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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.

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-d6 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 (0.0026 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 Il

and Ilh, 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 H2O. Evaporation of the chloroform afforded the crude anilide. In some cases a considerable amount of anilide product occluded with the aniline hydchloride 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.

Figure 1. Structures of the dichloronicotinanilides.
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 hydride 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 1b and 2a 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 (II and III).

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 frequency pairs of isomers; i.e. where there are large isomeric differences in 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>
<thead>
<tr>
<th>Cpd.</th>
<th>Yield</th>
<th>IR, ν.c, cm⁻¹</th>
<th>Elemental Anal.</th>
<th>Calc'd %</th>
<th>Found %</th>
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<tbody>
<tr>
<td>1a</td>
<td>30</td>
<td>3350 1637</td>
<td>53.92(53.91)</td>
<td>2.99(2.97)</td>
<td>10.49(10.30)</td>
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<tr>
<td>1b</td>
<td>73</td>
<td>3339 1668</td>
<td>52.52(52.63)</td>
<td>3.47(3.29)</td>
<td>9.46(9.36)</td>
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<tr>
<td>1c</td>
<td>77</td>
<td>3470 1648</td>
<td>50.50(50.50)</td>
<td>2.46(2.37)</td>
<td>9.28(9.46)</td>
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<tr>
<td>1d</td>
<td>72</td>
<td>3284 1659</td>
<td>61.21(61.16)</td>
<td>2.02(2.03)</td>
<td>6.26(6.26)</td>
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<tr>
<td>1e</td>
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<td>3329 1667</td>
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<td>2.24(2.32)</td>
<td>9.66(9.66)</td>
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<tr>
<td>1f</td>
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<td>3266 1656</td>
<td>44.43(44.43)</td>
<td>2.76(2.30)</td>
<td>8.33(8.50)</td>
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<tr>
<td>1g</td>
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<td>3237 1692</td>
<td>44.55(45.12)</td>
<td>2.24(2.24)</td>
<td>13.46(13.27)</td>
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</table>

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

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LITERATURE CITED

