Synthesis of 2,7-Disubstituted-5,6-dimethylpyrrolo-[2,3-*d*]-1,3-oxazin-4-ones as Antifungal Agents

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A series of novel 5,6-dimethylpyrrolo[2,3-*d*]-1,3-oxazin-4-ones were synthesized from 2-amino-3-*tert*-butoxycarbonyl-4,5-dimethylpyrroles. Two methods were used, cyclodehydration of 2-acylamino-3-carboxypyrroles with acetic anhydride and direct conversion of the 5,6-dimethylpyrrolo[2,3-*d*]-1,3-oxazin-2,4-diones to the title compounds with an anhydride directly providing the 2 substituent. Molecular modeling techniques revealed that these pyrrolo[2,3-*d*]oxazinones were rigid analogues of the allylamine antifungals. The compounds were tested for *in vitro* activity against *Tricophyton* and *Scopulariopsis* sp.

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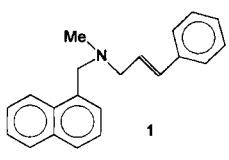
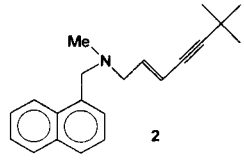
Introduction.

Recent years have witnessed a dramatic increase in opportunistic infections as a result of immunosuppressive conditions such as AIDS, cancer treatment and organ transplantation. By contrast, primary fungal infections such as the dermatophytoses have been and continue to be among the most prevalent infections in the world [1]. Although azoles and polyenes, *e.g.* fluconazole and amphotericin B, which have been classic weapons in the armamentarium, are being reformulated and modified with some success, new heterocyclic structures with fungicidal activity are not common [2]. Synthetic allylamine derivatives such as naftifine (**1**) and terbenafine (**2**) are fungicidal *in vitro* against a broad spectrum of dermatophytes and have good cutaneous bioavailability [3]. Although the exact mechanism of action of the allylamines has not yet been determined, they are thought to modify squalene-2,3-epoxidase, an enzyme important in the biosynthesis of fungal sterols.

Figure 1



1



2

Much recent work in our laboratory has revolved around the development of heterocyclic β-enamino esters as pharmaceutical intermediates [3-5] and as potential drugs, *e.g.* antimicrobial and antiinflammatory agents [6,7]. We realized that pyrrolo[2,3-*d*]oxazines might be developed which incorporated the allylamine backbone as rigid analogues. However, a method of synthesis was needed that would allow the 2 and 7 substituents to be easily varied in order to examine the effects of various groups. Molecular energy minimization and fitting of naftifine (**1**) and the most closely analogous pyrrolo[2,3-*d*]-1,3-oxazin-4-one (**5x**), confirmed our suspicion that this may be a reasonable approach.

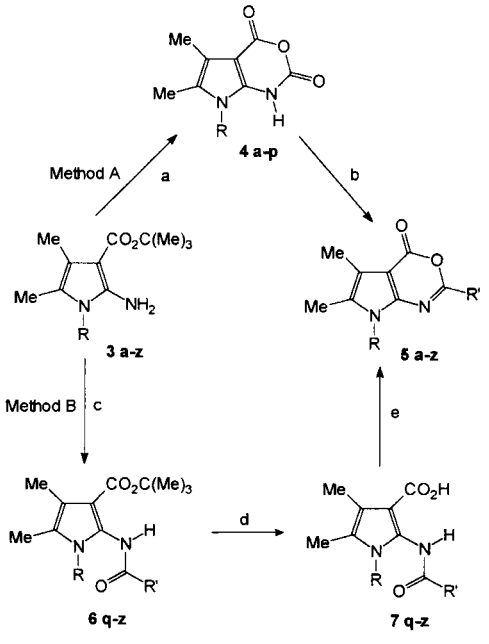
Benz-1,3-oxazin-6-ones are well represented in the literature. The most common preparative routes include acylation of 2,1-benzoxazoles with acid chlorides or anhydrides [8] and cyclodehydration of *N*-acylanthranilic acids with acetic anhydride, phosphorous oxychloride or thionyl chloride [9]. Cyclization of the ethyl esters of these *N*-acylanthranilic acids has also been accomplished with triphenyl phosphite or dibromtriphenylphosphorane [10]. These procedures are applicable to other heterocycles; furo[2,3-*d*]-1,3-oxazinones, pyrrolo[2,3-*d*]-1,3-oxazinones, isoxazolo-[5,4-*d*]-1,3-oxazinones and 1,3-oxazino[4,5-*c*]isoquinolinones have all been made in a similar fashion.

2-Amino-3-*t*-butoxycarbonyl-4,5-dimethylpyrroles **3a-z** are readily available from the condensation of a primary amine, acetoin and *t*-butyl cyanoacetate [3]. Ring closure and subsequent formation of the pyrrolo[2,3-*d*]-1,3-oxazin-2,4-dione (Scheme 1, Method A) using Triphosgene® and gentle heat gives superior yields to the standard method using phosgene/toluene [11,12], with less exposure to toxic phosgene.

Closure of the 1-substituted-2-acylamino-3-carboxy-4,5-dimethylpyrroles **7q-z** using acetic anhydride worked well (Scheme 1, Method B) but a less cumbersome higher yielding procedure was desired. We utilized a variation of Jacobs' procedure [13,14], *i.e.* treatment of the pyrrolo[2,3-*d*]-1,3-oxazin-2,4-diones **4a-p** with an anhydride that would directly afford the 2-substituent. This is a valuable procedure for anhydrides containing R′ groups are readily

available. We found that with Method A the average yield to product was indeed greater, 59% (range, 24-86%) compared to Method B, 51% (range, 31-67%).

Scheme 1



(a) Triphosgene®, MeCN; (b) $(R'CO)_2O$, Pyridine, 100 C; (c) R'COCl, Pyridine, MeCN, rt; (d) excess $MeSO_3H$; (e) excess Ac_2O, 100 C.

Table 1

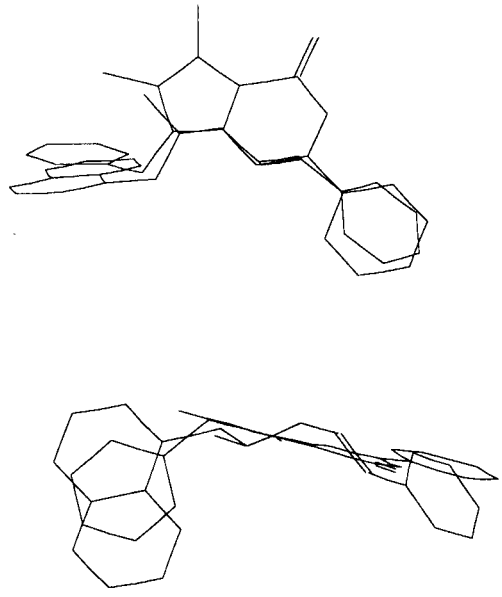
Physical Properties of Pyrrolo[2,3-*d*]oxazin-4-ones **5a-z**

Compound	R	R'	Mp(°C)	Yield	Method
5a	*n*-C_4H_9	*n*-C_3H_7	44-45	51	A
5b	*i*-C_4H_9	*n*-C_3H_7	31-32	62	A
5c	*c*-C_6H_{11}	*i*-C_3H_7	182-183	36	A
5d	*c*-C_6H_{11}	*n*-C_4H_9	76-77	51	A
5e	*c*-C_6H_{11}	*n*-C_3H_7	103-104	42	A
5f	*c*-C_6H_{11}	*n*-C_6H_{13}	48-49	24	A
5g	Bz	*n*-C_5H_{11}	63-64	76	A
5h	Bz	*i*-C_3H_7	99-100	81	A
5i	Bz	CH_3	132-133	86	A
5j	Bz	*n*-C_4H_9	56-57	46	A
5k	Bz	*n*-C_6H_{13}	51-53	49	A
5l	Bz	*n*-C_3H_7	82-83	84	A
5m	Bz	C_2H_4	105-106	76	A
5n	C_2H_4Ph	*n*-C_3H_7	38-39	61	A
5o	C_2H_4Ph-4-Cl	*n*-C_3H_7	93-94	55	A
5p	*c*-C_6H_{11}	*n*-C_5H_{11}	64-65	56	A
5q	*c*-C_6H_{11}	CF_3	195-196	46	B
5r	*c*-C_6H_{11}	Ph-3-Cl	175-176	67	B
5s	*c*-C_6H_{11}	Ph-4-OCH_3	231-232	44	B
5t	*c*-C_6H_{11}	Ph	195-196	56	B
5u	*c*-C_6H_{11}	Ph-4-Cl	207-208	55	B
5v	*c*-C_6H_{11}	Ph-2,4-Cl_2	155-156	43	B
5w	Bz	Ph-3-Cl	155-156	56	B
5x	Bz	Ph	188-189	63	B
5y	Bz	CF_3	104-105	31	B
5z	*c*-C_6H_{11}	CH_2Br	146-147	54	B

Molecular Modeling.

Conjugate gradient minimization was performed using the ALCHEMY® force field equations [15]. The molecules minimized were naftifine (**1**) and 2-phenyl-7-benzyl-5,6-dimethylpyrrolo[2,3-*d*]-1,3-oxazin-4-one (**5x**). These structures were then subjected to a four atom fit pairing N-CH_2-$CH=CH$(Ph) of **1** to N^7-C^{7a}-$N^1=C^2$(Ph) of the pyrrolo[2,3-*d*]oxazinone ring of **5x**. This fit resulted in a RMS value [16] of 0.489, which is moderate, reflecting that **1** is twisted out of the plane of the pyrrolo[2,3-*d*]oxazinone ring.

Figure 2



Least-squares fit of 1 and 5x viewed through and across the plane of the ring.

Biological Results.

Biological activity was determined against two members of the *Moniliaceae: Tricophyton* sp., anthropophilic dermatophytes responsible for tinea capitis, corporus and cruris, and *Scopulariopsis* sp., hyaline conidiophores responsible for pulmonary, intraocular and skin infections as well as external otomycoses. The most active compounds against *Tricophyton* sp. were **5c, d, r** and **v** and the most active against *Scopulariopsis* sp. were **5b, e** and **z**. Optimal substituents were 7-cyclohexyl and medium-sized alkyl groups in the 2 position. These agents had MIC_{50}'s ranging from 100-150 μg/ml.

EXPERIMENTAL

General Procedures.

The melting points were determined on an Electrothermal apparatus and are uncorrected. The tlc was performed on Merck silica gel plates, type 60-F_{254}. The flash chromatography was per-

formed with 32-64 μm silica gel from Selecto, Inc. The proton nmr spectra were obtained on a Varian EM-390 nmr spectrometer in deuteriochloroform and are reported in ppm from TMS. All solvents were purchased as ACS reagent grade from Baxter Diagnostics, Inc. and were used as obtained.

Preparation of 2-Amino-3-*t*-butoxycarbonyl-4,5-dimethylpyrroles **3a-z** [3].

The appropriate amine (RNH_2) (1 mole) was added to an 85% aqueous solution of 3-hydroxy-2-butanone (1 mole) in cyclohexane and refluxed under a Dean-Stark trap until the evolution of water had ceased. The solution was cooled, *t*-butyl cyanoacetate (1 mole) was added and the solution was refluxed until the evolution of water had again ceased. The cyclohexane was removed *in vacuo* and the crude product was recrystallized twice from methanol:water resulting in yields ranging from 36-87%. Because of the slow degradation of the 2-aminopyrroles to 2-iminopyrroles with subsequent polymerization over several weeks [17] (this may be retarded by dark storage at 0°), the 2-aminopyrroles were reacted to form the pyrrolo[2,3-*d*]-1,3-oxazine-2,4-diones **4a-p** (Method A) or the *N*-acylpyrroles **6q-z** (Method B). The latter compounds were stable for long periods.

Preparation of Pyrrolo[2,3-*d*]-1,3-oxazine-2,4-diones **4a-p** [11].

Method A.

The appropriate 2-amino-3-*t*-butoxycarbonyl-4,5-dimethylpyrrole, **3a-p**, (0.01 mole) was dissolved in 100 ml of acetonitrile. Triphosgene® (0.0043 mole) was added and within 5 minutes crude product precipitated as white crystals. The solution was stirred for an additional 30 minutes and filtered at 0°. The crude product was boiled in acetone, filtered at 0° and air-dried. It has been our experience that this method universally affords analytically pure sample.

Preparation of 2-Acylamino-3-*t*-butoxycarbonyl-4,5-dimethylpyrroles **6q-z.**

Method B.

The appropriate 2-amino-3-*t*-butoxycarbonyl-4,5-dimethylpyrrole, **3q-z**, (0.02 mole) was dissolved with pyridine (0.022 mole) in 50 ml of acetonitrile. The R'COCl (0.022 mole) was added dropwise to the solution over 5 minutes and the mixture was stirred at 25° for one hour. At this time 75 ml of water was added and the resulting solid collected by filtration. The crude material was recrystallized from methanol:water, filtered at 0°, air-dried and reacted in the next step without further purification.

Preparation of 2-Acylamino-3-carboxy-4,5-dimethylpyrroles **7a-z.**

Method B.

The appropriate 2-aminoacyl-3-*t*-butoxycarbonyl-4,5-dimethylpyrrole, **6q-z**, (0.02 mole) was added to 20 grams of methanesulfonic acid and stirred for 10 minutes. The solution was diluted with ice-water (200 ml) and the precipitate collected by filtration. The crude product was dissolved in 1*N* aqueous sodium hydroxide and filtered through a bed of Celite® . The filtrate was acidified to a *p*H of 2 with 1*N* aqueous hydrochloric acid and the precipitate again filtered and washed with water in order to remove traces of sodium chloride. This material was air-dried and used in the next step with no further purification.

Preparation of 2,7-Disubstituted-5,6-dimethylpyrrolo[2,3-*d*]-1,3-oxazin-4-ones **5a-p.**

Method A.

The appropriate 5,6-dimethylpyrrolo[2,3-*d*]-1,3-oxazine-2,4-dione, **4a-p**, (0.01 mole) was dissolved in pyridine (0.1 mole). The appropriate $(R'CO)_2O$ (0.05 mole) was added and this was heated in a boiling water bath for 1.5 hours. The reaction mixture was cooled, and a solution of 50 ml water containing 0.05 mole of sodium carbonate was slowly added. This mixture was stirred at 50° for 15 minutes, then diluted with 150 ml of ethyl acetate. This solution was washed successively with 100 ml of water, 100 ml of aqueous 1*N* sodium hydroxide, 100 ml of aqueous 1*N* hydrochloric acid, and saturated aqueous sodium chloride. The organic layer was dried with anhydrous sodium sulfate, filtered and the solvent was removed *in vacuo* to yield the crude product.

2-*n*-Propyl-7-*n*-butyl-5,6-dimethylpyrrolo[2,3-*d*]-1,3-oxazin-4-one (**5a**).

The crude product was eluted from a hexanes:ethyl acetate (9:1) mobile phase by flash chromatography and recrystallized from hexanes (50 ml) to yield white crystals, tlc R_f, hexanes:ethyl acetate (9:1), 0.66; ^{1}H-nmr: δ 0.8 (t, 3H, 7-$(CH_2)_3CH_3$), 0.9 (t, 3H, 2-$(CH_2)_2CH_3$), 1.2-1.9 (m, 6H, 7-$CH_2(CH_2)_2CH_3$ and $CH_2CH_2CH_3$), 2.19 (s, 3H, 5-CH_3), 2.23 (s, 3H, 6-CH_3), 2.6 (t, 2H, 2-$CH_2CH_2CH_3$), 3.9 (t, 2H, 7-$CH_2(CH_2)_2CH_3$).

Anal. Calcd. for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45; N, 10.68. Found: C, 68.56; H, 8.48; N, 10.65.

2-*n*-Propyl-7-isobutyl-5,6-dimethylpyrrolo[2,3-*d*]-1,3-oxazin-4-one (**5b**).

The crude product was eluted from a hexanes:ethyl acetate (9:1) mobile phase by flash chromatography to yield pale tan crystals, tlc R_f, hexanes:acetate (9:1), 0.63; ^{1}H-nmr: δ 0.85 (d, 6H, 7-$CH_2CH(CH_3)_2$), 0.95 (t, 3H, 2-$(CH_2)_2CH_3$), 1.65 (m, 2H, 2-$CH_2CH_2CH_3$), 1.95 (m, 1H, 7-$CH_2CH(CH_3)_2$), 2.15 (s, 3H, 5-CH_3), 2.2 (s, 3H, 6-CH_3), 2.6 (t, 2H, 2-$CH_2CH_2CH_3$), 3.65 (m, 2H, 7-$CH_2CH(CH_3)_2$).

Anal. Calcd. for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45; N, 10.68. Found: C, 68.56; H, 8.46; N, 10.62.

2-Isopropyl-7-cyclohexyl-5,6-dimethylpyrrolo[2,3-*d*]-1,3-oxazin-4-one (**5c**).

The crude product was eluted from a hexanes:ethyl acetate (7:1) mobile phase by flash chromatography and recrystallized twice from hexanes (100 ml) to yield pale tan crystals, tlc R_f, hexanes:ethyl acetate (9:1), 0.60; ^{1}H-nmr: δ 1.0-2.3 (m, 10H, 7-cyclohexyl CH_2), 1.3 (d, 6H, 2-$CH(CH_3)_2$), 2.15 (s, 3H, 5-CH_3), 2.25 (s, 3H, 6-CH_3), 2.8 (m, 1H, 2-$CH(CH_3)_2$), 4.05 (m, 1H, 7-cyclohexyl CH).

Anal. Calcd. for $C_{17}H_{24}N_2O_2$: C, 70.80; H, 8.39; N, 9.71. Found: C, 70.70; H, 8.42; N, 9.70.

2-*n*-Butyl-7-cyclohexyl-5,6-dimethylpyrrolo[2,3-*d*]-1,3-oxazin-4-one (**5d**).

The crude product was recrystallized sequentially from hexanes (100 ml) and methanol:water (4:1) to yield off-white crystals, tlc R_f, hexanes:ethyl acetate (9:1), 0.57; ^{1}H-nmr: δ 1.0-2.3 (m, 10H, 7-cyclohexyl CH_2), 0.9 (t, 3H, 2-$(CH_2)_3CH_3$), 1.5 (m, 4H, 2-$CH_2(CH_2)_2CH_3$), 2.15 (s, 3H, 5-CH_3), 2.2 (s, 3H, 6-CH_3), 2.6 (t, 2H, 2-$CH_2(CH_2)_2CH_3$), 4.0 (m, 1H, 7-cyclohexyl CH).

Anal. Calcd. for $C_{18}H_{26}N_2O_2$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.59; H, 8.70; N, 9.32.

2-*n*-Propyl-7-cyclohexyl-5,6-dimethylpyrrolo[2,3-*d*]-1,3-oxazin-4-one (**5e**).

The crude product was recrystallized sequentially from hexanes (100 ml) and methanol:water (4:1) to yield off-white crystals, tlc R_f, hexanes:ethyl acetate (9:1), 0.55; ^{1}H-nmr: δ 1.0-2.3 (m, 10H, 7-cyclohexyl CH_2), 1.0 (t, 3H, 2-(CH$_2$)$_2$CH_3), 1.5 (m, 2H, 2-CH$_2$CH_2-CH$_3$), 2.15 (s, 3H, 5-CH_3), 2.25 (s, 3H, 6-CH_3), 2.6 (t, 2H, 2-CH_2-CH$_2$CH$_3$), 4.05 (m, 1H, 7-cyclohexyl C*H*).

Anal. Calcd. for $C_{17}H_{24}N_2O_2$: C, 70.80; H, 8.39; N, 9.71. Found: C, 70.91; H, 8.40; N, 9.78.

2-*n*-Hexyl-7-cyclohexyl-5,6-dimethylpyrrolo[2,3-*d*]-1,3-oxazin-4-one (**5f**).

The crude product was eluted from a hexanes:ethyl acetate (9:1) mobile phase by flash chromatography and recrystallized sequentially from methanol:water (4:1) and hexanes (20 ml) to yield coarse white crystals, tlc R_f, hexanes:ethyl acetate (9:1), 0.60; ^{1}H-nmr: δ 1.0-2.3 (m, 10H, 7-cyclohexyl CH_3), 0.8 (t, 3H, 2-(CH$_2$)$_5$CH_3), 1.4 (m, 8H, 2-CH$_2$(CH_2)$_4$CH$_3$), 2.15 (s, 3H, 5-CH_3), 2.2 (s, 3H, 6-CH_3), 2.55 (t, 2H, 2-CH_2(CH$_2$)$_4$CH$_3$), 4.05 (m, 1H, 7-cyclohexyl C*H*).

Anal. Calcd. for $C_{20}H_{30}N_2O_2$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.61; H, 9.07; N, 8.40.

2-*n*-Pentyl-7-benzyl-5,6-dimethylpyrrolo[2,3-*d*]-1,3-oxazin-4-one (**5g**).

The crude product was eluted from a hexanes:ethyl acetate (9:1) mobile phase by flash chromatography and recrystallized sequentially from hexanes (60 ml) and methanol:water (4:1) to yield pale tan crystals, tlc R_f, hexanes:ethyl acetate (4:1), 0.79; ^{1}H-nmr: δ 0.85 (t, 3H, 2-(CH$_2$)$_4$CH_3), 1.3 (m, 6H, 2-CH$_2$(CH_2)$_3$CH$_3$), 2.1 (s, 3H, 5-CH_3), 2.3 (s, 3H, 6-CH_3), 2.6 (t, 2H, 2-CH_2(CH$_2$)$_3$CH$_3$), 5.2 (s, 2H, 7-CH_2-benzyl), 7.1 (m, 5H, Ar*H*).

Anal. Calcd. for $C_{20}H_{24}N_2O_2$: C, 74.04; H, 7.46; N, 8.64. Found: C, 74.16; H, 7.49; N, 8.67.

2-Isopropyl-7-benzyl-5,6-dimethylpyrrolo[2,3-*d*]-1,3-oxazin-4-one (**5h**).

The crude product was eluted from a hexanes:ethyl acetate (4:1) mobile phase by flash chromatography and recrystallized from hexanes (50 ml) to yield pale yellow crystals, tlc R_f, hexanes:ethyl acetate (4:1), 0.81; ^{1}H-nmr: δ 1.25 (d, 6H, 2-CH(CH_3)$_2$), 2.1 (s, 3H, 5-CH_3), 2.35 (s, 3H, 6-CH_3), 2.9 (m, 1H, 2-C*H*(CH$_3$)$_2$), 5.2 (s, 2H, 7-CH_2-benzyl), 7.15 (m, 5H, Ar*H*).

Anal. Calcd. for $C_{18}H_{20}N_2O_2$: C, 72.94; H, 6.80; N, 9.45. Found: C, 73.03; H, 6.85; N, 9.46.

2-Methyl-7-benzyl-5,6-dimethylpyrrolo[2,3-*d*]-1,3-oxazin-4-one (**5i**).

The crude product was recrystallized from hexanes (150 ml) to yield pale yellow crystals, tlc R_f, hexanes:ethyl acetate (4:1), 0.57; ^{1}H-nmr: δ 2.0 (s, 3H, 2-CH_3), 2.2 (s, 3H, 5-CH_3), 2.3 (s, 3H, 6-CH_3), 5.2 (s, 2H, 7-CH_2-benzyl), 7.1 (m, 5H, Ar*H*).

Anal. Calcd. for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.68; H, 6.04; N, 10.42.

2-*n*-Butyl-7-benzyl-5,6-dimethylpyrrolo[2,3-*d*]-1,3-oxazin-4-one (**5j**).

The crude product was eluted from a hexanes:ethyl acetate (8:1) mobile phase by flash chromatography and recrystallized sequentially from methanol:water (4:1) and hexanes (50 ml) to yield white crystals, tlc R_f, hexanes:ethyl (9:1), 0.77; ^{1}H-nmr: δ 0.85 (t, 3H, 2-(CH$_2$)$_3$CH_3), 1.5 (m, 4H, 2-CH$_2$(CH_2)$_2$CH$_3$), 2.05 (s, 3H, 5-CH_3), 2.25 (s, 3H, 6-CH_3), 2.6 (t, 2H, 2-CH_2(CH$_2$)$_3$CH$_3$), 5.2 (s, 2H, 7-CH_2-benzyl), 7.1 (m, 5H, Ar*H*).

Anal. Calcd. for $C_{19}H_{22}N_2O_2$: C, 73.52; H, 7.14; N, 9.03. Found: C, 73.43; H, 7.19; N, 9.07.

2-*n*-Hexyl-7-benzyl-5,6-dimethylpyrrolo[2,3-*d*]-1,3-oxazin-4-one (**5k**).

The crude product was eluted from a hexanes:ethyl acetate (9:1) mobile phase by flash chromatography and recrystallized sequentially from hexanes (50 ml) and methanol:water (4:1) to yield white crystals, tlc R_f, hexanes:ethyl acetate (4:1), 0.87; ^{1}H-nmr: δ 0.85 (t, 3H, 2-(CH$_2$)$_5$CH_3), 1.4 (m, 8H, 2-CH$_2$(CH_2)$_4$CH$_3$), 2.1 (s, 3H, 5-CH_3), 2.3 (s, 3H, 6-CH_3), 2.65 (t, 2H, 2-CH_2(CH$_2$)$_4$CH$_3$), 5.2 (s, 2H, 7-CH_2-benzyl), 7.1 (m, 5H, Ar*H*).

Anal. Calcd. for $C_{21}H_{26}N_2O_2$: C, 74.52; H, 7.74; N, 8.28. Found: C, 74.62; H, 7.78; N, 8.23.

2-*n*-Propyl-7-benzyl-5,6-dimethylpyrrolo[2,3-*d*]-1,3-oxazin-4-one (**5l**).

The crude product was recrystallized sequentially from hexanes (50 ml) and methanol:water (4:1) to yield pale yellow crystals, tlc R_f, hexanes:ethyl acetate (4:1), 0.76; ^{1}H-nmr: δ 0.9 (t, 3H, 2-(CH$_2$)$_2$CH_3), 1.7 (m, 2H, 2-CH$_2$CH_2CH$_3$), 2.1 (s, 3H, 5-CH_3), 2.3 (s, 3H, 6-CH_3), 2.6 (t, 2H, 2-CH_2CH$_2$CH$_3$), 5.2 (s, 2H, 7-CH_2-benzyl), 7.1 (m, 5H, Ar*H*).

Anal. Calcd. for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 72.98; H, 6.81; N, 9.42.

2-Ethyl-7-benzyl-5,6-dimethylpyrrolo[2,3-*d*]-1,3-oxazin-4-one (**5m**).

The crude product was eluted from a hexanes:ethyl acetate (4:1) mobile phase by flash chromatography and recrystallized from hexanes (120 ml) to yield off-white crystals, tlc R_f, hexanes:ethyl acetate (4:1), 0.75; ^{1}H-nmr: δ 1.2 (t, 3H, 2-CH$_2$CH_3), 2.1 (s, 3H, 5-CH_3), 2.35 (s, 3H, 6-CH_3), 2.7 (t, 2H, 2-CH_2CH$_3$), 5.2 (s, 2H, 7-CH_2-benzyl), 7.1 (m, 5H, Ar*H*).

Anal. Calcd. for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.26; H, 6.48; N, 9.97.

2-*n*-Propyl-7-(2-phenylethyl)-5,6-dimethylpyrrolo[2,3-*d*]-1,3-oxazin-4-one (**5n**).

The crude product was eluted from a hexanes:ethyl acetate (9:1) mobile phase by flash chromatography and recrystallized from hexanes (50 ml) to yield off-white crystals, tlc R_f, hexanes:ethyl acetate (9:1), 0.57; ^{1}H-nmr: δ 1.0 (t, 3H, 2-(CH$_2$)$_2$CH_3), 1.7 (m, 2H, 2-CH$_2$CH_2CH$_3$), 2.0 (s, 3H, 5-CH_3), 2.3 (s, 3H, 6-CH_3), 2.6 (t, 2H, 2-CH_2CH$_2$CH$_3$), 3.0 (t, 2H, 7-CH$_2$CH_2-phenyl), 4.2 (t, 2H, 7-CH_2CH$_2$-phenyl), 7.1 (m, 5H, Ar*H*).

Anal. Calcd. for $C_{19}H_{22}N_2O_2$: C, 73.52; H, 7.14; N, 9.03. Found: C, 73.57; H, 7.16; N, 9.00.

2-*n*-Propyl-7-(2-(4-chlorophenyl)ethyl)-5,6-dimethylpyrrolo[2,3-*d*]-1,3-oxazin-4-one (**5o**).

The crude product was eluted from a hexanes:ethyl acetate (4:1) mobile phase by flash chromatography and recrystallized from hexanes (100 ml) to yield white spicules, tlc R_f, hexanes:ethyl acetate (4:1), 0.59; ^{1}H-nmr: δ 1.0 (t, 3H, 2-(CH$_2$)$_2$CH_3), 1.75 (m, 2H, 2-CH$_2$CH_2CH$_3$), 2.05 (s, 3H, 5-CH_3), 2.4

(s, 3H, 6-CH_3), 2.55 (t, 2H, 2-CH_2CH$_2$CH$_3$), 2.9 (t, 2H, 7-CH$_2$CH_2-phenyl), 4.2 (t, 2H, 7-CH_2CH$_2$-phenyl), 7.0 (m, 5H, Ar*H*).

Anal. Calcd. for $C_{19}H_{21}ClN_2O_2$: C, 66.18; H, 6.14; N, 8.12; Cl, 10.28. Found: C, 66.24; H, 6.15; N, 8.19; Cl, 10.34.

2-*n*-Pentyl-7-cyclohexyl-5,6-dimethylpyrrolo[2,3-*d*]-1,3-oxazin-4-one (**5p**).

The crude product was sequentially recrystallized from methanol:water (4:1) and hexanes (50 ml) to yield white crystals, tlc R_f, hexanes:ethyl acetate (9:1), 0.56; ^{1}H-nmr: δ 1.0-2.3 (m, 10H, 7-cyclohexyl CH_2), 0.9 (t, 3H, 2-CH$_2$)$_4$CH_3), 1.8 (m, 6H, 2-CH$_2$(CH_2)$_3$-CH$_3$), 2.2 (s, 3H, 5-CH_3), 2.25 (s, 3H, 6-CH_3), 2.7 (t, 2H, 2-CH_2(CH$_2$)$_3$CH$_3$), 4.1 (m, 1H, 7-cyclohexyl C*H*).

Anal. Calcd. for $C_{19}H_{28}N_2O_2$: C, 72.12; H, 8.92; N, 8.86. Found: C, 72.21; H, 8.92; N, 8.81.

Preparation of 2,7-Disubstituted-5,6-dimethylpyrrolo[2,3-*d*]-1,3-oxazin-4-ones **5q-z**.

Method B.

The appropriate 2-acylamino-3-carboxy-4,5-dimethylpyrrole **7q-z** (0.01 mole) was dissolved in 15 ml of acetic anhydride and refluxed for 10 minutes. The solution was cooled and diluted with 75 ml of of water and 100 ml of ethyl acetate. This solution was washed successively with 1*N* aqueous sodium hydroxide (200 ml), 1*N* aqueous hydrochloric acid (200 ml) and saturated aqueous sodium chloride (200 ml). The organic layer was dryed with anhydrous sodium sulfate, filtered and the solvent removed *in vacuo* to leave an oil.

2-Trifluoromethyl-7-cyclohexyl-5,6-dimethylpyrrolo[2,3-*d*]-1,3-oxazin-4-one (**5q**).

This crude product was eluted from a hexanes:ethyl acetate (1:1) mobile phase by flash chromatography and recrystallized from hexanes (200 ml) to yield white crystals, tlc R_f, hexanes:ethyl acetate (4:1), 0.80; ^{1}H-nmr: δ 1.0-2.3 (m, 10H, 7-cyclohexyl CH_2), 2.2 (s, 6H, 5 and 6-CH_3), 4.05 (m, 1H, 7-cyclohexyl C*H*).

Anal. Calcd. for $C_{15}H_{17}F_3N_2O_2$: C, 57.32; H, 5.45; N, 8.91. Found: C, 57.16; H, 5.42; N, 8.99.

2-(3-Chlorophenyl)-7-cyclohexyl-5,6-dimethylpyrrolo[2,3-*d*]-1,3-oxazin-4-one (**5r**).

The crude product was eluted from a hexanes:ethyl acetate (1:1) mobile phase by flash chromatography and recrystallized from methanol (400 ml) to yield off-white crystals, tlc R_f, hexanes:ethyl acetate (4:1), 0.77; ^{1}H-nmr: δ 1.0-2.3 (m, 10H, 7-cyclohexyl CH_2), 2.15 (s, 3H, 5-CH_3), 2.2 (s, 3H, 6-CH_3), 4.05 (m, 1H, 7-cyclohexyl C*H*), 7.1-8.2 (m, 4H, Ar*H*).

Anal. Calcd. for $C_{20}H_{21}ClN_2O_2$: C, 67.32; H, 5.93; N, 7.85; Cl, 9.94. Found: C, 67.42; H, 5.99; N, 7.82; Cl, 9.91.

2-(4-Methoxyphenyl)-7-cyclohexyl-5,6-dimethylpyrrolo[2,3-*d*]-1,3-oxazin-4-one (**5s**).

The crude product was recrystallized from hexanes:ethyl acetate (1:1) (300 ml) to yield pale yellow crystals, tlc R_f, hexanes:ethyl acetate (9:1), 0.53; ^{1}H-nmr: δ 1.1-2.4 (m, 10H, 7-cyclohexyl CH_2), 2.25 (s, 3H, 5-CH_3), 2.3 (s, 3H, 6-CH_3), 3.8 (s, 3H, OCH_3), 4.1 (m, 1H, 7-cyclohexyl C*H*), 7.4-8.3 (m, 4H, Ar*H*).

Anal. Calcd. for $C_{21}H_{24}N_2O_3$: C, 71.57; H, 6.86; N, 7.95. Found: C, 71.47; H, 6.87; N, 7.89.

2-Phenyl-7-cyclohexyl-5,6-dimethylpyrrolo[2,3-*d*]-1,3-oxazin-4-one (**5t**).

The crude product was recrystallized from methanol (225 ml) to yield pale yellow crystals, tlc R_f, hexanes:ethyl acetate (9:1), 0.53; ^{1}H-nmr: δ 1.0-2.3 (m, 10H, 7-cyclohexyl CH_2), 2.15 (s, 3H, 5-CH_3), 2.2 (s, 3H, 6-CH_3), 4.05 (m, 1H, 7-cyclohexyl C*H*), 7.1-8.2 (m, 5H, Ar*H*).

Anal. Calcd. for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.37; H, 6.91; N, 8.50.

2-(4-Chlorophenyl)-7-cyclohexyl-5,6-dimethylpyrrolo[2,3-*d*]-1,3-oxazin-4-one (**5u**).

The crude product was sequentially recrystallized from methanol (50 ml) and ethyl acetate (75 ml) to yield pale yellow crystals, tlc R_f, hexanes:ethyl acetate (9:1), 0.53; ^{1}H-nmr: δ 1.2-2.4 (m, 10H, 7-cyclohexyl CH_2), 2.15 (s, 3H, 5-CH_3), 2.2 (s, 3H, 6-CH_3), 4.1 (m, 1H, 7-cyclohexyl C*H*), 7.4-8.3 (m, 4H, Ar*H*).

Anal. Calcd for $C_{20}H_{21}ClN_2O_2$: C, 67.32; H, 5.93; N, 7.85; Cl, 9.94. Found: C, 67.61; H, 5.95; N, 7.86; Cl, 9.84.

2-(2,4-Dichlorophenyl)-7-cyclohexyl-5,6-dimethylpyrrolo[2,3-*d*]-1,3-oxazin-4-one (**5v**).

The crude product was eluted recrystallized from methanol (100 ml) to yield pale yellow crystals, tlc R_f, hexanes:ethyl acetate (9:1), 0.54; ^{1}H-nmr: δ 1.0-2.3 (m, 10H, 7-cyclohexyl CH_2), 2.1 (s, 3H, 5-CH_3), 2.3 (s, 3H, 6-CH_3), 4.05 (m, 1H, 7-cyclohexyl C*H*), 7.3-8.0 (m, 3H, Ar*H*).

Anal. Calcd. for $C_{20}H_{20}Cl_2N_2O_2$: C, 61.39; H, 5.15; N, 7.16; Cl, 18.12. Found: C, 61.24; H, 5.18; N, 7.18; Cl, 18.21.

2-(3-Chlorophenyl)-7-benzyl-5,6-dimethylpyrrolo[2,3-*d*]-1,3-oxazin-4-one (**5w**).

The crude product was recrystallized from methanol (650 ml) to yield yellow spicules, tlc R_f, hexanes:ethyl acetate (4:1), 0.72; ^{1}H-nmr: δ 2.1 (s, 3H, 5-CH_3), 2.3 (s, 3H, 6-CH_3), 5.3 (s, 2H, 7-CH_2-benzyl), 7.0 (m, 5H, Ar*H*), 7.2-8.2 (m, 4H, Ar*H*).

Anal. Calcd. for $C_{21}H_{17}ClN_2O_2$: C, 69.13; H, 4.70; N, 7.68; Cl, 9.72. Found: C, 69.05; H, 4.70; N, 7.63; Cl, 9.65.

2-Phenyl-7-benzyl-5,6-dimethylpyrrolo[2,3-*d*]-1,3-oxazin-4-one (**5x**).

The crude product was recrystallized from methanol (300 ml) to yield pale tan crystals, tlc R_f, hexanes:ethyl acetate (4:1), 0.71; ^{1}H-nmr: δ 2.1 (s, 3H, 5-CH_3), 2.3 (s, 3H, 6-CH_3), 5.3 (s, 2H, 7-CH_2-benzyl), 7.0 (m, 5H, Ar*H*), 7.1-8.2 (m, 5H, Ar*H*).

Anal. Calcd. for $C_{21}H_{18}N_2O_2$: C, 76.34; H, 5.49; N, 8.48. Found: C, 76.07; H, 5.54; N, 8.41.

2-Trifluoromethyl-7-benzyl-5,6-dimethylpyrrolo[2,3-*d*]-1,3-oxazin-4-one (**5y**).

The crude product was recrystallized twice from methanol (75 ml) to yield off-white crystals, tlc R_f, hexanes:ethyl acetate (9:1), 0.68; ^{1}H-nmr: δ 2.3 (s, 3H, 5-CH_3), 2.4 (s, 3H, 6-CH_3), 5.3 (s, 2H, 7-CH_2-benzyl), 7.1 (m, 5H, Ar*H*).

Anal. Calcd. for $C_{16}H_{13}F_3N_2O_2$: C, 59.63; H, 4.06; N, 8.69. Found: C, 59.71; H, 4.09; N, 8.63.

2-Bromomethyl-7-cyclohexyl-5,6-dimethylpyrrolo[2,3-*d*]-1,3-oxazin-4-one (**5z**).

The crude product was eluted from a hexanes:ethyl acetate (1:1) mobile phase by flash chromatography, recrystallized from hexanes:ethyl acetate (2:1) to yield tan crystals, tlc R_f, hexanes:ethyl acetate (4:1), 0.83; ^{1}H-nmr: δ 1.0-2.3 (m, 10H, 7-cyclohexyl CH_2), 2.2 (s, 6H, 5 and 6-CH_3), 4.1 (m, 1H, 7-cyclohexyl CH), 4.2 (s, 2H, 2-CH_2Br).

Anal. Calcd. for $C_{15}H_{19}BrN_2O_2$: C, 53.11; H, 5.65; N, 8.26; Br, 23.56. Found: C, 53.28; H, 5.63; N, 8.35; Br, 23.39.

REFERENCES AND NOTES

[1] T. G. Mitchell, Dermatophytosis and Other Cutaneous Mycoses, in Zinsser, Microbiology, W. K. Joklik, H. P. Willett and D. B. Amos, eds, Appleton-Century Crofts, New York, 1980, pp 1396-1407.

[2] J. F. Barrett and D. F. Klaubert, Recent Advances in Antifungal Agents, in Annual Reports in Medicinal Chemistry, Vol **27**, J. A. Bristol, ed, Academic Press, Inc.; New York, 1992, pp 149-158.

[3] J. A. Laks, J. R. Ross, S. M. Bayomi and J. W. Sowell, *Synthesis*, 291 (1985).

[4] M. R. Player, L.-C. Wang, S. M. Bayomi and J. W. Sowell, *J. Heterocyclic Chem.*, **29**, 51 (1992).

[5] M. R. Player and J. W. Sowell, *J. Heterocyclic Chem.*, **30**, 125 (1993).

[6] J. R. Ross and J. W. Sowell, *J. Heterocyclic Chem.*, **24**, 757 (1987).

[7] S. M. Bayomi, K. E. Price and J. W. Sowell, *J. Heterocyclic Chem.*, **22**, 729 (1985).

[8] K.-H. Wünsch and A. J. Boulton, *Adv. Heterocyclic Chem.*, **8**, 322 (1967).

[9] D. R. Desai, V. S. Patel and S. R. Patel, *J. Indian Chem. Soc.*, **43**, 351 (1966).

[10] Y. Ming, N. Harlemann and H. Wamhoff, *Chem. Ber.*, **120**, 1427 (1987).

[11] J. R. Ross, J. A. Laks, L. C. Wang and J. W. Sowell, *Synthesis*, 796 (1985).

[12] G. M. Coppola, G. Hardtmann and O. R. Pfister, *J. Heterocyclic Chem.*, **19**, 717 (1982).

[13] R. L. Jacobs and R. L. Hively, German Offen. 2556590 (1976); *Chem. Abstr.*, **85**, 160115z (1976).

[14] G. M. Coppola, *Synthesis*, 505 (1980).

[15] J. G. Vinter, A. Davis and M. R. Saunders, *J. Comput.-Aided Mol. Des.*, **1**, 31 (1987).

[16] RMS $= ((\sum_{i=1}^{n} d_i^2)/n)^{1/2}$, where d_i is the distance between paired atoms and n is the number of pairs of atoms.

[17] R. A. Jones and G. P. Bean, The Chemistry of Pyrroles, Academic Press, New York, 1977, p 397.