND 5,6 - DICHLORONICOTINIC ACID. POTENTIAL AGRICULTURAL AGENTS.

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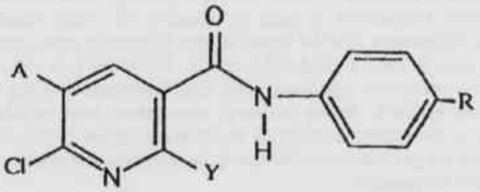
ABSTRACT

A series of 4-substituted anilides of 2,6- and 5,6-dichloronicotinic acid were prepared. The acids were first converted to their acid chlorides, which were in turn treated with the appropriate 4-substituted aniline in chloroform. A total of 16 anilides was thus prepared, and their structures confirmed. These compounds were prepared for testing as possible herbicidal, pesticidal or fungicidal agents.

INTRODUCTION

For over two decades, we have been engaged in the preparation of dihalogenated nicotinic acids and their derivatives, together with their subsequent evaluation as potential herbicidal, fungicidal and pesticidal agents (Setliff, 1970). Most recently we reported the preparation and characterization of a series of substituted anilides of 5-bromo-2-chloronicotinic acid and 5-bromo-6-chloronicotinic acid (Setliff and Caldwell, 1991), and were encouraged by the moderate activity demonstrated by several of these derivatives. The details of these evaluations, performed by the Research Division of a leading Agricultural Chemical Company, are confidential and cannot be reported here. Unfortunately, the activities of these compounds were organism-specific, and further screening was not performed.

In view of the limited success of the bromochloro nicotinanilides, it was decided to prepare a series of anilides of the isomeric 2,6- and 5,6-dichloronicotinic acids, in the hope that enriching the chlorine content might result in a more active and broader spectrum activity profile. We thus prepared the eight 4-substituted 2,6-dichloronicotinanilides (Ia-h) and the eight 4-substituted 5,6-dichloronicotinanilides (IIa-h), all of which are depicted in Figure 1.



I
A = H Y = Cl

II
A = Cl Y = H

Compound	R
a.	H
b.	OCH_3
c.	CH_3
d.	F
e.	Br
f.	$COCH_3$
g.	CF_3
h.	NO_2

Figure 1. Structures of the dichloronicotinanilides.

MATERIALS AND METHODS

Melting points were determined on a Mel-Temp II apparatus and are uncorrected. Infrared spectra were taken on a Perkin Elmer 1430 ratio recording instrument equipped with a Model 7300 data station and with samples prepared as KBr disks. ^1H nmr spectra were determined in DMSO-d_6 containing 1% TMS and were obtained on a Bruker 200 MHz FTAC-F superconductivity spectrometer equipped with ASPECT 300 computer control. Carbon, hydrogen, and nitrogen elemental analyses were done by Desert Analytics Organic Microanalysis, Inc., Tucson, Arizona.

Technical grade 2,6-dichloronicotinic acid (m.p. 141°-143°C) was obtained from Aldrich Chemical Company and was used without further purification. 5,6-Dichloronicotinic acid was prepared by oxidation of 5,6-dichloro-3-picoline (Setliff and Lane, 1976), and after recrystallization from water melted at 162-163°C.

The following general procedure was employed in the preparation of both the series I and II anilides. The dichloroacid (0.50 g; 0.0026 mol) and thionyl chloride (3 ml) were combined and magnetically stirred under gentle reflux for 30 minutes, whereupon the acid dissolved. The reaction mixture was allowed to cool to room temperature, and the excess thionyl chloride was removed under reduced pressure on a rotary evaporator. The residual acid chloride was taken up in dry chloroform (3 ml) and added to the appropriately substituted aniline (0.0058 mol) which had been dissolved in dry chloroform (10 ml). The resulting suspension was then stirred under reflux for 30 minutes. (Note: In case of the 4-nitroanilides Ih and IIh, dry benzene was used as solvent and the reflux time was extended to 1 hour). The reaction mixture was cooled, and the solid collected by vacuum filtration. The chloroform filtrate was washed with 2 x 10 ml water, then 2 x 10 ml 10% HCl, followed again by 2 x 10 ml H_2O. Evaporation of the chloroform afforded the crude anilide. In some cases a considerable amount of anilide product occluded with the aniline hydrchloride that was filtered from the reaction mixture. In those instances, the solid from the reaction mixture was dried, stirred vigorously with 100 ml water for 30 minutes, and then filtered by vacuum. The water insoluble anilide, and the residue from the chloroform evaporation were combined and recrystallized from aqueous ethanol. A second recrystallization was performed to produce a sharp melting analytical sample for C,H,N and spectroscopic analysis.

RESULTS AND DISCUSSION

Preliminary experiments showed that the Schotten Bauman method (reaction of the acid chloride with the aniline in the presence of 5% NaOH) was unacceptable for the preparation for these particular anilides, since products were isolated in only trace amounts and were attended by large quantities of intractable material. Therefore, it was decided to conduct the reactions using a 2.25:1 molar ratio of amine to acid chloride, so that the excess amine rather than sodium hydroxide would catalyze the reaction. The transformations were thus accomplished smoothly and without complication.

Yields and melting points of the anilides are reported in Tables 1 and 2. With the exception of compounds Ih and IIa, yields were extremely good. Repeated attempts to improve the yields of the aforementioned anilides proved unrewarding and the reason for these exceptions remains unexplained. The melting characteristics of the isomeric anilides followed the general pattern of a higher melting 5,6-dichloro isomer, with the notable exception being the 4-trifluoromethylanilides (Ig and IIg).

The infrared spectra of the anilides (Tables 1 and 2) revealed the expected sharp single band absorption of the amide N-H stretch in the range 3250 to 3500 cm^{-1}. There does not appear to be a clear trend in the N-H stretch frequences of pairs of isomers; *i.e.* where there are large isomeric differences in v the lower stretch frequency seems to be equally divided among the 2,6- and 5,6-isomers. Therefore it is not possible to draw any conclusion regarding solid state hydrogen bonding tendencies of the two systems. Strong carbonyl absorptions were exhibited by all anilides in the expected range of an aromatic amide (1640-1700 cm^{-1}). There are no particular trends noted in isomeric comparisons of these absorption frequencies.

Elemental analyses clearly support the structures of all compounds, since observed C, H, and N percentages are within 0.4% of the calculated values. (Tables 1 and 2).

Table 1. Experimental, Infrared, and Elemental Analysis Data for the 4-substituted-2, 6-Dichloronicotinanilides (I).

Cpd.	%Yld.	MP°C	IR,v, cm^{-1}		Elemental Anal.	Calc'd %	(Found %)
			NH	C=O	C	H	N
Ia	94	147	3472	1647	53.93(53.74)	2.99(2.97)	10.49(10.36)
Ib	82	160	3287	1637	52.52(52.63)	3.37(3.29)	9.43(9.36)
Ic	93	181	3298	1658	55.52(55.56)	3.56(3.53)	9.96(9.76)
Id	77	154	3470	1648	50.53(50.91)	2.46(2.37)	9.82(9.84)
Ie	72	180	3284	1659	41.62(41.76)	2.02(2.03)	8.09(8.06)
If	87	173	3329	1667	54.37(54.38)	3.24(3.22)	9.06(9.13)
Ig	90	172	3252	1659	46.43(46.43)	2.38(2.03)	8.33(8.50)
Ih	48	187	3337	1692	46.15(46.12)	2.24(2.24)	13.46(13.27)

Table 2. Experimental, Infrared, and Elemental Analysis Data for the 4-substituted-5, 6-Dichloronicotinanilides (II).

Cpd.	%Yld.	MP°C	IR,v, cm^{-1}		Elemental Anal.	Calc'd %	(Found %)
			NH	C=O	C	H	N
IIa	30	162	3358	1657	53.93(53.87)	2.99(3.05)	10.49(10.16)
IIb	71	188	3339	1668	52.52(52.80)	3.37(3.41)	9.43(9.26)
IIc	73	179	3401	1648	55.52(55.38)	3.56(3.59)	9.96(9.77)
IId	74	163	3254	1646	50.53(50.65)	2.46(2.55)	9.82(9.83)
IIe	88	222	3344	1677	41.62(41.81)	2.02(2.06)	8.09(8.14)
IIf	87	254	3314	1677	54.37(54.46)	3.24(3.30)	9.06(9.04)
IIg	90	196	3333	1682	46.43(46.54)	2.38(2.29)	8.33(8.17)
IIh	85	223	3327	1685	46.15(46.12)	2.24(2.30)	13.46(13.47)

The ^1H nmr spectra of all compounds were very definitive (Tables 3 and 4). Proton integration yielded the expected relative area ratios in all cases. Dimethyl sulfoxide was the solvent of choice, not only for its excellent solvation properties, but also for the fact that amide proton chemical shifts in DMSO were clearly separable from the aromatic region. In $CDCl_3$ the amide protons were farther upfield and often buried in the aromatic proton signals. The downfield chemical shifts in DMSO (δ 10.5-11.3 ppm) are undoubtedly due to hydrogen bonding of the amide proton with solvent. The vicinal phenyl protons in position 2 and 3 exhibited the expected pair of AB doublets (J = 8 Hz) in the general range δ 6.9-8.3 ppm. The lower field signal was assigned to the H_2 protons except in the case of the 4-nitro derivatives Ih and IIh where H_3 was the more deshielded proton set. In the cases of the 4-fluoro-derivatives Id and IId, proton coupling with fluorine produced triplets for the protons in position 3. In the I series of anilides the vicinal protons in the 4 and 5 positions on the pyridine ring gave rise to AB doublets (J = 8 Hz). The lower field signal was assigned to H_4 due to its closer proximity to the amide function. In the II series of anilides the meta-oriented pyridine protons at H_2 and H_4 had the expected small coupling constant of 2 Hz. The H_2 proton was deshielded to nearly δ 9ppm in all cases because of its position between the ring nitrogen and the amide group. It is noteworthy that the chemical shift of H_4 is farther downfield in the II series when the chlorine is in position 5, than in the I series where the 5 position is unsubstituted. This is to be expected, and offers further evidence that the pyridine proton assignments are correct.

Table 3. ^1H NMR Chemical Shift Data (δ ppm) for the 4- Substituted-2, 6-Dichloronicotinanilides (I).

Cpd.	Amide Proton[a]	Pyridine Protons[b]		Benzene Protons[c]		Other
		H_4	H_5	H_2	H_3	
Ia	10.69	8.19	7.74	7.71	7.38	H_4, 7.14(t)
Ib	10.53	8.16	7.72	7.60	6.95	OCH_3, 3.75(s)
Ic	10.59	8.17	7.73	7.57	7.17	CH_3, 2.28(s)
Id	10.75	8.19	7.75	7.67(m)	7.22(t)	
Ie	10.83	8.20	7.75	7.66	7.56	
If	11.02	8.23	8.01	7.82	7.76	$COCH_3$, 2.55(s)
Ig	11.06	8.24	7.90	7.78	7.74	
Ih	11.30	8.26	7.77	7.76	8.31	

[a] singlets; [b] 1:1 doublets with J = 8 Hz; [c] 1:1 doublets with J = 8.5-9.0 Hz unless otherwise indicated. s = singlet, t = triplct, m = multiplet

Table 4. ^1H NMR Chemical Shift Data (δ ppm) for the 4- Substituted-5, 6-Dichloronicotinanilides (II).

Cpd.	Amide Proton[a]	Pyridine Protons[b]		Benzene Protons[c]		Other
		H_2	H_4	H_2	H_3	
IIa	10.55	8.91	8.63	7.79	7.42(t)	H_4, 7.15(t)
IIb	10.43	8.89	8.61	7.63	6.95	OCH_3, 3.75(s)
IIc	10.48	8.89	8.62	7.63	7.19	CH_3, 2.29(s)
IId	10.59	8.89	8.61	7.68(m)	7.23(t)	
IIe	10.65	8.89	8.61	7.73	7.58	
IIf	10.82	8.91	8.64	8.01	7.90	$COCH_3$, 2.56(s)
IIg	10.86	8.91	8.65	7.99	7.76	
IIh	11.04	8.91	8.65	8.01	8.29	

[a] singlets; [b] 1:1 doublets with J = 2 Hz; [c] 1:1 doublets with J = 8.5-9.0 Hz unless otherwise indicated. s = singlet, t = triplet, m = multiplet

ACKNOWLEDGMENTS

The author gratefully acknowledges the UALR Faculty Research Fund for partial support of this work and Mr. Alan D. Toland for his help in obtaining the ^{1}H nmr spectra.

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