Note

Germination Inhibitory Activity of Grandinol Analogues

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Through studies on the structure/activity relationships of grandinol, a germination inhibitor in *Eucalyptus*,¹⁾ Bolte *et al.* showed that a combination of two carbonyl functionalities on a phloroglucinol nucleus was necessary for inhibition, and that the ketonic side chain must be less than four carbon units in length.²⁾ As their work mainly focused on the formyl/ketone and diketone types of compounds, we synthesized grandinol analogues in which the formyl group was replaced with an amide or thioamide group (I), and examined their activities on cress seed germination. We selected phloropropiophenone as the starting material because of its easy availability, and also because its ketonic side chain fitted the above-mentioned prerequisite for activity.

Compounds I were synthesized by direct (thio)amidation of the phlorophenone.³⁻⁶⁾ The *N*-methylbenzamide derivative (1) was prepared as follows; In a 100 ml flask, 1.77 g (13.3 mmol) of anhydrous aluminum chloride was mixed with a solution of 1.32 g (10 mmol) of phloropropiophenone in dry nitrobenzene (50 ml), and the mixture was stirred for 30 minutes at room temperature. To the clear yellowish solution was added 0.86 g (15 mmol) of methyl isocyanate, and the mixture was stirred for 24 hours at room temperature. The subsequent work-up and

purification by silica gel chromatography afforded pure **1** in a 58% yield, mp 221~222°C. IR_v_{max} (KBr) cm⁻¹: 3380, 1640, 1580, 1410. NMR δ_H (acetone-*d*₆): 1.13 (3H, t, *J*=7 Hz), 1.90 (3H, d), 3.11 (2H, q), 5.86 (1H, s). *Anal.* Found: C, 54.87; H, 5.64; N, 6.24. Calcd. for C₁₁H₁₃NO₅: C, 55.22; H, 5.47; N, 5.85%. In a similar manner, compounds **2~15** were prepared, satisfactory analytical data being obtained for all the compounds. Reactions of phloropropiophenone with other isocyanates and, in particular, with isothiocyanates required higher reaction temperatures (at 60~80°C for 2~3 hr). These reactions afforded compounds **1** as the main products. In some cases, however, migration of the acyl group in the starting material occurred during the reactions, resulting in the formation of diketones and diamides as by-products; for example, compound **16** was thus obtained.

The inhibitory activities of the compounds on cress seed germination were determined as reported previously,²⁾ and their activities listed in Table I as the GI₅₀ values refer to the concentration of the compound (10⁻⁵M) for which the germination rate was 50% that of untreated plots. Table I shows that not only the amide type but also the thioamide type with short *N*-alkyl chains had strong activity, the most active one being **12**, which was as active as grandinol. Both with the amide (**1~10**) and the thioamide types

TABLE I. GERMINATION INHIBITORY ACTIVITY OF GRANDINOL ANALOGUES

Compound	X	R	mp (°C)*	GI ₅₀ (× 10 ⁻⁵ M)
1	O	Methyl	221~222	40
2	O	Ethyl	210~211	41
3	O	Isopropyl	203	39
4	O	Butyl	185~186	>200
5	O	Hexyl	140~141	>200
6	O	Phenyl	dec. 210~212	138
7	O	3-Me-Phenyl	dec. 181~182	120
8	O	4-Me-Phenyl	dec. 229~230	>200
9	O	2-Cl-Phenyl	dec. 229~231	>200
10	O	4-Cl-Phenyl	dec. 219~221	>200
11	S	Methyl	192~194	25
12	S	Ethyl	170~172	7.7
13	S	Propyl	144~145	35
14	S	Butyl	132~133	>200
15	S	Hexyl	114~115	>200
16		Diamide	dec. 226~229	82
		(<i>N,N'</i> -diisopropyl)		
		Grandinol		9.8

* All melting points (mp) were not corrected.

(11~15), the inhibitory activity decreased dramatically when the number of carbon atoms in the *N*-alkyl chain exceeded three. In the case of the diketone type of analogues, similar effects from the length of the ketonic side chain on the activity were observed; the number of carbon atoms in the second ketonic side chain should be less than four for activity. These results indicate that the presumptive site of action requires strict steric limitation of the size of the substituent as proposed by Bolte *et al.*²⁾ The diamide type (16) showed only weak activity, indicating that at least one of the acyl groups in the structure should be a ketone or another group which has stronger electron-withdrawing power than the amide group. Since the thioamide analogues (11~13) were more active than the corresponding amide analogues (1~3), a greater difference in the electron-withdrawing potency between the two substituents in the structure may be preferable for optimum activity.

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