Synthesis and Herbicidal Activity of N-Substituted 2,6-Bis(polyfluoromethyl)dihydropyridine-3,5-dicarboxylates

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The synthesis and SAR of herbicidal N-substituted 2,6-bis(polyfluoromethyl)-1,2-dihydropyridine-3,5-dicarboxylates are described. N-Substituted dihydropyridines were readily prepared by treatment of the corresponding dihydropyridyl anions with electrophiles. Herbicidal activity of the N-substituted dihydropyridines is correlated with the rate of hydrolytic cleavage of the N-substituent to afford **2** or **3**. Dihydropyridine **2** is shown to undergo oxidation in the soil to afford herbicidal **1**, thereby relating the activity of N-substituted dihydropyridines to the corresponding aromatic herbicides.

INTRODUCTION

In 1985, Lee first described the herbicidal activity of 2,6-bis(polyfluoromethyl)dihydropyridine-3,5-dicarboxylates (Lee, 1985). Four isomers of the dihydropyridines have been shown to exhibit herbicidal activity—1,4-, 3,4-, 1,2-, and 1,6-dihydropyridines. (In spite of formal nomenclature rules, but for the sake of consistency, the 2- and 6-positions of the pyridines and dihydropyridines are arbitrarily assigned to those pyridine ring carbons attached respectively to the difluoromethyl and trifluoromethyl groups.) More recently, 2,6-bis(polyfluoromethyl)pyridine-3,5-dicarboxylates have also been reported as herbicides (Lee, 1986). The effect of substituent modifications at all five carbon atoms of the pyridine ring upon the herbicidal activity of both the dihydro and aromatic 2,6-bis(polyfluoromethyl)pyridine-3,5-dicarboxylates has been extensively studied (Lee, 1985; Lee and Sing, 1988; Lee and Miller, 1987a,b, 1989; Lee, 1987, 1988, 1989; Chupp et al., 1990). However, the effects of incorporation and structural modifications of a nitrogen substituent on the herbicidal activity of 2,6-bis(polyfluoromethyl)dihydropyridine-3,5-dicarboxylates have not been reported.

On the basis of SAR studies comparing the herbicidal activity of 2,6-bis(polyfluoromethyl)dihydropyridine-3,5-dicarboxylates to that of the corresponding aromatic 2,6-bis(polyfluoromethyl)pyridine-3,5-dicarboxylates (Lee, 1985, 1986; Chupp et al., 1990) it is postulated that the activity of dihydropyridine-3,5-dicarboxylates is due to oxidation, either in the soil or in vivo, to the herbicidally active pyridine-3,5-dicarboxylates. On the basis of this postulate, we investigated the preparation and biological activity of N-substituted dihydropyridines in hopes of obtaining herbicides with more desirable physical properties (water solubility, volatility, soil residual, etc.) than the corresponding aromatic pyridines. Following application, cleavage of the N-substituent, either in the soil or in vivo, would release the N-H dihydropyridine and, following oxidation, the herbicidally active pyridine.

We now report the synthesis and comparative herbicidal activities of N-substituted 1,2- and 1,6-dihydropyridine analogues and relate this activity to the corresponding aromatic pyridine herbicides.

EXPERIMENTAL PROCEDURES

Melting points were taken in open capillary tubes and are uncorrected. ^{1}H NMR spectra were recorded on a Varian XL-400 (400 MHz) spectrometer and are reported on the δ scale relative to TMS. ^{19}F NMR spectra were recorded on an IBM AF-300 (300 MHz) spectrometer, and chemical shifts are reported on the δ scale relative to $CFCl_3$. Chromatographic separations were performed on a Waters Prep 500A HPLC or a Harrison Research Chromatotron radial TLC. Pyridine **1** (Lee, 1986) and dihydropyridines **2** and **3** (Lee, 1985) and **5** and **16** (Chupp, 1990) were prepared as previously described. All new compounds reported herein have been fully characterized by elemental analysis and ^{1}H and ^{19}F NMR spectroscopy. See paragraph at the end of the paper regarding supplementary material for physical constants, elemental analysis, and spectroscopic data for all compounds.

Dimethyl *N*-Alkyl-, Acetyl-, and Benzoyl-2,6-bis(fluoroalkyl)-4-isobutyl-1,2-dihydropyridine-3,5-dicarboxylates (4, 6–15, and 17–25). *General Procedure.* To a stirred suspension of 1.05 equiv of 50% NaH in dry THF under an atmosphere of dry N_2 and cooled to −5 °C was added a THF solution of 1 equiv of dihydropyridine (**2** or **3**) at a rate such that the reaction temperature did not exceed 10 °C. In the case of compounds **6–8**, **11**, and **19**, a mixture of **2** and **3** was used, thereby accounting for the lower yields. When the addition was complete, the reaction was allowed to warm to ambient temperature and was stirred at ambient temperature for 30 min. The resulting slurry was cooled to 0 °C, and 1.1 equiv of the appropriate acyl or alkyl halide dissolved in THF was added dropwise. When this latter addition was complete, the reaction was allowed to warm to ambient temperature and the disappearance of **2** or **3** was monitored by GLC. External heat was applied as necessary to drive the reaction to completion. When the reaction was complete, an equal volume of ether and water was added, and the layers were separated. The organic layer was washed with 5% HCl, dried, filtered, and concentrated to afford the crude product. The crude product was further purified by silica gel chromatography and/or recrystallization to afford the compounds **4**, **6–15**, and **17–25** (see supplementary material for physical constants, elemental analysis, and spectroscopic data for all compounds).

Dimethyl *N*-Acyl-2-(difluoromethyl)-4-isobutyl-6-(trifluoromethyl)-1,2-dihydropyridine-3,5-dicarboxylates (26, 29, and 31–51). *General Procedure A.* To a vigorously stirred CH_2Cl_2 solution of **4** (10 ml of CH_2Cl_2/g of **4**) was added an equal volume of 10% aqueous Na_2CO_3 followed by a large excess of the appropriate amine or thiol in the case of **29**. After stirring for 15 min, the reaction was diluted with an equal volume of water, and the layers were separated. The organic phase was washed with 5% HCl, dried, filtered, and concentrated to afford the crude product. The crude product was further purified by silica gel chromatography and/or recrystallization to afford compounds **26**, **29**, and **31–43** (see supplementary material for physical constants, elemental analysis, and spectroscopic data for all compounds). For the preparation of **32** and **34**, unpurified carbamyl chloride prepared from **3** following the same procedure for the preparation of **4** from **2** was employed as a starting material.

General Procedure B. To a stirred acetonitrile solution of **4** was added dropwise 2.2 equiv of the appropriate aniline. When

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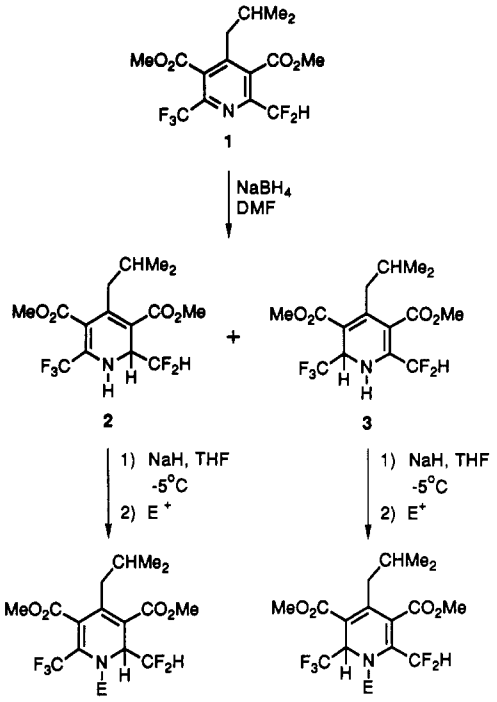
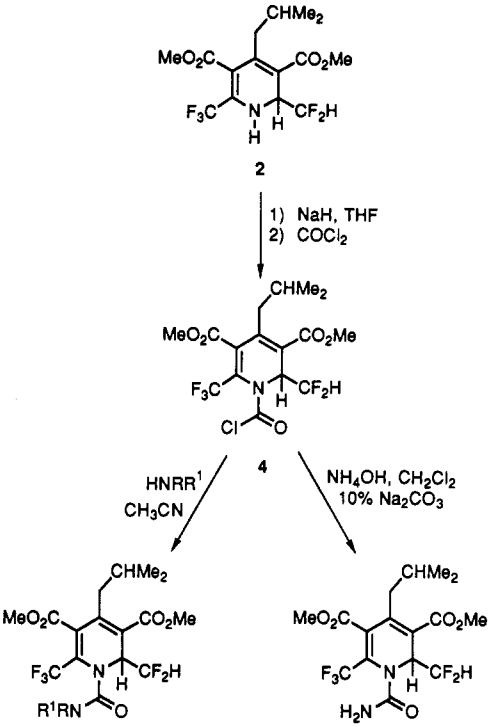
Scheme I



Scheme II



the addition was complete, the reaction was stirred at ambient temperature for 30 min. An equal volume of water and ether was added, and the layers were separated. The organic phase was washed with 5% HCl, dried, filtered, and concentrated to afford crude product. The crude product was further purified by silica gel chromatography and/or recrystallization to afford compounds **44–51** (see supplementary material for physical constants, elemental analysis, and spectroscopic data for all compounds).

Pre-emergence Herbicidal Activity. A topsoil mixture was placed in an aluminum pan and compacted to a depth of about 1.27 cm from the top of the pan. A predetermined number of Downy Brome, Proso Millet, Barnyard Grass, Large Crab Grass, and Green Foxtail seeds were placed on top of the soil. The soil required to level fill a pan after seeding was weighed into another pan. A known amount of the test compound was dissolved or suspended in a 50% acetone/water solution such that a 1% solution or suspension was obtained, and the resultant solution or suspension was applied to the cover soil as a spray at the desired rate. The amount of applied herbicide corresponded to application rates that ranged from 0.01 to 2.5 lb/acre in multiples of 2 (2.5, 1.25, 0.62 lb/acre, etc.). The cover soil was thoroughly mixed with the spray, and the herbicide/soil mixture was used as a cover layer for the previously prepared pan. Untreated soil was used as a cover layer for control pans. After treatment, the pans were moved to a greenhouse bench. Moisture was supplied to each pan as needed for germination and growth. Approximately 10–14 days (usually 11 days) after planting and treating, the pans were observed and the results were recorded. Herbicidal activity is expressed as a narrow leaf weed GR80 (pounds per acre) which is the amount of herbicide, averaged over all five weed species tested, required to inhibit 80% of weed growth relative to that of the untreated control.

RESULTS AND DISCUSSION

Synthesis. The synthesis of N-substituted dihydropyridine-3,5-dicarboxylates is depicted in Scheme I. Sodium borohydride reduction of dimethyl 2-(difluoromethyl)-4-isobutyl-6-(trifluoromethyl)pyridine-3,5-dicarboxylate (**1**) affords approximately at 50/50 mixture of 1,2- and 1,6-dihydropyridines **2** and **3** (Lee, 1985), which can be separated by silica gel chromatography. The 1,2-dihydropyridine isomer proved to be more easily purified than the 1,6 isomer; thus, most of the analogues prepared were N-substituted 1,2-dihydropyridines. Only a limited number of N-substituted 1,6-dihydropyridines were prepared for comparative purposes. Treatment of the purified 1,2- or 1,6-dihydropyridines with NaH followed by reaction of the resulting dihydropyridyl anion with electrophiles afforded the corresponding N-substituted dihydropyridines in good to excellent yield (Stout and Meyers, 1982). It is known that treatment of 2,6-bis(polyfluoromethyl)-dihydropyridine-3,5-dicarboxylates with amine bases results in the elimination of hydrogen fluoride followed by rearrangement to the corresponding aromatic pyridines (Lee et al., 1990). In contrast, the sodium salts of **2** and **3** were found to be surprisingly stable. Thus, relatively unreactive electrophiles such as cyclopropylmethyl bromide were successfully reacted with the requisite sodium salts of **2** and **3** in refluxing THF. Interconversion of the sodium salts of **2** and **3** did not occur under the reaction conditions. Attempted preparation of *N*-carbamyldihydropyridine-3,5-dicarboxylates via reaction of the sodium salts of **2** and **3** with isocyanates failed. However, reaction of the sodium salt of **2** with phosgene afforded carbamyl chloride **4**, which upon treatment with ammonia or amines gave the corresponding ureas (Scheme II).

Herbicidal Activity. Comparison of the herbicidal activity of analogous 1,2- and 1,6-dihydropyridine isomers fails to reveal a consistent trend (Tables I and II). Although in general the 1,2-dihydropyridine isomers were less active than the 1,6 isomers, several exceptions exist. Thus, in the case of compounds **6** and **7** and **33** and **34**, the 1,2-dihydropyridine isomers were more efficacious than the 1,6 isomers. However, compounds **10** and **11**, **23** and **24**, and **31** and **32** exhibited the reverse relationship.

N-Alkyldihydropyridine-3,5-dicarboxylates displayed moderate herbicidal activity (Table I, compounds **5–9**), although they were less active than the corresponding unsubstituted dihydropyridines or aromatic pyridines (Table I, compounds **1–3**). The *N*-alkyl substituents in compounds **5–9** would generally not be expected to be readily cleaved, either in the soil or in vivo. Thus, the herbicidal activity of **5–9** could be interpreted as resulting from the inherent activity of the N-substituted dihydropyridine-3,5-dicarboxylates. However, the activity of **5–9** is also

Table I. Percent Yield, Structure, and Herbicidal Activity of Alkyl-, Acetyl-, and Benzoyl-Substituted Dimethyl 2-(Difluoromethyl)-4-isobutyl-6-(trifluoromethyl)-1,2-dihydropyridine-3,5-dicarboxylates

compd	% yield	N substituent	narrow leaf weed GR80, lb/acre
1			0.03
2		H	0.04
3[a]		H	0.04
5[b]		CH_3	0.15
6	31	CH_2SCH_3	0.22
7[a]		CH_2SCH_3	0.61
8	8.3	$CH_2(C_3H_5)$	0.52
9	58	$CH_2(C_6H_5)$	0.97
10	68	$COCH_3$	1.12
11[a]	19	$COCH_3$	0.18
12	52	$COCH_2CH_3$	0.95
13	68	$COCH(CH_3)_2$	4.24
14	62	$COCH_2F$	0.04
15	55	$COCHF_2$	0.05
16		$COCH_2Cl$	0.06
17	50	$COCHCl_2$	0.06
18	53	$COCCl_3$	0.05
19	6	$COCH_2Br$	0.13
20	80	$COCH_2OCH_3$	0.17
21	35	$COCH_2OC_6H_5$	0.30
22	62	$COCHCHCH_3$	0.16
23	77	CO*p*-$(NO_2)C_6H_4$	0.65
24[a]	37	CO*p*-$(NO_2)C_6H_4$	0.06
25[a]	84	COC_6H_5	0.47

[a] 1,6-Dihydropyridine isomer. [b] 51/49 mixture of 1,2- and 1,6-dihydropyridine isomers.

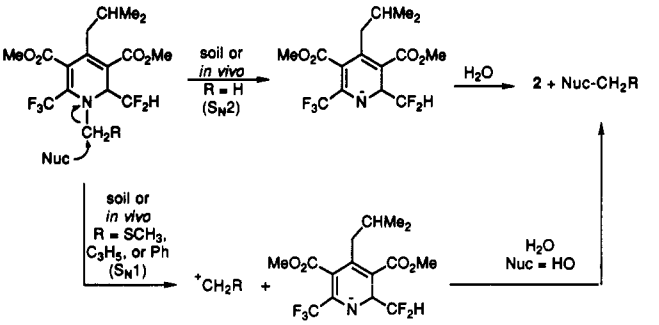
Table II. Percent Yield, Structure, and Herbicidal Activity of Dimethyl *N*-Acyl-2-(difluoromethyl)-4-isobutyl-6-(trifluoromethyl)-1,2-dihydropyridine-3,5-dicarboxylates

compd	% yield	N substituent	narrow leaf weed GR80, lb/acre
4	75	COCl	0.02
26	81	CO-1-pyrazole	0.02
28[a]	84	CO_2Et	1.28
29	80	$COSC_6H_5$	2.58
30	65	$CO_2C_6H_5$	inactive
31	89	$CONH_2$	0.26
32[a]	26	$CONH_2$	0.05
33	78	$CONHCH_2CH_3$	0.01
34[a]	75	$CONHCH_2CH_3$	0.13
35	72	$CONHCH_2CHCH_2$	0.05
36	62	$CONHCH(CH_3)CH_2CH_3$	0.05
37	83	$CONHOCH_3$	0.06
38	69	$CONHCH_2CH(OCH_3)_2$	0.06
39	66	$CONHCH_2C_6H_5$	0.06
40	51	$CONHCH_2CO_2CH_3$	0.07
41	71	$CONHCH_2CO_2H$	3.69
42	81	$CONHC(CH_3)_3$	1.69
43	56	$CON(CH_3)_2$	11.22
44	71	$CONHC_6H_5$	0.06
45	67	$CONH(4\text{-}OCH_3C_6H_4)$	0.03
46	61	$CONH(3\text{-}OCH_3C_6H_4)$	0.05
47	69	$CONH(3\text{-}CH_3C_6H_4)$	0.05
48	62	$CONH(3\text{-}CF_3C_6H_4)$	0.03
49	65	$CONH[3,5\text{-}(CF_3)_2C_6H_3]$	0.02
50	57	$CONH(2\text{-}FC_6H_4)$	0.06
51	61	$CON(C_2H_5)C_6H_5$	1.00

[a] 1,6-Dihydropyridine isomer.

consistent with partial cleavage of the N-substituent as shown in Scheme III to afford low levels of the N–H dihydropyridine. Thus, for example in the case of **5**, S_N2 displacement of the *N*-alkyldihydropyridine by nucleophiles (e.g., H_2O) would afford the dihydropyridinium anion as a leaving group, which, upon proton abstraction from water, would yield **2** or **3**. Alternatively, **6–9** could afford **2** or **3** via a S_N1 process involving the intermediacy of the stabilized methylthiomethyl, cyclopropylmethyl,

Scheme III



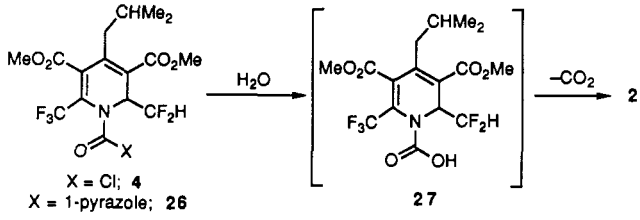
and benzyl carbenium ions. Both of these processes would be facilitated due to the electron-withdrawing carboxy and fluorinated alkyl groups on the dihydropyridine ring which would stabilize the resultant dihydropyridinium anion. Attempts to prepare *N*-isopropyl or *N*-*tert*-butyl analogues to prevent N-substituent cleavage failed.

N-Acetyl-substituted dihydropyridines exhibited a large range of herbicidal activity. Those compounds with electron donating or weakly electron withdrawing substituents on the acetyl carbon possessed only moderate herbicidal activity (**10–13**, **20** and **21**). For these compounds, a decrease in herbicidal activity is observed with an increase in steric bulk at the acetyl carbon. Thus, replacing an ethyl group in **12** with an isopropyl group in **13** results in a 4-fold decrease in herbicidal activity. Electronic factors also affect the herbicidal activity of the *N*-acetyldihydropyridines. Thus, replacing OMe in **20** with halogen results in an increase in herbicidal activity that is proportional to the electronegativity of the halogen (**20** < **19** < **16** < **14**). A similar trend is found with **12** and **22**, in which the increased electronegativity of an sp^2 hybridized carbon compared to that of an sp^3 hybridized carbon leads to increased activity. Incorporation of two or more halogens, however, did not further increase herbicidal activity (**15**, **17**, **18**). The halogenated *N*-acetyldihydropyridines **14–18** all exhibited essentially identical herbicidal activity, which was also equivalent to that of **1**, **2**, or **3**, despite rather substantial changes in both steric and electronic environments surrounding the acetyl carbon. This is consistent with **14–18** breaking down to a common, herbicidally active moiety.

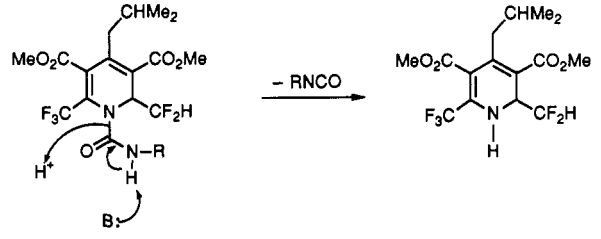
Amide hydrolysis normally requires rather harsh conditions (Ogliaruso and Wolfe, 1979). Therefore, facile cleavage of the *N*-acetyl substituent from the compounds in Table I might not be expected. However, the fluorinated alkyl and carboxyl groups on the dihydropyridine ring greatly stabilize the dihydropyridyl anion, thereby facilitating hydrolytic cleavage of the *N*-acetyl group. This is the most consistent explanation of the SAR displayed by the compounds shown in Table I. The herbicidal activity of these compounds is proportional to the predicted rate of hydrolysis of the *N*-acetyl group on the basis of a consideration of Taft's E_s and σ^* values (Shorter, 1970). Thus, the decrease in herbicidal activity as hydrogens are replaced with methyls parallels the predicted decreased rate of hydrolysis based on both steric and polar parameters. This same trend is found for the halogenated and oxygenated *N*-acetyl compounds, although it is less straightforward due to contradictory steric and electronic effects for these substituents. The activity of **24** compared to that of **25** is also proportional to the predicted rate of hydrolytic cleavage of the benzoyl groups.

Thus, we propose that the herbicidal activity of the compounds in Table I is a result of cleavage, either in the soil or in vivo, of the N-substituent to afford herbicidally active **2** or **3**. Those N-substituted dihydropyridines

Scheme IV



Scheme V



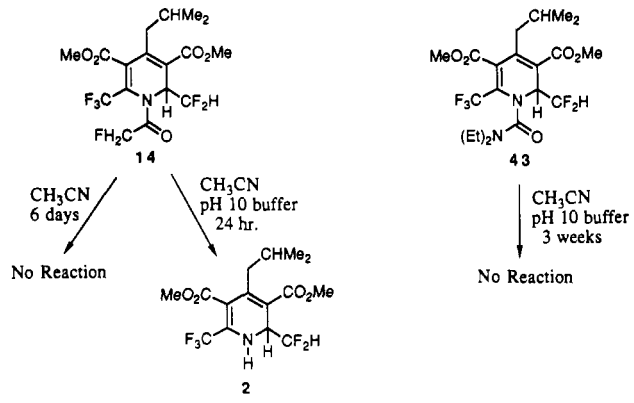
containing more labile substituents (e.g., **15**, **17**, **18**) are cleaved more rapidly and afford higher concentrations of **2** or **3**, therefore displaying greater herbicidal activity. In contrast, those compounds containing more robust N-substituents (e.g., **8**, **9**, **13**) undergo less N-substituent cleavage and afford lower concentrations of **2** or **3** and as a result show less herbicidal activity. When the rate of cleavage of N-substituted dihydropyridine-3,5-dicarboxylates is sufficiently rapid (e.g., **15**, **16**, **18**), the concentration of **2** or **3** will be equal to that of the applied N-substituted dihydropyridine, and thus the herbicidal activity cannot exceed that of **2** or **3**.

Hydrolytic cleavage of the N-substituent to afford herbicidal **2** also explains the activity of **4** and **26** (Table II). Upon exposure to dilute aqueous acid, **4** is readily hydrolyzed to **2**, presumably via the intermediacy of carbamic acid **27** which losses CO_2 to afford **2** (Scheme IV). Rapid hydrolysis of **26** to **2** is consistent with the known ability to azole amides to readily hydrolyze (Staab, 1962) and accounts for the fact that the herbicidal activity of **26** is comparable to that of **2**.

Ethyl carbamate **28** and phenyl thiocarbamate **29** exhibit moderate herbicidal activity. In contrast, phenylcarbamate **30** failed to exhibit any herbicidal activity. Although **29** and **30** would be predicted to be less susceptible to hydrolysis than **28** (Janssen, 1969), thereby accounting for their reduced herbicidal activity, the total lack of herbicidal activity for **30** cannot be readily explained. Moreover, thioesters are more slowly hydrolyzed than the corresponding oxyesters (Janssen, 1969); thus, the herbicidal activity of **29** and **30** is the reverse of that predicted on the basis of hydrolysis arguments. We currently do not have an explanation for these results.

The herbicidal activity of the *N*-carbamyl compounds in Table II might also, on cursory examination, be considered inconsistent with N-substituent cleavage to afford herbicidally active **2** or **3**. However, primary and secondary carbamic esters and ureas are known to undergo base-induced hydrolysis via an elimination–addition mechanism (Scheme V) rather than an addition–elimination mechanism that is common for esters and tertiary carbamic esters and ureas (Williams and Douglas, 1975). The SAR for the *N*-carbamyldihydropyridines in Table II is consistent with loss of the N-substituent by such a process. Thus, *N*,*N*-dimethylcarbamyldihydropyridine **43**, which lacks an abstractable hydrogen on nitrogen, is 500–1000-fold less active than the other analogues in Table II. In the case of alkyl substituents (compounds **33–40**) little change in activity was found with structural variations.

Scheme VI



The acetic acid analogue **41** was less active, as would be expected for a compound with two acidic protons. Since the carboxylic acid proton is more acidic than the N–H proton (Williams and Douglas, 1975), cleavage of the N-substituent will be reduced due to the proximity of a carboxylic anion to the base abstractable N–H. The reduced herbicidal activity of *tert*-butyl analogue **42** is also in keeping with known effects of steric hindrance upon the rate of elimination of carbamic esters and ureas (Williams and Douglas, 1975). The anilinocarbamyl N-substituted dihydropyridines **44–50** all exhibited essentially identical herbicidal activity despite rather substantial steric and electronic changes. This is again most consistent with **44–50** breaking down to a common, herbicidally active moiety. Thus, as was the case with alkyl and acetyl N-substituted dihydropyridine-3,5-dicarboxylates, the herbicidal activity of the ureas in Table II is most readily rationalized by cleavage of the N-substituent to give **2** or **3**.

Unambiguous evidence for the rapid decomposition of various N-substituted dihydropyridines to **2** was obtained by HPLC, HPLC/MS, and ^1H NMR studies. Thus, **14** was stable in acetonitrile for 6 days without decomposition as judged by HPLC/MS. However, addition of pH 10 buffer resulted in rapid (within 1 day) appearance of **2** (Scheme VI). In contrast, in the presence of pH 10 buffer *N*-dimethylcarbamyl dihydropyridine **43** was unchanged after 3 weeks as determined by HPLC/MS.

Initially confusing and apparently contradictory results were obtained when ureas such as **44** were analyzed by ^1H NMR in different solvents (Scheme VII). In $CDCl_3$ solution, **44** was unchanged after storage for a week at room temperature. In contrast, when CD_3CN was used as the solvent, **2** was detected within minutes by its characteristic six-line pattern (J = 4.1, 12.1, 12.1 Hz) centered at δ 4.87 (assigned to the proton at C-2). This signal is separated significantly from the corresponding signal for **44** at δ 5.58, thereby allowing quantitation of the extent of degradation by simple integration. Within 3 min after dissolution in CD_3CN, 38% conversion to **2** was measured by NMR integration. After 30 min, 65% decomposition to **2** had occurred, and after 17 h, 20% unchanged **44** remained (80% decomposition to **2**).

Careful examination of the spectrum of the degradation mixture after 17 h in the aromatic region allowed assignment of a complex 5-proton multiplet between δ 7.13 and 7.45 as that belonging to phenyl isocyanate. This was confirmed by comparison of the pattern to that of authentic phenyl isocyanate in CD_3CN. When D_2O (50 μL) was added to the 17-h mixture, followed by incubation at room temperature for an additional 5 days, further change occurred. After D_2O addition, the phenyl isocyanate

Scheme VII

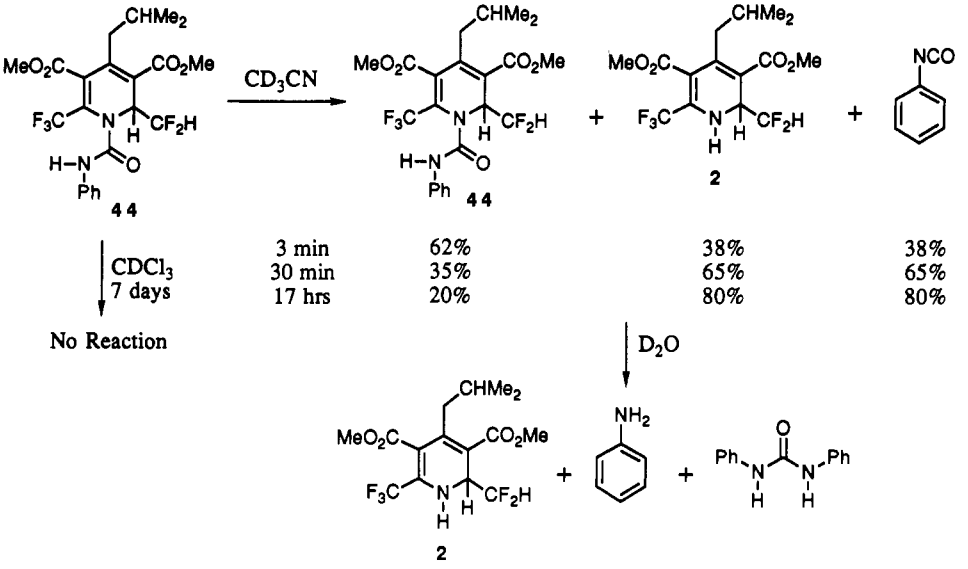


Table III. Stability of Urea Analogues in Solutions of Different pH As Determined by HPLC Analysis

pH	age of solution, h	% 31 remaining	% 33 remaining	% 44 remaining	% 48 remaining
3	2–3	98	100	100	95
3	22–24			100	26
4	3–5	98	100	97	91
4	22–24			74	4
5	5–6	98	100	52	15
5	22–24	88			
6	6–8	83	100	6	0
6	22–24		97		
7	7–9	14	91	0	0
8	10	0	44		
9	11	0	8		

Table IV. Products Recovered from Soil Treated with Dihydropyridines and Aged 7 Days in the Greenhouse

compd	narrow leaf weed GR80, lb/acre	compd concn in soil 7 DAT,[a] ppm	1 concn in soil 7 DAT, ppm	2 concn in soil 7 DAT, ppm
1	0.03	13	13	0
2	0.04	0	11	0
14	0.04	0	8	0
31	0.26	60	19	9.5
33	0.01	152	1.8	12
44	0.06	13	9	1.2
45	0.03	1.1	20	1.6
48	0.03	1.2	7.5	0
51	1.0	106	0	0

[a] DAT, days after treatment.

signals disappeared and were replaced by aromatic signals attributable to aniline (δ 6.63) and *N,N'*-diphenylurea (δ 7.42 and 7.31). The hydrolysis of phenyl isocyanate in CD_3CN was reproduced in a separate NMR experiment without the presence of the dihydropyridine components, and precisely the same NMR signals were observed. In addition to the changes in the aromatic region, the addition of D_2O caused the remaining 20% of **44** to degrade and yield a very clean set of signals for **2** in the aliphatic region of the spectrum. The identity of **2** was confirmed by comparison with the ^1H NMR spectrum of an authentic sample taken in CD_3CN.

The above results suggest that under acidic conditions breakdown of the arylureas such as **44** should be retarded. Indeed, **44** and **48** were found to be stable for several hours in pH 3–4 buffer when analyzed by HPLC but were unstable at pH 6 and above (Table III). After 22 h at pH 3, essentially all of **44** remained, but only 26% of **48** remained. These results are consistent with the increased acidity of the N–H proton due to the presence of the electron-withdrawing CF_3 group in **48**. The acidity of the N–H proton is decreased in unsubstituted or alkyl-substituted ureas, such as **31** and **33**, thus accounting for increased stability of **31** and **33** at pH 6 compared to that of **44** and **48**.

One final set of experiments was conducted to directly determine the fate of N-substituted dihydropyridines and N–H dihydropyridines in aged, treated soils. Each of eight compounds (Table IV) was mixed with soil to achieve concentrations of 92 μg of compound/g of soil. This soil was added as a cover layer, in duplicate, to unseeded 2.5-in. pots containing about 7 cm of untreated soil beneath. The cover layers were about 1 cm thick, so that this treatment corresponds to a nominal 11 lb/acre application rate. The pots were placed in the greenhouse for 7 days.

After 7 days in the greenhouse, the pots were sampled by careful removal of a 2.0-g soil sample from the central surface area of each pot. Since the soil was moist at sampling, this probably corresponded to less actual chemical than for the equivalent weight of dry soil at treatment time; no correction for this difference was made. The soil samples were extracted twice with 90:10 acetonitrile/pH 3.0 phosphate buffer or 90:10 acetonitrile/0.1 N HCl, and the combined supernatants were adjusted to 4.0 mL and analyzed by HPLC. These were compared to standard samples containing 10 μg/mL of the applied compounds.

Qualitatively, the duplicate samples from each treatment were very similar, and quantitatively, the integral values were within a factor of 2 of each other. The concentrations in the two duplicates were averaged and are presented in Table IV. Recoveries from control soil samples which were extracted 15 min after treatment showed that 87–96% of **2**, 79% of **44**, and 67% of **1** were recovered by this method. In the case of dihydropyridines such as **44**, which had been shown to be unstable in solution, the use of 0.1 N HCl in the extraction solvent allowed recovery of the urea from the soil without contamination by **2** formed during workup.

Although the experiment could be improved by more sampling over time and by more thorough accounting of all of the applied herbicide in each pot, the results are qualitatively conclusive. The major component detected

in the extracts of soils treated with dihydropyridines displaying high herbicidal activity was **1**. Pyridine **1** was clearly formed from **2**, from the *N*-acetyldihydropyridine **14**, and from arylureas such as **44**, **45**, and **48**. In these cases, very little to none of the applied compound was present 7 days after treatment. The amount of **1** recovered from these treatments was approximately the same as from the pots that had been treated directly with **1**, and this amount represented only about 20% of the applied concentration, the remainder presumably having been lost to volatilization. These results are consistent with the hypothesis that the N-substituted dihydropyridines, in the soil, undergo N-substituent cleavage to give **2** (or **3**) which undergoes oxidative conversion to **1**.

In contrast to the results of the arylureas, the ethylurea **33** and the unsubstituted area **31** were still present in the soil in large amounts at 7 days, accompanied by smaller amounts of **1** and **2**. The decomposition of these compounds is much slower than that of the aryl analogues. However, in the case of **31**, the concentration of **1** is comparable to that of the control, thereby accounting for its high herbicidal activity. Thus, these results support the idea that alkylureas represent "chemical-timed-released" forms of the herbicidally active pyridine **1**. The disubstituted urea, **51**, which possessed low herbicidal activity, was still present in large amounts in the 7-day-old soil, but in this case, no **1** or **2** was detected. This result is consistent with the idea that facile loss of the N substituent is required for formation of herbicidally significant levels of **1** or **2** in the soil.

Little can be said about the rates of decomposition of the N-substituted dihydropyridines or **2** itself from these data since sampling at early time points was not conducted. We can speculate that the degradation may have been quite rapid since the residual levels of **1** were essentially identical with each other and with the level resulting from direct application of **1**.

CONCLUSIONS

The results of these studies have established a credible explanation for the herbicidal activity of N-substituted dihydropyridine-3,5-dicarboxylates. It is demonstrated that N-unsubstituted 1,2-dihydropyridines undergo oxidation in soil to readily regenerate aromatic pyridines with known herbicidal activity. When the nitrogen atom is substituted with acyl or certain other substituents, these groups can be lost with unexpected ease, regenerating the unsubstituted dihydropyridine, which can in turn yield the pyridine. Apparently, the electron-withdrawing ability of the two adjacent fluoroalkyl groups makes the dihydropyridyl anion a very good leaving group, allowing these normally stable amide bonds to hydrolyze readily in polar organic solvents or with mild base. The stability of the N-substituted dihydropyridines parallels the trends in their herbidical activity. When soil, which had been treated with various N-substituted dihydropyridines, was aged for 7 days in the greenhouse and extracted, it was possible to completely explain the pattern of herbicidal activity on the basis of the compound's abilities to regenerate **1** in the soil.

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Supplementary Material Available: Physical constants, percent yield, elemental analysis, complete NMR spectral data, and the solvents used for chromatographic purifications and/or recrystallizations are available for all compounds reported herein (8 pages). Ordering information is given on any current masthead page.

LITERATURE CITED

Chupp, J. P. Derivation of Fluorine-Containing Pyridine Dicarboxylates IV. N-Substituted Dihydropyridine Derivatives. *J. Heterocycl. Chem.* **1990**, *27*, 1697.

Chupp, J. P.; Lee, L. F.; Goure, W. F.; Molyneaux, J. M. (to Monsanto Co.) U.S. Patent 4,908,057, March 13, 1990.

Janssen, M. J. Thiolo, Thiono and Dithio Acids and Esters. In *The Chemistry of Carboxylic Acids and Esters*; Patai, S., Ed.; Interscience Publishers: New York, 1969; Chapter 15.

Lee, L. F. (to Monsanto Co.). Eur. Pat. Appl. EP 135,491, March 27, 1985; *Chem. Abstr.* **1985**, *103*, 178173s.

Lee, L. F. (to Monsanto Co.). Eur. Par. Appl. EP 133,612, Feb 27, 1985; *Chem. Abstr.* **1986**, *104*, 19514h.

Lee, L. F. (to Monsanto Co.) U.S. Patent 4,692,184, Sept 8, 1987.

Lee, L. F. (to Monsanto Co.) U.S. Patent 4,741,766, May 3, 1988.

Lee, L. F. (to Monsanto Co.) U.S. Patent 4,826,530, May 2, 1989.

Lee, L. F.; Miller, M. L. (to Monsanto Co.) U.S. Patent 4,655,816, April 7, 1987a.

Lee, L. F.; Miller, M. L. (to Monsanto Co.) U.S. Patent 4,698,093, Oct 6, 1987b.

Lee, L. F.; Miller, M. L. (to Monsanto Co.) U.S. Patent 4,835,279, May 30, 1989.

Lee, L. F.; Sing, Y. L. (to Monsanto Co.) Eur. Pat. Appl. EP 278,944, Aug 17, 1988; *Chem. Abstr.* **1988**, *109*, 230818.

Lee, L. F.; Stikes, G. L.; Molyneaux, J. M.; Sing, Y. L.; Chupp, J. P.; Woodard, S. S. *J. Org. Chem.* **1990**, *55*, 2872.

Ogliaruso, M. A.; Wolfe, J. F. The Synthesis of Carboxylic Acids and Esters and their Derivatives. In *The Chemistry of Acid Derivatives*; Patai, S., Ed.; Wiley: New York, 1979; Chapter 7.

Shorter, J. The Separation of Polar, Steric, and Resonance Effects in Organic Reactions by the Use of Linear Free Energy Relationships. *Q. Rev., Chem. Soc.* **1970**, *24*, 433.

Staab, H. A. New Methods of Preparative Organic Chemistry IV. Syntheses Using Heterocyclic Amides (Azolides). *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 351.

Stout, D. M.; Meyers, A. I. Recent Advances in the Chemistry of Dihydropyridines. *Chem. Rev.* **1982**, *82*, 223, and references cited therein.

Williams, A.; Douglas, K. T. Elimination–Addition Mechanisms of Acyl Transfer Reactions. *Chem. Rev.* **1975**, *75*, 627.

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Registry No. **1**, 97887-77-9; **2**, 97898-32-3; **3**, 97898-33-4; **4**, 133040-92-3; **5** (1,2-dihydro), 132368-80-0; **5** (1,6-dihydro), 132368-81-1; **6**, 133040-93-4; **7**, 133040-94-5; **8**, 133040-95-6; **9**, 133040-96-7; **10**, 133040-97-8; **11**, 133040-98-9; **12**, 133040-99-0; **13**, 133041-00-6; **14**, 133041-01-7; **15**, 133041-02-8; **16**, 132368-82-2; **17**, 133041-03-9; **18**, 133041-04-0; **19**, 133041-05-1; **20**, 133041-06-2; **21**, 133041-07-3; **22**, 133041-08-4; **23**, 133041-09-5; **24**, 133041-10-8; **25**, 133041-11-9; **26**, 133041-12-0; **28**, 133041-13-1; **29**, 133041-14-2; **30**, 133041-15-3; **31**, 133041-16-4; **32**, 133041-17-5; **33**, 133041-18-6; **34**, 133041-19-7; **35**, 133041-20-0; **36**, 133041-21-1; **37**, 133041-22-2; **38**, 133041-23-3; **39**, 133041-24-4; **40**, 133041-25-5; **41**, 133041-26-6; **42**, 133041-27-7; **43**, 133041-28-8; **44**, 133041-29-9; **45**, 133041-30-2; **46**, 133041-31-3; **47**, 133041-32-4; **48**, 133041-33-5; **49**, 133041-34-6; **50**, 133041-35-7; **51**, 133041-36-8.