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Supplementary Material Available: Table giving final fractional coordinates and average temperature factors for the non-hydrogen atoms of **29** (2 pages). Ordering information is given on any current masthead page.

Pyrido[3,4-*e*]-1,2,4-triazines and Related Heterocycles as Potential Antifungal Agents[1]

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The preparation and biological activities of a series of pyrido[3,4-*e*]-1,2,4-triazines, 1,2,4-triazino[5,6-*c*]quinolines, and related fused triazines are described. Methyl, amino, and acylamino substituents were placed in the pyridyl ring of the former system. Other structural modifications included various alkyl, cycloalkyl, substituted phenyl, and heterocyclic groups in the 3-position of these ring systems. In agar dilution assays, actives in this series inhibited strains of *Candida*, *Aspergillus*, *Mucor*, and *Trychophyton* species at MIC's of ≤16 μg/mL.

The incidence of diseases caused by fungi pathogenic to man has increased significantly over the past 30 years.[2] Superficial infections caused by dermatophytes and *Candida* species may be extremely uncomfortable or disfiguring but are rarely life threatening. Systemic infections are more severe and can often be fatal, due to the involvement of internal organs and the bloodstream. The deep mycoses (blastomycosis, coccidioidomycosis, histoplasmosis) can affect normal individuals, while opportunistic infections (aspergillosis, candidiasis, cryptococcosis) require predisposing factors in the host.[3] These contributing factors include drug treatment (antibiotics, steroids, immunosuppressives, antineoplastics), invasive surgery and associated procedures (parenteral nutrition, indwelling catheters), and various diseases (cancer, AIDS, diabetes). As these have become more prevalent in recent years, so has the incidence of opportunistic mycoses.[4]

In contrast to antibacterial chemotherapy, there are few agents effective against the more serious types of fungal diseases.[5] Although it has severe side effects, amphotericin B is the agent of choice, and sometimes the only effective one, for both deep and opportunistic infections. The imidazoles, miconazole and ketoconazole, are used for both superficial and systemic mycoses, but they also have their limitations as to efficacy and toxicity. There is thus a need for new drugs effective against a variety of fungi, but having low toxicity. The search for such agents has been difficult due to both host and pathogen being eucaryotic organisms with similar metabolism and the lack of detailed biochemical information about the infecting organism.

This paper describes the preparation and biological evaluation of a series of pyrido-1,2,4-triazines and related compounds. Previous efforts in this area have been reported from our laboratory,[6] as well as others.[7-9] In these cases, detailed antifungal data were generally lacking. We have expanded upon the earlier chemical work and also present more extensive in vitro testing results. This has enabled us to draw conclusions about the structure–activity relationships in this class of compounds.

Results and Discussion

Chemical Results. In general, the preparation of 3-substituted pyrido[3,4-*e*]-1,2,4-triazines (**10**) followed previously reported methods[6,7] (Figure 1). These compounds are listed in Table I. Intermediates **7f**, **7g**, **7j**, **7l**, and **7o** could be isolated in pure form by filtration of the reaction mixture, washing with THF and Et_2O, and drying the insoluble product. In all other cases, final products in acceptable yield and purity were obtained without purification of intermediates. Crude **10** was filtered through Magnesol and then recrystallized from an appropriate solvent to obtain analytically pure material.

4-Hydroxypyridine (**1**) was nitrated in a refluxing mixture of red fuming HNO_3 (d = 1.6, Baker) and fuming H_2SO_4 (18–24% SO_3) to give **2**.[10] This was then chlorinated to give **3**.[11] The substituted hydrazide **7** could be

(1) A portion of this work has been previously presented. Reich, M. F.; Fabio, P. F.; Lee, V. J.; Kuck, N. A.; Testa, R. T. *Ann. N.Y. Acad. Sci.* **1988**, *544*, 101.
(2) Shadomy, S.; Shadomy, H. J; Wagner, G. E. In *Antifungal Compounds*; Siegel, M. R., Sisler, H. D., Eds.; Marcel Dekker: New York, 1977; Vol. I, Chapter 13.
(3) (a) Hart, P. D.; Russell, E.; Remington, J. S. *J. Infect. Dis.* **1969**, *120*, 169. (b) Edwards, J. E.; Lehrer, R. I.; Stiehm, E. R.; Fischer, T. J.; Young, L. S. *Ann. Intern. Med.* **1978**, *89*, 91.
(4) Seeliger, H. P. R. In *Opportunistic Fungal Infections*; Chick, E. W., Balows, A., Furcolow, M. L., Eds.; Charles C. Thomas: Springfield, IL, 1975; pp 5–21.
(5) *The Merck Manual of Diagnosis and Therapy*, 14th ed.; Berkow, R., Ed.; Merck, Sharp and Dohme: Rahway, 1982; pp 148–159.
(6) (a) Lewis, A.; Shepherd, R. G. *J. Heterocycl. Chem.* **1971**, *8*, 47. (b) Lewis, A.; Shepherd, R. G. Ibid., 41.
(7) Pyrido[3,4-*e*]-1,2,4-triazines: (a) Reference 6a. (b) Wright, G. C.; Bayless, A. V.; Gray, J. E. U.S. Patents 3,882,111 and 3,883,526, 1975. (c) Benko, P.; Messmer, A.; Gelleri, A.; Pallos, L. *Acta Chim. Acad. Sci. Hung.* **1976**, *90*, 285. (d) Plē, N.; Queguiner, G.; Pastour, P. *C. R. Seances Acad. Sci., Ser. C.* **1976**, *283*, 487. (e) Armard, J.; Chekir, K.; Plē, N.; Queguiner, G.; Simonnin, M. P. *J. Org. Chem.* **1981**, *46*, 4754.
(8) Pyrido[3,2-*e*]-1,2,4-triazines: (a) Reference 6b. (b) Gelleri, A.; Messmer, A.; Benko, P.; Pallos, L. *Acta Chim. Acad. Sci. Hung.* **1976**, *90*, 301.
(9) 1,2,4-Triazino[5,6-*c*]quinolines: (a) Wright, G. C.; Gray, J. E.; Yu, C.-N. *J. Med. Chem.* **1974**, *17*, 244. (b) Berenyi, E.; Benko, P.; Pallos, L. *Acta Chim. Acad. Sci. Hung.* **1976**, *90*, 399. (c) Albert, L.; Ispas, F.; Antal, I. *Farmacia (Bucharest)* **1984**, *32*, 43.
(10) Kruger, S.; Mann, F. G. *J. Chem. Soc.* **1955**, 2755.
(11) Bishop, R. R.; Cavell, E. A. S.; Chapman, N. B. Ibid. **1952**, 437.

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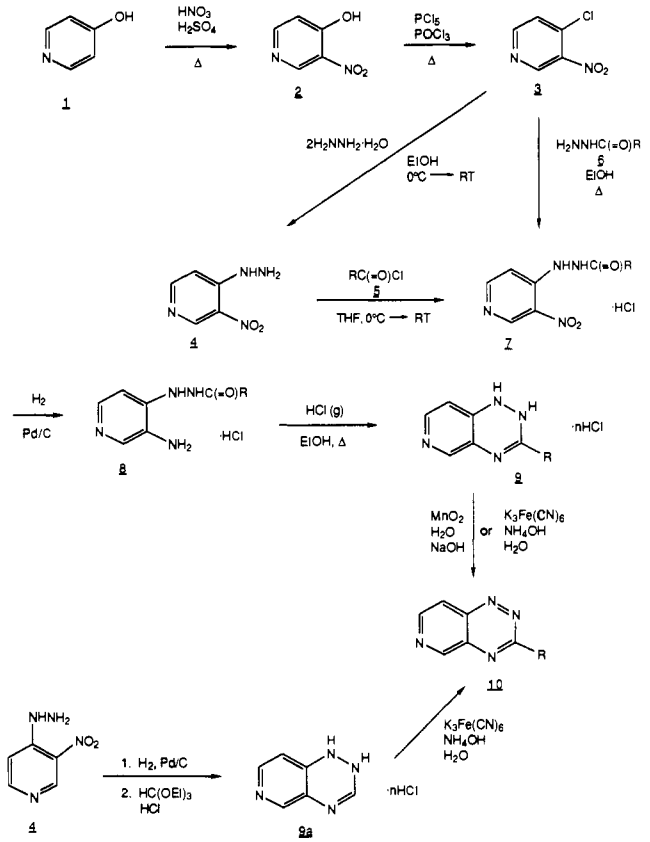


Figure 1.

prepared in either of two ways. Method A involved formation of 4-hydrazino-3-nitropyridine (**4**) and subsequent reaction with an acid chloride (**5**). Method B utilized direct reaction of **3** with an acylhydrazine (**6**). The choice of route A or B depended upon the commercial availability of **5** and **6**. The nitro group in **7** was rapidly reduced to the amine **8** over a palladium catalyst. Ring closure was then effected with ethanolic HCl to give the dihydrotriazine **9**. Oxidation was done with either activated MnO_2 or $K_3Fe(CN)_6$. The former generally gave higher yields. In either case, it was necessary to neutralize the mixture prior to addition of oxidant because the final product (**10**) was unstable to strong acid. We also noticed that compounds with a methyl or methylene group adjacent to the ring gave poor yields on oxidation. The dihydro compounds **9** where R was 1-naphthylmethyl, carbethoxy, pentafluorophenyl, and cyanomethyl decomposed on oxidation with MnO_2.

Preparation of the parent pyridotriazine ring system (**10**, R = H) first required reduction of **4** to 3-amino-4-hydrazinopyridine. This material is unstable on standing in air but may be dried in vacuo for a few hours and then used immediately. Ring closure was done with $HC(OEt)_3$ to give **9a**, which was stable. However, crude **10** (R = H) decomposed on standing unless it was purified as soon as possible.

Three enamine derivatives were prepared by treatment of the methyl compound (**10b**) with *tert*-butoxybis(dimethylamino)methane and subsequent reaction with amines (Figure 2 and Table I). The products could not be hydrolyzed due to instability of the ring system to strong acid.

The 5-methyl-3-substituted series (structure **19**, Figure 3) was prepared from 4-nitro-2-picoline *N*-oxide (**15**). This commercially available compound was modified so that it was in a form which could be used in the previous synthesis. Catalytic hydrogenation of **15** (PtO_2, HOAc) followed by diazotization and hydrolysis[12] ($NaNO_2$, aqueous

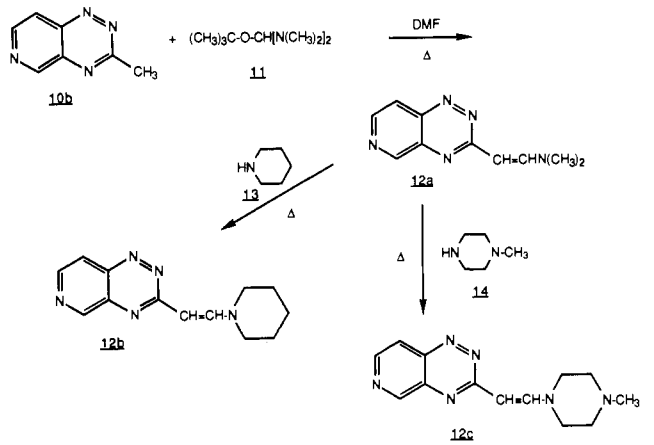


Figure 2.

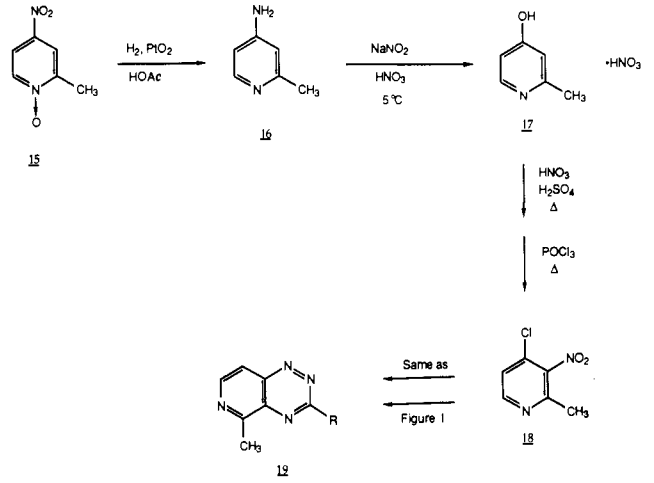


Figure 3.

HNO_3) yielded the nitrate salt of 4-hydroxy-2-methylpyridine (**17**). The subsequent steps were the same as shown in Figure 1 (see Experimental Section for details). Intermediates in this sequence were usually used without purification. The analogues prepared are described in Table II.

2,6-Dimethyl-4-pyrone (**20**) was reacted with NH_4OH in a sealed tube to produce the corresponding pyridone (**21**).[13] This then served as the starting material for a series of 5,7-dimethyl-3-substituted-pyridotriazines (structure **25**, Figure 4). The next step can produce either mono- or dinitration (**22** or **23**) depending on reaction conditions. Compound **23** ultimately led to a final product containing an amino function in the 8-position. The remaining steps were the same as shown in Figure 1 (see Experimental Section). The amino group was also acylated to see if changing its basicity had an effect on biological activity. The derivatives prepared are shown in Table II.

Three examples of the previously unreported 3,4-dihydropyrido[3,4-*e*]-1,2,4-triazine ring system were synthesized as shown in Figure 5. Compound **4** was hydrogenated and the resulting amino hydrazine was immediately condensed with a ketone in the presence of HCl to give **29**. This was then dehydrogenated with activated MnO_2, yielding **30**. The intermediates in this sequence were not purified. When R_1 = methyl and R_2 = phenyl, 4-pyridyl, or cyclopropyl, the oxidation step resulted in

(12) Nantka-Namirski, P.; Kaczmarczyk, C.; Toba, L. *Acta Pol. Pharm.* **1967**, *24*, 231; *Chem. Abstr.* **1968**, *69*, 2827.

(13) Bellingham, P.; Johnson, C. D.; Katritzky, A. R. *J. Chem. Soc. B* **1968**, 866.

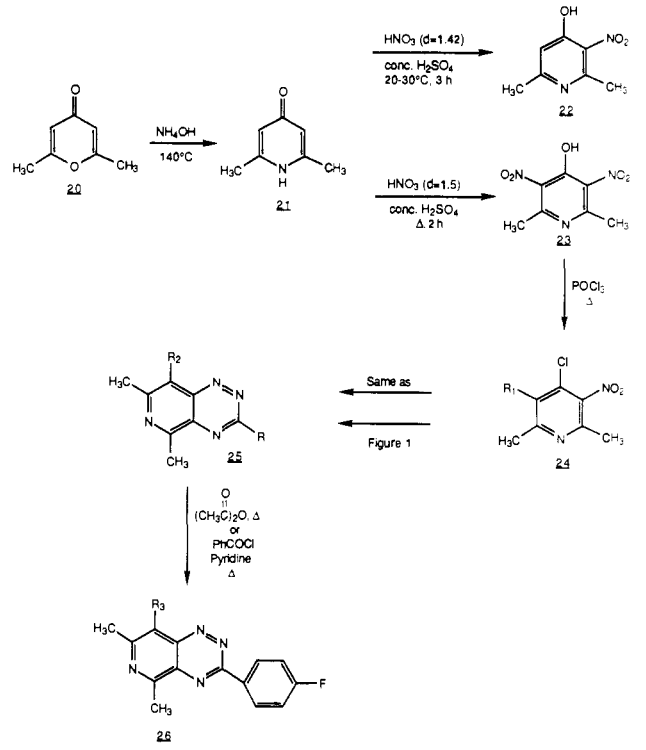


Figure 4.

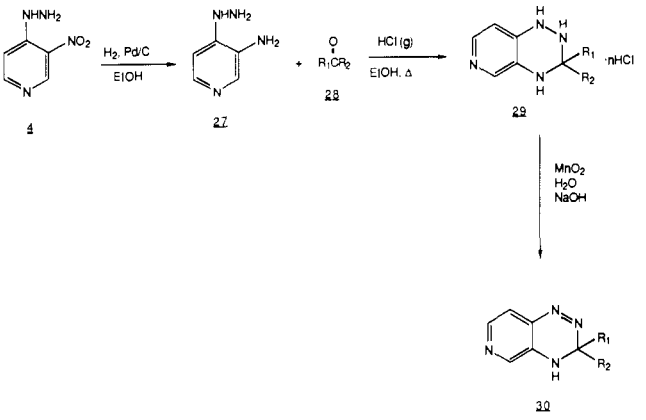


Figure 5.

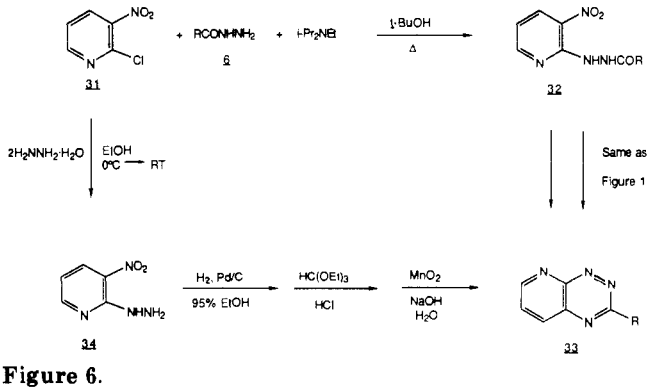


Figure 6.

extensive decomposition. The derivatives prepared are shown in Table III.

The synthesis of several 3-substituted-pyrido[3,2-*e*]-1,2,4-triazines (**33**) followed known methods[8] (Figure 6). The intermediates were similar to those shown for the isomeric [3,4-*e*] series and were carried through without extensive purification. The final products are shown in Table IV. The dihydro derivative decomposed on oxidation when R was 4-pyridyl. A recent report described

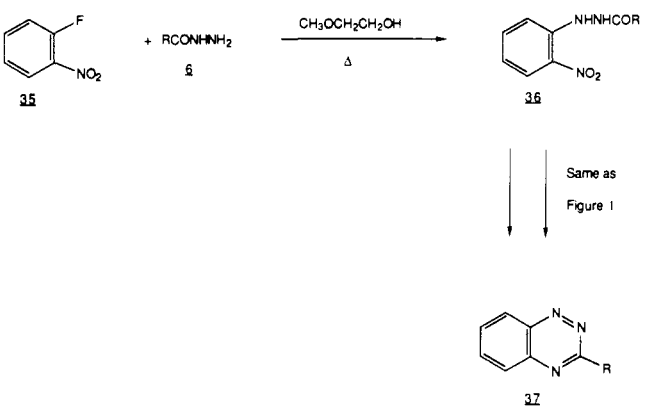


Figure 7.

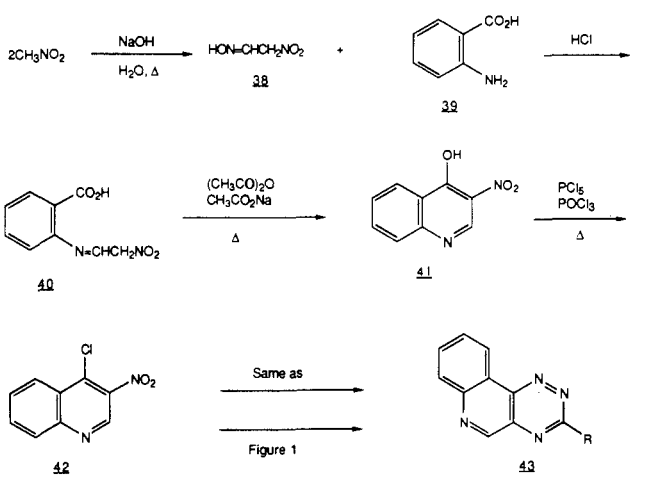


Figure 8.

the antifungal activity of 1,2-dihydro-3-methylpyrido-[3,2-*e*]-1,2,4-triazine dihydrochloride.[14] We repeated the experimental procedure given in this publication and obtained the corresponding monohydrochloride monohydrate (**33b'**) as shown by elemental analysis.

Two examples of 3-substituted-benzo-1,2,4-triazines (**37**) were prepared to see if the fused pyridine ring was necessary for biological activity (Table V). The synthetic sequence started from 2-nitrofluorobenzene (Figure 7). It was similar to that used in the pyridotriazine series, but overall yields were lower.

The preparation of some 1,2,4-triazino[5,6-*c*]quinolines followed previously described procedures[9a,15] with the modifications given in the Experimental Section (Figure 8 and Table VI). Briefly, self-condensation of nitromethane gave adduct **38**, which was added directly to a solution of anthranilic acid in aqueous HCl. Overnight reaction yielded 2-(β-nitroethylidene)aminobenzoic acid (**40**). Ring closure to 4-hydroxy-3-nitroquinoline (**41**) was effected with Ac_2O (reflux for 1 h) followed by NaOAc (100 °C, then 25 °C overnight). Chlorination (PCl_5, $POCl_3$, reflux) then gave **42**. This intermediate was converted into compounds of type **43** as described above for 4-chloro-3-nitropyridine (**3**).

Two analogues based on the previously unreported 3,4-dihydro-1,2,4-triazino[5,6-*c*]quinoline ring system were prepared as shown in Figure 9 and Table VII. 4-Chloro-3-nitroquinoline (**42**) was reacted with hydrazine and then reduced to give the unstable **44**. This material

(14) Wieczorek, J.; Mordarski, M.; Rykowsi, A.; Nantka-Namirski, P. *Arch. Immunol. Ther. Exp.* **1985**, *33*, 339.
(15) Backman, G. B.; Welton, D. E.; Jenkins, G. L.; Christian, J. E. *J. Am. Chem. Soc.* **1947**, *69*, 365.

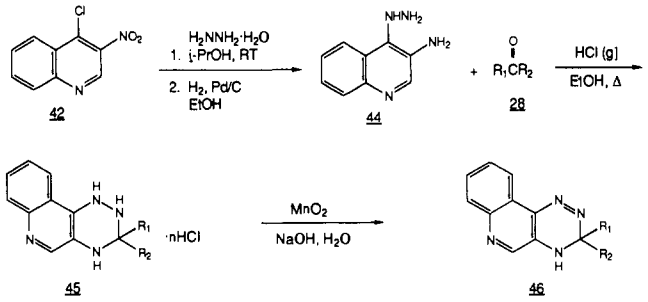


Figure 9.

was immediately dissolved in EtOH and treated successively with ketone **28** and ethanolic HCl. The resulting tetrahydro derivative **45** was oxidized with activated MnO_2 to **46**. The intermediates in this sequence were not purified. When R_1 = methyl and R_2 = 3-thienyl, or R_1 = ethyl and R_2 = benzyl, extensive decomposition occurred in the oxidation step.

Biological Results (Table IX). **1. Pyrido[3,4-*e*]-1,2,4-triazines (10).** Derivatives in which R = hydrogen (**10a**), methyl (**10b**), 4-fluorophenyl (**10o**), or 3- and 4-pyridyl (**10aa**, **10bb**) had the best overall antifungal activity. Extending the hydrocarbon side chain beyond methyl or replacement with cycloalkyl or trifluoromethyl tended to decrease potency. Good biological activity was retained when the 3-substituent was phenoxymethyl (**10g**), phenyl (**10l**), 3-fluorophenyl (**10n**), or 3,4-difluorophenyl (**10q**). Other phenyl substituents, including 2-fluoro (**10m**), 2,4-difluoro (**10p**), and electron-withdrawing groups (CF_3, CN) were less potent. The 2-pyridyl isomer (**10z**) and pyrazine substituent (**10cc**) had decreased activity, but a quinoxaline group (**10dd**) was still effective against some *Candida* species. The 3-[2-(dialkylamino)vinyl]-substituted pyrido[3,4-*e*]-1,2,4-triazines (**12**) were substantially less active.

2. 5-Methyl- and 5,7-Dimethylpyrido[3,4-*e*]-1,2,4-triazines (19, 25, 26). Methylation of the fused pyridyl ring in the 5-position decreased overall antifungal activity. The parent 5,7-dimethylpyridotriazine (**25a**) was comparable to the best derivatives in the unsubstituted series (**10**). However, addition of substituents at C-3 such as methyl, 4-fluorophenyl, and 4-pyridyl, which retained high activity in the latter case, had the opposite effect in **25**. Addition of an amino or acylamino group at C-8 in **25** produced nearly inactive compounds.

3. 3,4-Dihydropyrido[3,4-*e*]-1,2,4-triazines (30), Pyrido[3,2-*e*]-1,2,4-triazines (33), and Benzo-1,2,4-triazines (37). All of these variations had decreased antifungal activity. The weak activity of the benzotriazines indicates the importance of a fused pyridine ring.

4. 1,2,4-Triazino[5,6-*c*]quinolines (43) and 3,4-Dihydro-1,2,4-triazino[5,6-*c*]quinolines (46). The unsubstituted triazinoquinoline (**43a**) was comparable to the analogous pyridotriazine (**10a**). Addition of a fused benzene ring had no effect in this case. However, the 3-methyl (**43b**) and 3-(4-pyridyl) (**43c**) derivatives were less potent. The corresponding dihydro series was also weakly active.

5. Several of the analogues that we prepared had overall in vitro antifungal activity equal to or greater than miconazole and nystatin. They are **10a**, **10b**, **10o**, **10aa**, **10bb**, **25a**, and **43a**. None of the synthetic compounds approached the potency of amphotericin B.

Experimental Section

Biological Methods. The in vitro antifungal effects of these compounds were determined by an agar dilution method. Twofold serial dilutions of the drugs were prepared in yeast nitrogen base medium (Difco) supplemented with 1% dextrose, 0.15% asparagine, and 1.5% agar. Amphotericin B, miconazole, and nystatin were used as controls. The agar surfaces in petri plates were inoculated with the organisms by means of the Steers multiple inocula replicator. Incubation was at 35 °C for 24–48 h. The lowest concentration that inhibited the visible growth of a culture was recorded as the minimum inhibitory concentration (MIC).

Chemical Methods. Unless otherwise noted, materials were obtained from commercial sources and were used without further purification. Activated MnO_2 was supplied by Aldrich. Column chromatography was done on silica gel 60 (E. Merck, 230–400 mesh). Thin-layer chromatography was done on commercial silica gel plates (Analtech) containing $CaSO_4$ binder and fluorescent indicator. The solvents were generally $CHCl_3$–MeOH mixtures. Organic extracts were dried over anhydrous $MgSO_4$. Melting points were determined in open Pyrex capillary tubes on a Meltemp melting point apparatus and are uncorrected. Elemental analyses were obtained for all new compounds reported and are within ±0.4% of theoretical value unless otherwise specified. ^1H nuclear magnetic resonance (^1H NMR) spectra were determined with either a Varian FT 80 (80-MHz) or General Electric QE-300 (300-MHz) spectrometer in appropriate deuterated solvents and are expressed in parts per million (δ, ppm) downfield from tetramethylsilane (internal standard). Significant ^1H NMR data are given as multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; br, broad), coupling constant in Hz, number of protons, and assignments. ^1H NMR spectra for all final products are given in Table VIII. Infrared (IR) spectra were taken with either a Perkin-Elmer Model 1310 or Nicolet Model 7199 recording spectrophotometer. Only important diagnostic peaks for the infrared are listed below. Mass spectra (MS) were obtained on a Finnigan MAT CH-7 mass spectrometer in the electron impact mode. A molecular ion was usually observed in the mass spectrum, together with a significant M-28 (N_2) peak.

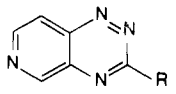
4-Hydroxy-3-nitropyridine (2).[10] Red fuming HNO_3 (288 mL, 460 g; d = 1.6, Baker) was chilled in ice while 240 mL (460 g; d = 1.92, 18–24% SO_3, Baker) of fuming H_2SO_4 was slowly added. This was followed by 98.6 g (1.03 mol) of 4-hydroxypyridine added over 15 min. The solution was slowly heated until an exothermic reaction and N_2O_4 evolution occurred. The heat source was removed, and after the reaction had subsided, it was refluxed for 1 h. It was then cooled to room temperature and poured slowly over ice. The resulting suspension was recooled, treated cautiously with 850 mL of concentrated NH_4OH, and chilled overnight. The precipitated product was collected, washed with ice water (2×), and dried. The yield was 104 g (72%) of light yellow crystals, mp 276–278 °C (lit. 278–279 °C). It was used without purification.

4-Chloro-3-nitropyridine (3).[11] 4-Hydroxy-3-nitropyridine (106 g, 0.757 mol) was added to a stirred slurry of 173 g (0.833 mol) of PCl_5 and 170 mL of $POCl_3$ held at 60–70 °C. The mixture solidified and the temperature was raised to 130–140 °C as the solids gradually dissolved. The reaction was held at this temperature for 6 h, and then volatile material was removed in vacuo. The residue was poured onto ice and H_2O. After the ice had melted, solid Na_2CO_3 was slowly added until the mixture was basic. The organic material was extracted into Et_2O, Darco was added, and the mixture was filtered through $MgSO_4$ and evaporated. The residue was distilled (air cooled short path; bp = 53–80 °C/0.2–0.4 mmHg) into an ice-cooled receiver to give 105.7 g (87%) of light yellow crystals. The product was stored under Ar in a freezer. Material obtained prior to distillation could also be used in subsequent reactions.

4-Hydrazino-3-nitropyridine (4). A solution of 64 mL (66.2 g, 1.32 mol) of $H_2NNH_2 \cdot H_2O$ in 225 mL of EtOH was added dropwise with rapid overhead stirring to a solution of 105.2 g (0.662 mol) of **3** in 850 mL of EtOH with ice cooling. Addition was complete after 1.5 h, and stirring was continued for 0.75 h at 0 °C and at 25 °C for 3.5 h. After chilling overnight, the product was collected by filtration, washed with cold EtOH and H_2O (3×), and dried. The crude material was recrystallized from methyl Cellosolve (Darco) to yield 77.9 g (77%) of brick red crystals, mp 202–203 °C dec (lit.[16] 200 °C).

(16) Koenigs, E.; Freter, K. *Chem. Ber.* **1924**, *57*, 1187.

Table I. Pyrido[3,4-*e*]-1,2,4-triazines



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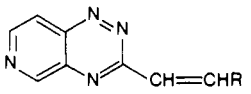


12

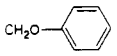
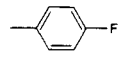
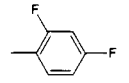
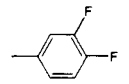
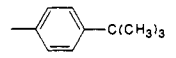
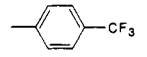
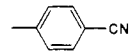
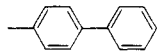
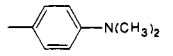
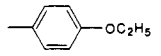
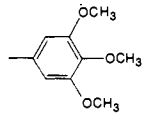
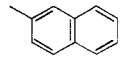
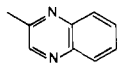
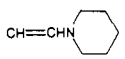
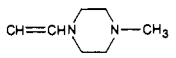
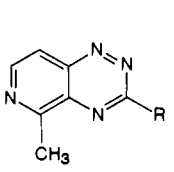
compd no.	R	method of preparation[a]	method of oxidation	yield, %[b]	mp, °C/ recrystn solvent	formula[c]
10a	H		$K_3Fe(CN)_6$	36	88–90/hexanes	$C_6H_4N_4$
10b	CH_3	B	MnO_2	52	111–113/EtOH	$C_7H_6N_4$
10c	C_3H_7	B	MnO_2	25	27.5–29.5/hexanes	$C_9H_{10}N_4$
10d	$(CH_2)_{16}CH_3$	B	MnO_2	18	64–65.5/hexanes	$C_{23}H_{38}N_4$
10e	$C(CH_3)_3$	A[d]	$K_3Fe(CN)_6$	25	oil	$C_{10}H_{12}N_4$
10f	CF_3	A[e]	$K_3Fe(CN)_6$	45	37–39/heptane, then hexanes	$C_7H_3F_3N_4$
10g		A[f]	MnO_2	45	115–116/EtOH	$C_{13}H_{10}N_4O$
10h		A	MnO_2	15	113.5–116.5/EtOH	$C_9H_8N_4$
10i		A	MnO_2	40	57.5–58.5/EtOH	$C_{10}H_{10}N_4$
10j		A	$K_3Fe(CN)_6$	37	39–41/hexanes	$C_{11}H_{12}N_4$
10k		A	$K_3Fe(CN)_6$	72	65–67/hexanes	$C_{12}H_{14}N_4$
10l		B	$K_3Fe(CN)_6$	9	124–127/EtOH	$C_{12}H_{18}N_4$
10m		A	MnO_2	10	131–132/EtOH	$C_{12}H_7FN_4$
10n		A	$K_3Fe(CN)_6$	46	111–113/EtOH	$C_{12}H_7FN_4$
10o		A	$K_3Fe(CN)_6$	61	157–158/EtOH	$C_{12}H_7FN_4$
10p		A	MnO_2	70	124–125/EtOH	$C_{12}H_6F_2N_4$
10q		A	MnO_2	32	157.5–159/EtOH	$C_{12}H_6F_2N_4$
10r		B	MnO_2	76	164.5–165.5/EtOH	$C_{16}H_{16}N_4$
10s		A	MnO_2	77	209–210/methyl Cellosolve	$C_{13}H_7F_3N_4$
10t		A	MnO_2	61	236–238/methyl Cellosolve	$C_{13}H_7N_5$
10u		B	MnO_2	59	201–202/methyl Cellosolve	$C_{18}H_{12}N_4$
10v		B	MnO_2	20	205–207/EtOH	$C_{14}H_{13}N_5$
10w		B	MnO_2	63	153–155/methyl Cellosolve	$C_{14}H_{12}N_4O$
10x		A	MnO_2	15	170–171/EtOH	$C_{15}H_{14}N_4O_3$
10y		A	MnO_2	73	180–182/methyl Cellosolve	$C_{16}H_{10}N_4$
10z		B	$K_3Fe(CN)_6$	8	159–161/*g*	$C_{11}H_7N_5$
10aa		B	$K_3Fe(CN)_6$	18	166–168/EtOH	$C_{11}H_7N_5$
10bb		B	MnO_2	17	178–179.5/$CHCl_3$	$C_{11}H_7N_5$

Table I (Continued)

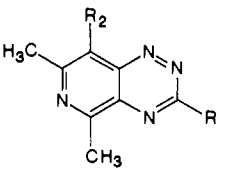
compd no.	R	method of preparation[a]	method of oxidation	yield, %[b]	mp, °C/ recrystn solvent	formula[c]
10cc		B	$K_3Fe(CN)_6$	25	176–177/EtOH	$C_{10}H_6N_6$
10dd		A	MnO_2	27	217–219/methyl Cellosolve	$C_{14}H_8N_6$
12a	$CH{=}CHN(CH_3)_2$			21	152–154/*h*	$C_{10}H_{11}N_5$
12b				11	150–152/EtOH (2×)	$C_{13}H_{15}N_5$
12c				8	138–140/$PhCH_3$	$C_{13}H_{16}N_6$

[a] See Results and Discussion. [b] Overall from 3 or 4. [c] Analyzes to within ±0.4% for each element unless otherwise noted. [d] Compound **9e** must be oxidized with ferricyanide to avoid contamination of the final product with Mn. Compound **10e** was purified by flash chromatography (silica, 30% EtOAc in hexanes). [e] Acylation was with $(CF_3CO)_2O$. [f] The oxidation of **9g** must be done with MnO_2. [g] Recrystallized from *i*-PrOH, filtered through Magnesol (EtOAc), and evaporated. [h] The reaction was evaporated and the residue was filtered through Magnesol (EtOAc) and dried in vacuo.

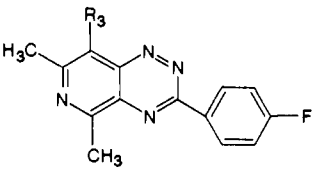
Table II. 5-Methyl- and 5,7-Dimethylpyrido[3,4-*e*]-1,2,4-triazines



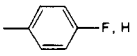
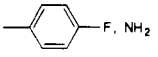
19



25

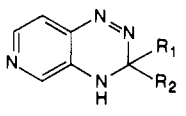


26

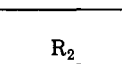
compd no.	R, R_2, R_3 (**26**)	method of oxidation	yield, %[a]	mp, °C/ recrystn solvent	formula[b]
19a	H	MnO_2	15[c]	116–117.5/hexanes	$C_7H_6N_4$
19b	CH_3	MnO_2	5	72–74/hexanes (2×)	$C_8H_8N_4$
19c		MnO_2	46	151.5–153.5/EtOH	$C_{12}H_9N_5$
25a	H, H	MnO_2	18[d]	62–63/petroleum ether (2×)	$C_8H_8N_4$
25b	CH_3, H	MnO_2	35	97.5–98/hexanes	$C_9H_{10}N_4$
25c		MnO_2	31	189–190/cyclohexane	$C_{14}H_{11}FN_4$
25d		MnO_2	23	160–162/hexanes	$C_{13}H_{11}N_5$
25e	CH_3, NH_2	MnO_2	17	171–173/cyclohexane	$C_9H_{11}N_5$
25f		$K_3Fe(CN)_6$	10	228–231/CH_3CN	$C_{14}H_{12}FN_5$
25g		MnO_2	17	221–224/EtOH–EtOAc	$C_{13}H_{12}N_6$
26a	$NHCOCH_3$		46	280–285/methyl Cellosolve (2×)	$C_{16}H_{14}FN_5O$[e]
26b	NHCOPh		8	242–244/methyl Cellosolve (2×)	$C_{21}H_{16}FN_5O$

[a] Compounds **19**: overall from **18**. Compounds **25** and **26**: overall from **24**. [b] See footnote *c*, Table I. [c] Based on 2-methyl-3-nitro-4-(1*H*)pyridinone hydrazone. [d] Based on 2,6-dimethyl-3-nitro-4(1*H*)pyridinone hydrazone. [e] Analyzes for 0.125 mol of H_2O.

Table III. 3,4-Dihydropyrido[3,4-*e*]-1,2,4-triazines

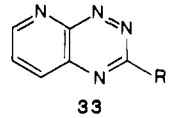


30

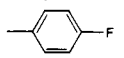
compd no.	R_1	R_2	yield, %[a]	mp, °C/ recrystn solvent	formula[b]
30a	CH_3	CH_3	48	143–145/$PhCH_3$[c]	$C_8H_{10}N_4$
30b		$-(CH_2)_5-$	63	127–129/*d*	$C_{11}H_{14}N_4$
30c	CH_2CH_3		46	136–138/$PhCH_3$ (2×)	$C_{15}H_{16}N_4$[e]

[a] Overall from 4. [b] See footnote *c*, Table I. [c] Recrystallized from PhCH, filtered through Magnesol (EtOAc), and evaporated. [d] Filtered twice through Magnesol (10% MeOH/EtOAc, then EtOAc) and evaporated. [e] C: calcd, 71.40; found, 71.86.

Table IV. Pyrido[3,2-*e*]-1,2,4-triazines



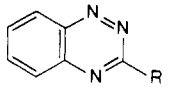
33

compd no.	R	yield, %[a]	mp, °C/ recrystn solvent	formula[b]
33a	H	26	145–148/EtOH	$C_6H_4N_4$
33b	CH_3	44	170–171/EtOH	$C_7H_6N_4$
33c		30	223–224/methyl Cellosolve	$C_{12}H_7N_4F$

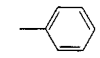
[a] Overall from 31. [b] See footnote *c*, Table I.

Acyl Derivatives of 4-Hydrazino-3-nitropyridine (7). Compounds of this type were prepared in two ways: method A, acylation of **4** with an acid chloride, or method B, reaction of **3** with a hydrazide. A specific example of each procedure is given.

Table V. Benzo-1,2,4-triazines

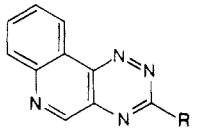


37

compd no.	R	yield, %[a]	mp, °C/ recrystn solvent	formula[b]
37a	CH_3	1	89–92/c	$C_3H_7N_3$
37b		12	120–124/cyclohexane	$C_{13}H_9N_3$

[a] Overall from 35. [b] See footnote c, Table I. [c] See Experimental Section.

Table VI. 1,2,4-Triazino[5,6-c]quinolines

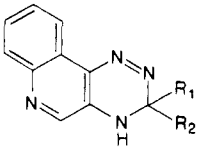


43

compd no.	R	yield, %[a]	mp, °C/ recrystn solvent	formula[b]
43a	H	45	162–163/EtOH	$C_{10}H_6N_4$
43b	CH_3	21	128–130/c	$C_{11}H_8N_4$
43c		25	216–217/methyl Cellosolve	$C_{15}H_9N_5$[d]

[a] Overall from 42. [b] See footnote c, Table I. [c] Filtered through Magnesol (EtOAc) and evaporated. [d] C: calcd, 69.49; found, 69.02.

Table VII. 3,4-Dihydro-1,2,4-triazino[5,6-c]quinolines



46

compd no.	R_1	R_2	yield, %[a]	mp, °C/ recrystn solvent	formula[b]
46a	CH_3	CH_3	35	166–168/$PhCH_3$ (2×)	$C_{12}H_{12}N_4$
46b	$-(CH_2)_5-$		19	151–153/EtOAc–hexanes, then $PhCH_3$	$C_{15}H_{16}N_4$

[a] Overall from 4-hydrazino-3-nitroquinoline. [b] See footnote c, Table I.

Method A. A slurry of 6.00 g (0.0390 mol) of 4 in 150 mL of THF at 0 °C under Ar was treated dropwise with a solution of 6.70 mL (9.36 g, 0.0449 mol) of 4-(trifluoromethyl)benzoyl chloride in 8 mL of THF. The thick mixture was stirred at 0 °C for 1.5 h and at 25 °C overnight. It was then filtered, and the product was washed with THF and with Et_2O and dried in vacuo over KOH. The yield of **7s** was 13.8 g of yellow crystals.

When R = CF_3, trifluoroacetic anhydride was used as the acylating agent and **7f** was obtained as the free base. Although pure samples of **7f**, 7l, and **7o** could be obtained and characterized, the crude products were generally used directly in the next step.

Method B. A mixture of 6.00 g (0.0377 mol) of **3** and 6.94 g (0.0377 mol) of 4-phenylbenzhydrazide in 60 mL of EtOH was refluxed for 5 h and then chilled overnight. The product was collected by filtration, washed with cold EtOH, and dried in vacuo. The yield of **7u** was 12.5 g of yellow crystals. The crude products made in this way were carried on to the next step without being purified or characterized. Pyrazinoic acid hydrazide (**6cc**) was prepared by reaction of methyl pyrazinecarboxylate with H_2N-NH_2·H_2O in refluxing EtOH; other hydrazides were commercially available.

2-(3-Amino-4-pyridinyl)-4-(trifluoromethyl)benzoic Acid Hydrazide Hydrochloride (8s). A mixture of 13.8 g (0.0394 mol) of **7s** in 300 mL of 95% EtOH containing 1 g of 5% Pd/C was hydrogenated in a Parr apparatus at ca. 45 psi until there was no more H_2 uptake. The reaction was then filtered through Celite, and the filter cake was washed well with 95% EtOH. The filtrate and wash were combined and evaporated to give 13.6 g of gray crystals.

This procedure is typical for all the compounds of this type. They could not be purified due to their instability and were used as is. The hydrogenation was sometimes run as a slurry in EtOH or aqueous EtOH. In the case of **7r** and **7u**, TFA was added to dissolve the starting material; HCl was used for this purpose with **7bb** and **7cc**. Water or EtOH could be added to the reduced product in order to solubilize it prior to filtering off the catalyst.

3-[4-(Trifluoromethyl)phenyl]-1,2-dihydropyrido[3,4-e]-1,2,4-triazine·*n*HCl (9s). The crude amine, **8s** (13.6 g), was dissolved in 375 mL of EtOH, and 35 mL of ethanolic HCl was added. The thick mixture was stirred for 5h at 25 °C and refluxed for 1.5 h. The solvent was then removed, and the residue was dried in vacuo to give **9s**.

All other compounds of type **9** were prepared in this way. They could not be adequately purified and characterized due to their instability. However, purification at this stage was unnecessary in order to obtain analytical samples of **10**.

3-[4-(Trifluoromethyl)phenyl]pyrido[3,4-e]-1,2,4-triazine (10s). The crude dihydro compound **9s** prepared above was dissolved in 600 mL of H_2O, and the pH was adjusted to ca. 6 with 5 M NaOH. The thick precipitate was stirred vigorously while 13.7 g (0.158 mol) of activated MnO_2 was added. After 50 min, TLC indicated no starting material. The reaction was continued for an additional 0.5 h and then filtered through Celite. The filter cake was washed with H_2O, EtOH, and $CHCl_3$ until all colored material was eluted. The filtrate and washes were combined and evaporated, and the residue was recrystallized from methyl Cellosolve. The yield was 8.32 g (77% overall from 4) of orange crystals, mp 209–210 °C.

Although $K_3Fe(CN)_6$ has been used for this reaction, activated MnO_2 is preferred because it produces fewer byproducts and higher yields. In either case, it is essential to keep the reaction from becoming acidic because this leads to product decomposition. Concentrated NH_4OH was used with $K_3Fe(CN)_6$ and dilute NaOH with MnO_2 for this purpose. If significant lower R_f impurities were seen by TLC, then the crude product was filtered through Magnesol ($CHCl_3$ or 3–5% MeOH in $CHCl_3$) prior to recrystallization. When R = CH_2OPh, oxidation with ferricyanide failed and MnO_2 was used. When R = $C(CH_3)_3$, **10e** contained Mn which could not be easily removed; ferricyanide was used as oxidant in this case. A procedure for the use of $K_3Fe(CN)_6$ is given below.

The crude dihydro compound **9** was dissolved in H_2O and the pH adjusted to 8 with concentrated NH_4OH. An aqueous solution of $K_3Fe(CN)_6$ (1 equiv) was added all at once. The mixture was stirred for 3 min and then extracted with $CHCl_3$. The extracts were combined, dried, and evaporated. The residue was purified by filtration through Magnesol followed by recrystallization. Compound **10e** was purified by flash chromatography (silica gel, 30% EtOAc in hexanes).

Pyrido[3,4-e]-1,2,4-triazine (10a).[6a] A mixture of 6.16 g (0.04 mol) of 4 in 200 mL of 95% EtOH containing 0.750 g of 5% Pd/C was hydrogenated on a Parr apparatus. After H_2 uptake had ceased, the reaction was filtered through Celite and the filter cake was washed well with additional solvent. The combined filtrate and wash were evaporated, and the residue was dried in vacuo for several hours. The crude product (tan solid) weighed 4.9 g and was used immediately in the next step.

A slurry of 4.9 g (0.0395 mol) of the aminohydrazine in 105 mL of $HC(OEt)_3$ containing 6.5 mL of concentrated HCl was stirred for 2.5 h. The insoluble material was collected by filtration, washed with $HC(OEt)_3$, and dried. The yield of **9a** was 7.1 g (orange crystals). It was used directly in the next step.

Concentrated NH_4OH (70 mL, 1.02 mol) was added to 7.1 g (0.0343 mol) of **9a** in 140 mL of H_2O. This solution was then treated with 22.6 g (0.0686 mol) of $K_3Fe(CN)_6$ in 345 mL of H_2O for 2 min. The reaction was extracted several times with $CHCl_3$. These extracts were combined, treated with Darco, filtered through $MgSO_4$, and evaporated. In one experiment, this crude material decomposed on standing overnight, so it should be purified immediately. The residue from the $CHCl_3$ extracts was boiled with

hexanes and deposited some brown tarry material. Darco was added, and the mixture was filtered through Celite. Crystals formed on standing overnight in a freezer. They were collected, washed with hexanes, and dried to yield 1.9 g (36% from **4**) of **10a** (orange crystals), mp 88–90 °C (lit. 90–91.5 °C).

***N*,*N*-Dimethyl-2-(pyrido[3,4-*e*]-1,2,4-triazin-3-yl)-ethenamine (12a).** A mixture of 0.731 g (0.005 mol) of **10b** in 40 mL (3.38 g, 0.0194 mol) of *tert*-butoxybis(dimethylamino)-methane (**11**) was heated in an oil bath (90–100 °C) for 2 h. Volatile material was then removed in vacuo, and the residue was filtered through Magnesol (EtOAc) until no more colored material was eluted. Solvent removal yielded 0.410 g (41%) of purple crystals: mp 152–154 °C; IR (KBr) ν 1628 cm^{-1} (C=C).

3-[2-(1-Piperidinyl)ethenyl]pyrido[3,4-*e*]-1,2,4-triazine (12b). A solution of 1.00 g (0.00497 mol) of **12a** in 20 mL (17.2 g, 0.202 mol) of piperidine was refluxed for 20 h. Most of the piperidine was evaporated, and the residue was azeotroped with EtOH. The solid that remained was recrystallized twice from EtOH to yield 0.640 g (53%) of dark purple crystals: mp 150–152 °C; IR (KBr) ν 1625 cm^{-1} (C=C).

3-[2-(4-Methyl-1-piperazinyl)ethenyl]pyrido[3,4-*e*]-1,2,4-triazine (12c). A solution of 0.500 g (0.00248 mol) of **12a** in 5 mL (4.51 g, 0.0452 mol) of *N*-methylpiperazine was refluxed for 17 h. Volatile material was removed in vacuo, and the residue was dissolved in hot $PhCH_3$. This solution was diluted with 2 volumes of hexanes and chilled. The resulting precipitate was collected, redissolved in 5% MeOH in EtOAc, and eluted through Magnesol. Solvent evaporation and recrystallization from $PhCH_3$ gave 0.240 g (38%) of dark purple crystals: mp 138–140 °C; IR (KBr) ν 1630 cm^{-1} (C=C).

4-Amino-2-picoline (16). 4-Nitro-2-picoline *N*-oxide (140.7 g, 0.914 mol) was hydrogenated in five batches on a Parr apparatus at ca. 40 psi; there was 28.1 g of nitro compound, 1.0 g of PtO_2, and 150 mL of glacial HOAc in each batch. The hydrogenation was rapid and exothermic. The combined reaction mixtures were filtered through Celite, the filter cake was washed with HOAc, and the solvent was evaporated. The residue was cooled in an ice bath and basified (pH ~11) with 10 M NaOH. The mixture was extracted repeatedly with Et_2O, and the extracts were combined, dried (K_2CO_3), and evaporated to give 12.8 g of product. The basified aqueous solution was then continuously extracted with $CHCl_3$ for 3 days. The $CHCl_3$ solution was dried and evaporated to give an additional 79.7 g of product. The total yield was 92.5 g (94% crude) of **16** as a reddish orange solid. The melting point range of this material was 77–89 °C, and a sample recrystallized from cyclohexane had mp 93–95 °C (lit.[17] 95 °C). The crude material was used in the next reaction.

2-Methyl-4-pyridinol Nitrate (17).[12] A solution of 50.4 g (0.0466 mol) of **16** in 278 mL of concentrated HNO_3 + 374 mL of H_2O was cooled in an ice bath. It was treated with 46.6 g (0.676 mol) of $NaNO_2$ in 137 mL of H_2O added dropwise with vigorous stirring (temperature ≤ 20 °C). After addition was complete (ca. 30 min), the reaction was stored at −2 °C overnight. The solid product was then collected, washed twice with ice water, and dried in vacuo (64 °C). The yield was 31.7 g (40%) of beige crystals, mp 164–165 °C (lit. 157–161 °C). Anal. Calcd: C, 41.86; H, 4.68; N, 16.28. Found: C, 41.48; H, 4.61; N, 16.27.

2-Methyl-3-nitro-4-pyridinol. Compound **17** (51.6 g, 0.300 mol) was added in portions to a solution of 115 mL of concentrated H_2SO_4 and 115 mL of fuming HNO_3 (d = 1.5). The reaction was refluxed for 2 h, cooled, and poured over cracked ice. The resulting clear solution was cautiously neutralized with 43 g of Na_2CO_3 and chilled. The product was collected, washed with ice water (2 × 50 mL), and dried in vacuo (60 °C), to give 30.7 g (66% crude) of pale yellow solid: ^1H NMR (DMSO-d_6) δ 2.33 (s, 3 H, CH_3), 6.35 (d, J = 4 Hz, 1 H, H-5), 7.73 (d, J = 4 Hz, 1 H, H-6).

4-Chloro-2-methyl-3-nitropyridine (18). A solution of 30.5 g (0.200 mol) of 2-methyl-3-nitro-4-pyridinol in 100 mL of $POCl_3$ was refluxed for 2 h. The $POCl_3$ was removed in vacuo, and the residue was poured over ice. Solid Na_2CO_3 and then $NaHCO_3$ were added to pH ~6. The mixture was extracted with $CHCl_3$, and the extract was washed with ice water (2×) and dried. Solvent evaporation gave 26.7 g of light brown solid, which was stored at 0 °C and used without further purification.

5-Methylpyrido[3,4-*e*]-1,2,4-triazine (19a) was prepared in four steps from **18** and $H_2NNH_2 \cdot H_2O$ without purification of intermediates as described for **10a**. The final oxidation was with MnO_2. Since this pyridotriazine was partially soluble in water, the oxidation mixture was filtered and the cake was washed well with $CHCl_3$. The aqueous filtrate was continuously extracted with $CHCl_3$ to obtain more crude product. Both batches of crude material were combined and recrystallized from hexanes to give a 15% overall yield of yellow crystals, mp 116–117.5 °C.

3,5-Dimethylpyrido[3,4-*e*]-1,2,4-triazine (19b) was prepared in four steps from **18** and acethydrazide without purification of intermediates as described for **10b**. The final oxidation was with MnO_2, and crude product was isolated both by filtration of the reaction and by $CHCl_3$ extraction of the aqueous filtrate. This material was then eluted through Magnesol (EtOAc) and recrystallized from hexanes (2×) to give a 5% overall yield of brown crystals, mp 72–74 °C.

5-Methyl-3-(4-pyridinyl)pyrido[3,4-*e*]-1,2,4-triazine (19c) was prepared in four steps from **18** and isonicotinic acid hydrazide without purification of intermediates as described for **10bb**. Oxidation was with MnO_2, and purification was similar to **19b**. The overall yield was 46% of brown crystals after recrystallization from EtOH, mp 151.5–153.5 °C.

2,6-Dimethyl-4-pyridone (21). The procedure of Bellingham et al.[13] was utilized, the yield of gray solid was 90%, and it melted at 231–233 °C (lit. 222–224 °C).

2,6-Dimethyl-3-nitro-4-pyridinol (22). Compound **21** (68.5 g, 0.557 mol) was added in portions to concentrated HNO_3 (257 mL, d = 1.42). Concentrated H_2SO_4 (368 mL) was then added slowly while keeping the temperature below 20 °C. Stirring was continued at room temperature for 3 h. The reaction was then slowly poured onto cracked ice and neutralized with K_2CO_3 and finally with concentrated NH_4OH to pH 8. The chilled mixture was filtered, and the product was washed well with H_2O and dried in vacuo at 72 °C. The yield of off-white solid was 87 g: ^1H NMR (DMSO-d_6) δ 2.18 (s, 3 H, C-6 CH_3), 2.22 (s, 3 H, C-2 CH_3), 6.03 (s, 1 H, H-5).

2,6-Dimethyl-3,5-dinitro-4-pyridinol (23). Compound **21** (67.4 g, 0.547 mol) was added in portions to a chilled mixture of fuming HNO_3 (203 mL, d = 1.5) and concentrated H_2SO_4 (305 mL). The solution was refluxed for 2 h and then poured onto cracked ice. Concentrated NH_4OH was cautiously added to pH 6, the chilled mixture was filtered, and the solid product was washed with H_2O and dried in vacuo (60 °C). The yield of yellow solid was 99 g. The NMR spectrum of the crude material showed a single peak at δ 2.38 (DMSO-d_6).

4-Chloro-2,6-dimethyl-3-nitropyridine (24) (R_1 = H) was prepared according to ref 18. The yield of white solid was 20% and had mp 68–70 °C (lit. 70–71 °C). This material was used without further purification.

4-Chloro-2,6-dimethyl-3,5-dinitropyridine (24) (R_1 = NO_2) was prepared in the same way as **24** (R_1 = H). The yield of pale yellow solid was 41% and had mp 135–139 °C (lit.[19] 143.5–144 °C). This compound was used without further purification.

3-Substituted-5,7-dimethylpyrido[3,4-*e*]-1,2,4-triazines (25) (R_2 = H). This series of four compounds was prepared in four steps from **24** (R_1 = H) and $H_2NNH_2 \cdot H_2O/HC(OC_2H_5)_3$ or an acylhydrazine (**6**) without purification of intermediates. The procedures were essentially the same as described for compounds **10**. See Table II.

3-Substituted-8-amino-5,7-dimethylpyrido[3,4-*e*]-1,2,4-triazines (25) (R_2 = NH_2). This series of three compounds was prepared in four steps from **24** (R_1 = NO_2) and an acylhydrazine (**6**) without purification of intermediates. The procedure was similar to that described for compounds **10**. See Table II.

***N*-[3-(4-Fluorophenyl)-5,7-dimethylpyrido[3,4-*e*]-1,2,4-triazin-8-yl]acetamide (26a).** A solution of 2.00 g (0.00743 mol) of **25f** in 50 mL of Ac_2O was heated on a steam bath for 30 min.

(17) Walker, G. N.; Moore, M. A.; Weaver, B. N. *J. Org. Chem.* **1961**, *26*, 2740.

(18) Kato, T.; Hayashi, H.; Anzai, T. *Yakugaku Zasshi* **1967**, *87*, 387; *Chem. Abstr.* **1967**, *67*, 64211.

(19) Fujimoto, G. Japan Patent 1727, 1957; *Chem. Abstr.* **1958**, *52*, 5481g.

Table VIII. ^{1}H Nuclear Magnetic Resonance Spectra of Final Products[a,b]

compd no.	solvent	proton resonances
10a	$CDCl_3$	10.18 (s, 1 H, H-3)
10b	$CDCl_3$	3.23 (s, 3 H, CH_3)
10c	$CDCl_3$	1.11 (t, J = 7, 3 H, CH_3), 2.08 (m, 2 H, CH_2), 3.49 (t, J = 7, 2 H, CH_2)
10d	$CDCl_3$	0.876 (t, J = 7, 3 H, CH_3), 1.25 [s, 24 H, $(CH_2)_{12}$], 2.03 (m, 2 H, CH_2), 3.49 (t, J = 7, 2 H, CH_2)
10e	$CDCl_3$	1.66 [s, 9 H, $C(CH_3)_3$]
10g	DMSO-d_6	5.90 (s, 2 H, CH_2), 7.15 (m, 5 H, phenyl)
10h	$CDCl_3$	1.40 (m, 4 H, CH_2CH_2), 2.83 (m, 1 H, CH)
10i	$CDCl_3$	2.18 (m, 2 H, $CH_2CH_2CH_2$), 2.63 (m, 4 H, $CH_2CH_2CH_2$), 4.41 (quintet, J = 8, 1 H, CH)
10j	DMSO-d_6	1.83 [m, 4 H, $CH_2(CH_2)_2CH_2$], 2.18 [m, 4 H, $CH_2(CH_2)_2CH_2$], 3.93 (quintet, 1 H, CH)
10k	DMSO-d_6	1.75 [m, 10 H, $(CH_2)_5$], 3.38 (m, 1 H, CH)
10l	$CDCl_3$	7.65 (m, 3 H, phenyl), 8.84 (m, 2 H, phenyl)
10m	$CDCl_3$	7.45 (m, 3 H, phenyl), 8.50 (m, 1 H, phenyl)
10n	$CDCl_3$	7.50 (m, 2 H, phenyl), 8.55 (m, 2 H, phenyl)
10o	$CDCl_3$	7.35 (dd, J_{HH} = 8.8, J_{HF} = 8.4, 2 H, phenyl), 8.81 (dd, J_{HH} = 8.8, J_{HF} = 5.6, 2 H, phenyl)
10p	DMSO-d_6	7.55 (m, 2 H, phenyl), 8.41 (m, 2 H, phenyl)
10q	$CDCl_3$	7.42 (m, 1 H, phenyl), 8.60 (m, 2 H, phenyl)
10r	$CDCl_3$	1.40 [s, 9 H, $C(CH_3)_3$], 7.60 (d, J = 9, 2 H, phenyl), 8.68 (d, J = 9, 2 H, phenyl)
10s	DMSO-d_6	8.08 (m, 2 H, phenyl), 8.95 (m, 2 H, phenyl)
10t[c]	$CDCl_3$	7.94 (d, J = 9, 2 H, phenyl), 8.94 (d, J = 9, 2 H, phenyl)
10u	$CDCl_3$	7.56 (m, 5 H, phenyl), 7.83 (d, J = 8, 2 H, phenyl), 8.84 (d, J = 8, 2 H, phenyl)
10v	DMSO-d_6	3.10 [s, 6 H, $N(CH_3)_2$], 6.94 (d, J = 8, 2 H, phenyl), 8.53 (d, J = 8, 2 H, phenyl)
10w	$CDCl_3$	1.49 (t, J = 7, 3 H, CH_3), 4.16 (q, J = 7, 2 H, CH_2), 7.07 (d, J = 9, 2 H, phenyl), 8.70 (d, J = 9, 2 H, phenyl)
10x	$CDCl_3$	4.06 (s, 3 H, OCH_3), 4.13 (s, 6 H, OCH_3), 8.15 (s, 2 H, phenyl)
10y	$CDCl_3$	7.58 (m, 2 H, naphthalene), 7.96 (m, 3 H, naphthalene), 8.75 (dd, J = 8, J = 1, 1 H, naphthalene), 9.36 (s, 1 H, naphthalene)
10z	$CDCl_3$	7.58 (m, 1 H, pyridyl), 8.05 (m, 1 H, pyridyl), 9.00 (m, 3 H, H-7 and pyridyl)
10aa	$CDCl_3$	7.60 (dd, J = 8, J = 5, 1 H, pyridyl), 9.00 (m, 3 H, H-7, pyridyl), 9.78 (s, 1 H, pyridyl)
10bb	$CDCl_3$	8.61 (dd, J = 5, J = 1, 2 H, pyridyl), 8.93 (dd, J = 5, J = 1, 2 H, pyridyl)
10cc	$CDCl_3$	8.94 (m, 2 H, pyrazine), 10.11 (d, J = 2, 1 H, pyrazine)
10dd	$CDCl_3$	7.93 (m, 2 H, quinoxaline), 8.35 (m, 2 H, quinoxaline), 10.28 (s, 1 H, quinoxaline)
12a	$CDCl_3$	3.10 [s, 6 H, $N(CH_3)_2$], 5.62 (d, J = 13, 1 H, =CH), 8.03 (d, J = 6, 1 H, H-8), 8.26 (d, J = 13, 1 H, =CH), 8.55 (d, J = 6, 1 H, H-7), 9.20 (s, 1 H, H-5)
12b	$CDCl_3$	1.73 [s (br), 6 H, CH_2's], 3.43 [s (br), 4 H, CH_2's], 5.75 (d, J = 14, 1 H, =CH), 8.05 (d, J = 6, 1 H, H-8), 8.24 (d, J = 14, 1 H, =CH), 8.59 (d, J = 6, 1 H, H-7), 9.21 (s, 1 H, H-5)
12c	$CDCl_3$	2.38 (s, 3 H, CH_3), 2.53 (m, 4 H, CH_2's), 3.50 (m, 4 H, CH_2's), 5.79 (d, J = 14, 1 H, =CH), 8.08 (d, J = 5, 1 H, H-8), 8.23 (d, J = 14, 1 H, =CH), 8.63 (d, J = 5, 1 H, H-7), 9.25 (s, 1 H, H-5)
19a	$CDCl_3$	3.15 (s, 3 H, CH_3), 8.23 (d, J = 6, 1 H, H-8), 8.89 (d, J = 6, 1 H, H-7), 10.15 (s, 1 H, H-3)
19b	$CDCl_3$	3.08 (s, 3 H, C-5 CH_3), 3.25 (s, 3 H, C-3 CH_3), 8.15 (d, J = 5, 1 H, H-8), 8.78 (d, J = 5, 1 H, H-7)
19c	$CDCl_3$	3.25 (s, 3 H, CH_3), 8.25 (d, J = 5, 1 H, H-8), 8.63 (m, 2 H, pyridyl), 9.00 (m, 3 H, pyridyl and H-7)
25a	$CDCl_3$	2.83 (s, 3 H, C-7 CH_3), 3.10 (s, 3 H, C-5 CH_3), 8.03 (s, 1 H, H-8), 10.07 (s, 1 H, H-3)
25b	$CDCl_3$	2.75 (s, 3 H, C-7 CH_3), 3.00 (s, 3 H, C-5 CH_3), 3.15 (s, 3 H, C-3 CH_3), 7.91 (s, 1 H, H-8)
25c	$CDCl_3$	2.80 (s, 3 H, C-7 CH_3), 3.05 (s, 3 H, C-5 CH_3), 7.26 (m, 2 H, phenyl), 7.96 (s, 1 H, H-8), 8.75 (m, 2 H, phenyl)
25d	$CDCl_3$	2.84 (s, 3 H, C-7 CH_3), 3.15 (s, 3 H, C-5 CH_3), 8.05 (s, 1 H, H-8), 8.59 (dd, J = 6, J = 1, 2 H, pyridyl), 8.91 (dd, J = 6, J = 1, 2 H, pyridyl)
25e	$CDCl_3$	2.60 (s, 3 H, C-7 CH_3), 2.85 (s, 3 H, C-5 CH_3), 3.15 (s, 3 H, C-3 CH_3), 5.00 [s (br), 2 H, NH_2]
25f	$CDCl_3$	2.64 (s, 3 H, C-7 CH_3), 2.95 (s, 3 H, C-5 CH_3), 5.08 [s (br), 2 H, NH_2], 7.28 (m, 2 H, phenyl), 8.76 (m, 2 H, phenyl)
25g	$CDCl_3$	2.68 (s, 3 H, C-7 CH_3), 3.00 (s, 3 H, C-5 CH_3), 5.15 [s (br), 2 H, NH_2], 8.59 (dd, J = 6, J = 1, 2 H, pyridyl), 8.91 (dd, J = 6, J = 1, 2 H, pyridyl)
26a	$CDCl_3$	2.25 (s, 3 H, $COCH_3$), 2.63 (s, 3 H, C-7 CH_3), 3.10 (s, 3 H, C-5 CH_3), 7.30 (m, 2 H, phenyl), 8.75 (m, 2 H, phenyl), 10.28 [s (br), 1 H, NH]
26b	DMSO-d_6	2.65 (s, 3 H, C-7 CH_3), 3.05 (s, 3 H, C-5 CH_3), 7.60 (m, 5 H, phenyl and 4-fluorophenyl), 8.16 (m, 2 H, phenyl), 8.71 (m, 2 H, 4-fluorophenyl), 10.8 [s (br), 1 H, NH]
30a	$CDCl_3$	1.55 (s, 6 H, CH_3's), 4.08 [s (br), 1 H, NH], 7.64 (d, J = 6, 1 H, H-8), 8.16 (d, J = 6, 1 H, H-7), 8.19 (s, 1 H, H-5)
30b	$CDCl_3$	1.85 (m, 10 H, cyclohexyl), 4.09 [s (br), 1 H, NH], 7.63 (d, J = 6, 1 H, H-8), 8.14 (d, J = 6, 1 H, H-7), 8.20 (s, 1 H, H-5)
30c	$CDCl_3$	0.995 (t, J = 7, 3 H, CH_3), 1.76 (m, 1 H, CH_2CH_3), 2.31 (m, 1 H, CH_2CH_3), 2.91 (d, J = 13, 1 H, CH_2Ph), 3.00 (d, J = 13, 1 H, CH_2Ph), 3.80 [s (br), 1 H, NH], 7.09 (dd, J = 8, J = 2, 2 H, phenyl), 7.27 (m, 3 H, phenyl), 7.61 (d, J = 5, H-8), 8.12 (m, 2 H, H-5 and H-7)
33a	DMSO-d_6	8.19 (dd, J = 8, J = 4, 1 H, H-6), 8.66 (dd, J = 8, J = 2, 1 H, H-5), 9.43 (dd, J = 4, J = 2, 1 H, H-7), 10.23 (s, 1 H, H-3)
33b	$CDCl_3$	3.19 (s, 3 H, CH_3), 7.92 (dd, J = 8, J = 4, 1 H, H-6), 8.39 (dd, J = 8, J = 2, H-5), 9.25 (dd, J = 4, J = 2, H-7)
33c	DMSO-d_6	7.50 (m, 2 H, phenyl), 8.13 (m, 1 H, H-6), 8.63 (m, 3 H, phenyl and H-5), 9.30 (m, 1 H, H-7)
37a	$CDCl_3$	3.13 (s, 1 H, CH_3), 7.85 (m, 3 H, phenyl), 8.50 (m, 1 H, phenyl)
37b	$CDCl_3$	7.60 (m, 3 H, H-3, H-4, and H-5 of phenyl side chain), 7.83 (m, 1 H, H-6 or H-7 of fused phenyl), 7.97 (m, 1 H, H-6 or H-7 of fused phenyl), 8.10 (d, J = 8.3, 1 H, H-5 or H-8 of fused phenyl), 8.54 (d, J = 7.8, 1 H, H-5 or H-8 of fused phenyl), 8.77 (m, 2 H, H-2 and H-6 of phenyl side chain)
43a	$CDCl_3$	8.00 (m, 2 H, H-8 and H-9), 8.36 (m, 1 H, H-10), 9.44 (m, 1 H, H-7), 9.60 (s, 1 H, H-5), 10.2 (s, 1 H, H-3)
43b	$CDCl_3$	3.25 (s, 3 H, CH_3), 7.95 (m, 2 H, H-8 and H-9), 8.33 (m, 1 H, H-10), 9.41 (m, 1 H, H-7), 9.54 (s, 1 H, H-5)
43c	$CDCl_3$	8.00 (m, 2 H, H-8 and H-9), 8.38 (m, 1 H, H-10), 8.63 (d, J = 6, 2 H, pyridyl), 8.95 (d, J = 6, 2 H, pyridyl), 9.46 (m, 1 H, H-7), 9.68 (s, 1 H, H-5)
46a	$CDCl_3$	1.59 (s, 6 H, CH_3's), 4.27 [s (br), 1 H, NH], 7.59 (dd, J = 7.4, J = 7, 1 H, H-8 or H-9), 7.66 (dd, J = 7.4, J = 7, 1 H, H-8 or H-9), 8.02 (d, J = 7, 1 H, H-10), 8.58 (d, J = 7, 1 H, H-7), 8.59 (s, 1 H, H-5)
46b	$CDCl_3$	1.65 (m, 6 H, cyclohexyl), 1.90 (m, 2 H, cyclohexyl), 2.11 (m, 2 H, cyclohexyl), 4.00 [s (br), 1 H, NH], 7.56 (dd, J = 7.4, J = 7, 1 H, H-8 or H-9), 7.65 (dd, J = 7.4, J = 7, 1 H, H-8 or H-9), 8.00 (d, J = 7, 1 H, H-10), 8.55 (d, J = 7, 1 H, H-7), 8.61 (s, 1 H, H-5)

Footnotes to Table VIII

[a] The chemical shifts are recorded in δ values and the coupling constants in hertz. The spectra were recorded in the solvent specified with tetramethylsilane as internal reference. The NMR peaks are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; br, broad. [b] The 3-substituted pyrido[3,4-*e*]-1,2,4-triazines (**10**) displayed resonances in the following ranges: 8.28–8.58 (dd, J = 6–7, J = 1, or d, J = 6, 1 H, H-8); 8.86–9.25 (d, J = 6–7, 1 H, H-7); 9.94–9.98 (s or d, J = 1, 1 H, H-5). Spectral data unique to specific compounds are given in the table. [c] IR (KBr) ν 2235 cm^{-1} (CN).

Table IX. Antifungal Activity. Range of Minimum Inhibitory Concentrations (μg/mL)[a]

compd no.	organism (no. of strains)[b]									
	C.a. (4)	*C.p.* (1)	*C.t.* (2)	*C.ps.* (2)	*C.r.* (1)	*C.s.* (1)	*A.n.* (4)	*T.m.* (3)	*T.r.* (2)	*M.f.* (1)
10a	8–16	16	8–16	4	8	8	16–32	2–4	1–2	8
10b	8–16	16	8	8	16	32	16–32	16	4–8	16
10c	32–64	64	32–64	16	64	64	32–64	32	8–32	64
10d	128		128	128	>128	>128	128			128
10e	64	64	64	64			64	32–64	16–32	
10f	16–32		32	8–16	16	16	32			8
10g	8–16		16	8–16	8	16	16–32			4
10h	16		32	16	64	64	32			16
10i	8–16		32	16	32	32	16–32			16
10j	8–16		64	16	16	32	16–32			4
10k	16–64	64	32–64	32	32	32	32–64	16	4–16	64
10l	16	16	8–16	8–16	32	16	16–32	8	2–4	>128
10m	32	32	32	32	16	32	16	8	2–4	64
10n	16	16	8–16	8	16	32	16–32	4	1–2	16
10o	8–16	8	8–16	8	8	8	16–32	4–8	4	64
10p	16–32	16	16	32			16–32	8	2	
10q	16	16	4–16	8			32–64	4	1–2	
10r	128		128	128	>128	>128	128			128
10s	64–128	128	128	128	>128	>128	128	64	8–32	>128
10t	64	64	8–32	4–8	>128	128	32–128	4–8	2–4	128
10u	128		128	128	>128	>128	64–128			128
10v	64	64	64	32			32–128	8	2–4	
10w	64		64	64	>128	>128	64–128			128
10x	64–128		128	64	128	128	128			128
10y	128		128	128	>128	>128	128			128
10z	64	64	64	32–64	64	16	32	32	2–4	64
10aa	8–16	16	4–16	4	16	32	16–32	4	1–2	>128
10bb	8	8	4–8	2–4	32	32	8–16	4	2–4	32
10cc	64		64	32	64	64	32–64			64
10dd	8		8	8	32	32	32			32
12a	64		128	128	16	16	64–128			64
12b	64–128	128	128	128			64–128	16	4–8	
12c	128		128	128	32	32	64–128			128
19a	16–32	64	16–32	8			32	8–32	4	
19b	8–16	128	8–32	8–16			64	8	8	
19c	16	32	16–32	8–16			32–64	8–16	8–16	
25a	4–8	16	4–8	4–8			32	4–8	4	
25b	8		32	8–16	64	64	32–128	8–32	16–32	16
25c	128		128	128	>128	>128	128	64	64	64
25d	32–64		128	32	32	32	64–128	32–128	64–128	>128
25e	128	128	128	64–128			128	32–64	32–64	
25f	>128	>128	>128		>128	>128	>128	128	128	128
25g	128		128	128	>128	>128	64–128	32	16	64
26a	128	128	128	128			128	64–128	32–128	
26b	128	128	128	128			128	64–128	32–64	
30a	128	128	128	128			128	128	128	
30b	128	128	128	128			128	32–64	32–64	
30c	128	128	32–128	1–32			128	16–32	32	
33a	64	32	64	32			16–32	32	32	
33b	128	64	128	128			32–64	128	128	
33b′	64	64	64	64			32–64	32–64	8–32	
33c	128		128	128	128	128	16–128	32	>128	
37a	128	128	64–128	128			128	64–128	64–128	
37b	64		128	128	128	128	128		64	
43a	8–16	16	16	8			8–16	4	4–8	
43b	32	32	32	32			16–32	32	32	
43c	128	128	128	2–4			64–128	64	64	
46a	128	128	128	128			128	64–128	64–128	
46b	128	128	128	128			128	64	64	
amphotericin	0.25–0.5	0.5	0.25–0.5	0.5	>128	>128	0.5	1	0.5	0.25
miconazole	8–16	16	8–16	0.25–4	8	8	8	2	1	8
nystatin	16	16	16	8	>128	>128	16	16–32	32	16

[a] agar dilution assay (see Experimental Section). [b] Abbreviations: *C.a., Candida albicans*; *C.p., Candida parapsilosis*; *C.t., Candida tropicalis*; *C.ps., Candida pseudotropicalis*; *C.r., Candida rugosa*; *C.s., Candida stellatoidea*; *A.n., Aspergillus niger*; *T.m., Trychophyton mentagrophytes*; *T.r., Trychophyton rubrum*; *M.f., Mucor fragilis*.

The resulting solid was collected by filtration, washed with HOAc (2×), recrystallized from methyl Cellosolve (2×), and dried in vacuo (60 °C). The yield was 1.07 g (46%) of orange crystals: mp 280–285 °C; IR (KBr) ν 1660 cm^{-1} (CO).

***N*-[3-(4-Fluorophenyl)-5,7-dimethylpyrido[3,4-*e*]-1,2,4-triazin-8-yl]benzamide (26b).** A solution of 2.75 g (0.0102 mol)

of **25f** and 1.30 mL (1.58 g, 0.0112 mol) of benzoyl chloride in 50 mL of pyridine was heated on a steam bath for 2 h. Solvent was removed in vacuo, and the residue was triturated with H_2O and then extracted several times with $CHCl_3$. The organic extracts were combined, washed with H_2O (2×), dried, and evaporated. The residue was recrystallized from methyl Cellosolve (2×) to give 0.285 g (8%) of brown crystals: mp 242–244 °C; IR (KBr) ν 1662 cm^{-1} (CO).

1,2,3,4-Tetrahydro-3,3-dimethylpyrido[3,4-*e*]-1,2,4-triazine Dihydrochloride (29a). Compound 4 was reduced to **27** as described previously and used immediately after drying in vacuo. The aminohydrazine (4.03 g, 0.0324 mol) was dissolved in 100 mL of EtOH and treated with 4.76 mL (3.77 g, 0.0649 mol) of acetone and 22 mL of EtOH saturated with HCl. The reaction was stirred overnight and then refluxed for 1 h. It was filtered and the resulting solid was washed with EtOH and dried in vacuo (65 °C). The yield of off-white crystals was 5.28 g (69%) and had mp 185–187 °C dec. Anal. ($C_8H_{14}Cl_2N_4$) C, H, N, Cl.

1′,4′-Dihydrospiro[cyclohexane-1,3′(2′*H*)-pyrido[3,4-*e*]-[1,2,4]triazine] dihydrochloride (29b) was prepared as above in 64% yield from **4** and cyclohexanone, giving off-white crystals, mp 184–186 °C dec. Anal. ($C_{11}H_{18}Cl_2N_4$) C, H, N, Cl.

3-Ethyl-1,2,3,4-tetrahydro-3-(phenylmethyl)pyrido[3,4-*e*]-1,2,4-triazine hydrochloride (29c) was prepared in 83% yield from 4 and 1-phenyl-2-butanone, giving off-white crystals, mp 100–110 °C. Anal. ($C_{15}H_{18}N_4 \cdot 1.625HCl \cdot 0.625H_2O$) C, H, N; Cl: calcd, 17.74; found, 17.31.

Compounds **30** were prepared by oxidation of **29** with excess activated MnO_2. Product purification is given below.

3,4-Dihydro-3,3-dimethylpyrido[3,4-*e*]-1,2,4-triazine (30a) was filtered through Magnesol (10% MeOH in EtOAc), recrystallized from $PhCH_3$, and again filtered through Magnesol (EtOAc). After drying in vacuo, the yield was 48% of orange crystals.

Spiro[cyclohexane-1,3′(4′*H*)-pyrido[3,4-*e*][1,2,4]triazine] (30b) was filtered twice through Magnesol (10% MeOH in EtOAc, then EtOAc) to give a 63% yield of orange crystals.

3-Ethyl-3,4-dihydro-3-(phenylmethyl)pyrido[3,4-*e*]-1,2,4-triazine (30c) was filtered through Magnesol (EtOAc), recrystallized twice from $PhCH_3$ and dried in vacuo (64 °C) to give a 57% yield of orange crystals. The side chains of this compound show restricted rotation.

2-Hydrazino-3-nitropyridine (34)[6b] was prepared by reaction of 2-chloro-3-nitropyridine with $H_2NNH_2 \cdot H_2O$ in MeOH at 25 °C overnight. After solvent removal, the residue was partitioned between $CHCl_3$ and H_2O. The organic layer was drawn off, dried, and evaporated to give a quantitative yield of orange-brown crystals. This material was used without further purification.

An analytical sample was prepared by recrystallization from EtOH, mp 165.5–167.5 °C (lit. 170–171 °C). Anal. ($C_5H_6N_4O_2$) C, H, N.

Pyrido[3,2-*e*]-1,2,4-triazine (33a).[6b] This compound was prepared from **34** by reduction to the amine, cyclization, and dehydrogenation (Figure 6). Intermediates were not purified. The crude product from MnO_2 oxidation was filtered through Magnesol (5% MeOH in $CHCl_3$) and recrystallized from EtOH to give red-orange crystals, mp 145–148 °C (lit. 151–152 °C).

Acetic Acid 2-(3-Nitro-2-pyridyl)hydrazide (32b).[8b] A mixture of 10.0 g (0.0631 mol) of 2-chloro-3-nitropyridine, 5.84 g (0.0789 mol) of acethydrazide, and 16.5 mL (12.2 g, 0.0947 mol) of *i*-Pr_2NEt in 130 mL of *t*-BuOH was refluxed overnight. The solvent was removed in vacuo, and the residue was filtered through Magnesol (10% MeOH in $CHCl_3$) and recrystallized from EtOH. Filtration yielded 5.9 g of scarlet crystals. The evaporated mother liquors were boiled with hexanes and diluted with EtOH to obtain additional product, 3.38 g of red crystals. Both products were red initially and slowly turned yellow on standing. This has been ascribed to polymorphs.[8b] An analytical sample of this material could not be obtained, and it was used as is: ^1H NMR (DMSO-d_6) δ 1.95 (s, 3 H, CH_3), 6.95 (dd, J = 8 Hz, J = 5 Hz, 1 H, H-5), 8.50 (m, 2 H, H-4, NH), 9.74 [s (br), 1 H, H-6], 10.25 (s, 1 H, NH).

1,2-Dihydro-3-methylpyrido[3,2-*e*]-1,2,4-triazine Hydrochloride (33b′).[6b,8b] Compound **32b** (9.3 g, 0.0474 mol) was hydrogenated in 200 mL of EtOH containing 0.8 g of 5% Pd/C catalyst. The crude product was a tan foam (8.0 g). It was slurried in 150 mL of EtOH, 40 mL of EtOH saturated with HCl was added, and the mixture was stirred overnight. Solvent was then removed, and the residue was recrystallized from EtOH to yield 5.31 g (41% from **31**) of yellow crystals, mp 214–216 °C dec. Lewis and Shepherd[6b] report 220 °C and Gelleri et al.[8b] report 218–219 °C for the dihydrochloride salt. Our microanalytical data fit for the monohydrochloride monohydrate. Anal. Calcd. for $C_7H_9ClN_4 \cdot H_2O$: C, 41.49; H, 5.47; N, 27.65; Cl, 17.50. Found: C, 41.40; H, 5.35; N, 27.88; Cl, 17.61.

A Karl Fischer water analysis could not be done due to the reducing nature of the substrate.

The mother liquors from the first crop were evaporated to give an additional 3.3 g of material which was used in the next oxidation step.

3-Methylpyrido[3,2-*e*]-1,2,4-triazine (33b).[6b,8b] The corresponding dihydro compound (**33b′**, 7.11 g, 0.0323 mol) was dissolved in 150 mL of H_2O, neutralized with 5 M NaOH, and treated with 11.2 g (0.129 mol) of activated MnO_2 for 1.25 h. The mixture was filtered through Celite, the filter cake was washed with H_2O and EtOH, and the combined filtrate and washings were evaporated. The residue was heated with 5% MeOH in $CHCl_3$ and filtered. The filtrate was partially evaporated and passed through Magnesol. The eluent was evaporated and the residue was recrystallized from EtOH. The yield was 3.35 g (44% from **31**) of orange needles, mp 170–171 °C (lit.[6b] 171–172 °C).

3-(4-Fluorophenyl)pyrido[3,2-*e*]-1,2,4-triazine (33c). Compound **32c** was prepared from 2-chloro-3-nitropyridine, 4-fluorobenzhydrazide, and triethylamine as described for **32b**. The resulting material was hydrogenated (5% Pd/C, 95% EtOH) and cyclized with ethanolic HCl. The dihydro compound was dissolved in H_2O, neutralized with NH_4OH, and treated with $K_3Fe(CN)_6$ for 3 min. The crude final product was filtered through Magnesol (5% MeOH in $CHCl_3$) and recrystallized from methyl Cellosolve to give a 30% yield (overall from **31**) of red-brown crystals, mp 223–224 °C.

Acetic Acid 2-(2-Nitrophenyl)hydrazide (36a). A solution of 1-fluoro-2-nitrobenzene (14.8 g, 0.105 mol) and acethydrazide (7.40 g, 0.100 mol) in 100 mL of methyl Cellosolve was refluxed for 5.5 h. Solvent was removed in vacuo and the residual red-orange oil was crystallized with acetone. This yielded 7.23 g of orange solid which was slurried with H_2O, adjusted to pH 8 with aqueous $NaHCO_3$, and then extracted with CH_2Cl_2. The extracts were dried and evaporated to yield 2.07 g (11%) of yellow-orange solid, mp 139–142 °C (lit.[20] 142–144 °C). Anal. ($C_8H_9N_3O_3$) C, H, N. This product was carried through the subsequent steps.

3-Methylbenzo-1,2,4-triazine (37a). Crude **36a** was hydrogenated in 50% aqueous EtOH containing 6 M HCl and 5% Pd/C as catalyst. The product from this reaction was dissolved in 60 mL of EtOH and then chilled to −20 °C. After filtration, the solution was diluted with 100 mL of EtOH and 25 mL of 6 M HCl and refluxed for 1.5 h. Solvent was evaporated, and the residue was redissolved in 200 mL of H_2O and treated with excess activated MnO_2 for 2 h. The reaction was filtered through Celite, and the filter cake was washed well with 5% MeOH in CH_2Cl_2. The aqueous filtrate was extracted with CH_2Cl_2, and the organic material was combined and evaporated. The residue was filtered through Magnesol (10% EtOAc in hexanes), and the solvent was removed in vacuo to give 0.220 g (1% from **35**) of yellow-brown solid, mp 89–92 °C (lit.[20] 97–98 °C). Anal. ($C_8H_7N_3$) C, H, N.

Benzoic acid 2-(2-nitrophenyl)hydrazide (36b) was prepared in the same way as **36a**; reflux time was 20 h. The evaporated reaction mixture was dissolved in CH_2Cl_2, filtered, washed with aqueous $KHCO_3$, and H_2O, dried, and evaporated. The residue was recrystallized from EtOH (Darco) to give 10.6 g (41%) of orange crystals, mp 172–174 °C (lit.[20] 163–165 °C). Anal. ($C_{13}H_{11}N_3O_3$) C, H, N.

3-Phenylbenzo-1,2,4-triazine (37b). Compound **36b** was hydrogenated in absolute EtOH containing 5% Pd/C. The crude product was recrystallized from EtOAc to give 84% of white crystals, mp 165–166 °C (lit.[20] 163–164 °C). Anal. ($C_{13}H_{13}N_3O$) C, H, N.

The amine was cyclized and oxidized according to ref 19. The crude benzotriazine was extracted into CH_2Cl_2 and evaporated. Elution of the residue through Magnesol with hexanes–EtOAc (8:1) and recrystallization from cyclohexane gave **37b** (12% from

(20) Abramovitch, R. A.; Schofield, K. *J. Chem. Soc.* **1955**, 2326.

35) as orange-brown crystals, mp 120–124 °C (lit.[20] 126–127 °C). Anal. ($C_{13}H_9N_3$) C, H, N.

4-Chloro-3-nitroquinoline (42).[9a] This material was prepared according to refs 9a and 15, but with the following modifications. Compound **40** was refluxed with Ac_2O for 1 h. The reaction was held at 100 °C while anhydrous NaOAc was added. Stirring was continued at room temperature overnight. The crude product was isolated by pouring the reaction into H_2O. Chlorination was accomplished by heating the crude anhydrous nitroquinoline in a mixture of $POCl_3$ and PCl_5. After reaction was complete, volatiles were removed in vacuo and the residue was taken up in CH_2Cl_2. This solution was slowly poured into excess ice-cold NH_4OH and filtered to remove insoluble **41**. The organic layer was removed and combined with two additional CH_2Cl_2 extracts of the aqueous layer. Drying of the extract, filtration through Magnesol, and solvent removal gave crude **42** as light yellow crystals. This material was stable when stored cold and was used as is.

1,2,4-Triazino[5,6-*c*]quinoline (43a). 4-Hydrazino-3-nitroquinoline was prepared from **42** and $H_2NNH_2 \cdot H_2O$ (*i*-PrOH, room temperature, 20 h). It was then converted to **43a** by the procedure used for **10a**. Oxidation was with MnO_2. The crude product was filtered through Magnesol (EtOAc) and recrystallized from EtOH to give orange crystals (45% overall from **42**), mp 162–163 °C. Anal. ($C_{10}H_6N_4$) C, H, N.

3-Methyl-1,2,4-triazino[5,6-*c*]quinoline (43b) was prepared from **42** and acethydrazide in the same way as the analogous pyridotriazine. After oxidation with MnO_2, the crude product was filtered through Magnesol (EtOAc) and evaporated to give yellow crystals (21% overall from **42**), mp 128–130 °C. Anal. ($C_{11}H_8N_4$) C, H, N.

3-(4-Pyridinyl)-1,2,4-triazino[5,6-*c*]quinoline (43c) was prepared from **42** and isonicotinic acid hydrazide in the same way as the analogous pyridotriazine. After oxidation with MnO_2, the crude product was recrystallzed from methyl Cellosolve (2×) to give orange crystals (25% overall from **42**), mp 216–217 °C. Anal. ($C_{11}H_8N_4$) H, N; C: calcd, 69.49; found, 69.02.

3,4-Dihydro-3,3-dimethyl-1,2,4-triazino[5,6-*c*]quinoline (46a). 4-Hydrazino-3-nitroquinoline was hydrogenated over 10% Pd/C. A slurry of 1.18 g (0.00671 mol) of the reduction product (**44**) in 100 mL of acetone was refluxed for 1.5 h with 3.5 mL of ca. 6 M anhydrous HCl in absolute EtOH. The crude product (1.5 g) was collected by filtration, dissolved in 50 mL of H_2O, neutralized (1 M NaOH), and treated with MnO_2 (2.60 g, 0.0299 mol). Recrystallization from $PhCH_3$ gave 0.460 g (35% from the nitrohydrazine) of orange crystals, mp 166–168 °C. Anal. ($C_{12}H_{12}N_4$) C, H, N.

Spiro[cyclohexane-1,3′(4′*H*)-[1,2,4]triazino[5,6-*c*]quinoline] (46b). A mixture of 4.0 g (0.0230 mol) of **44**, 6.37 g (0.0459 mol) of cyclohexanone, and 22 mL of ca. 6 M anhydrous HCl in absolute EtOH was refluxed for 2 h. The reaction mixture was evaporated, and the residue was washed with Et_2O (2×) to give crude **45b**. This was oxidized with MnO_2 as above. Filtration through Magnesol (EtOAc) and recrystallization from EtOAc–hexanes gave 0.53 g (19% from the nitrohydrazine) of red-orange crystals, mp 146–148 °C. Anal. ($C_{15}H_{16}N_4$) C, H, N.

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Registry No. **1**, 626-64-2; **2**, 5435-54-1; **3**, 13091-23-1; **4**, 33544-42-2; **7s**, 121845-42-9; **7u**, 121845-72-5; **8s**, 121845-43-0; **9a**, 76603-03-7; **9s**, 121845-44-1; **10a**, 767-95-3; **10b**, 14612-29-4; **10c**, 121845-45-2; **10d**, 121845-46-3; **10e**, 121845-47-4; **10f**, 121845-48-5; **10g**, 55242-75-6; **10h**, 121845-49-6; **10i**, 121845-50-9; **10j**, 121845-51-0; **10k**, 121845-52-1; **10l**, 40848-48-4; **10m**, 121845-53-2; **10n**, 121845-54-3; **10o**, 121845-55-4; **10p**, 121845-56-5; **10q**, 121845-57-6; **10r**, 121845-58-7; **10s**, 121845-59-8; **10t**, 121845-60-1; **10u**, 121845-61-2; **10v**, 121845-62-3; **10w**, 121845-63-4; **10x**, 60445-73-0; **10y**, 121845-64-5; **10z**, 121845-65-6; **10aa**, 121845-66-7; **10bb**, 60097-07-6; **10cc**, 121845-67-8; **10dd**, 121845-68-9; **11**, 5815-08-7; **12a**, 121845-69-0; **12b**, 121845-70-3; **12c**, 121845-71-4; **16**, 18437-58-6; **17**, 18614-65-8; **18**, 23056-35-1; **19a**, 121845-73-6; **19b**, 121845-74-7; **19c**, 121845-75-8; **21**, 7516-31-6; **22**, 13603-45-7; **23**, 31872-55-6; **24** (R_1 = H), 15513-48-1; **24** (R_1 = NO_2), 25370-51-8; **25a**, 121845-76-9; **25b**, 121845-77-0; **25c**, 121845-78-1; **25d**, 121845-79-2; **25e**, 121845-80-5; **25f**, 121845-81-6; **25g**, 121845-82-7; **26a**, 121845-83-8; **26b**, 121845-84-9; **27**, 31481-86-4; **29a**, 121845-85-0; **29b**, 121845-86-1; **29c**, 121845-87-2; **30a**, 121845-88-3; **30b**, 121845-89-4; **30c**, 121845-90-7; **32b**, 30962-70-0; **33a**, 6133-44-4; **33b**, 30962-73-3; **33b′**, 121865-30-3; **33b′** (free base), 30962-74-4; **33c**, 121845-91-8; **34**, 15367-16-5; **36a**, 14674-17-0; **36b**, 14674-18-1; **37a**, 6299-94-1; **37b**, 6299-90-7; **38**, 5653-21-4; **39**, 118-92-3; **40**, 121845-92-9; **41**, 50332-66-6; **42**, 39061-97-7; **43a**, 39862-58-3; **43b**, 51093-11-9; **43c**, 51093-88-0; **44**, 60050-66-0; **45a**, 121845-93-0; **45b**, 121845-95-2; **46a**, 121845-94-1; **46b**, 121845-96-3; $(CH_3)_3CCOCl$, 3282-30-2; $PhOCH_2COCl$, 701-99-5; $CH_3(CH_2)_2CONHNH_2$, 3538-65-6; $CH_3(CH_2)_{16}CONHNH_2$, 4130-54-5; *p*-$FC_6H_4CONHNH_2$, 456-06-4; *p*-$(CH_3)_3CC_6H_4CONHNH_2$, 43100-38-5; *p*-$PhC_6H_4CONHNH_2$, 18622-23-6; *p*-$Me_2NC_6H_4CONHNH_2$, 19353-92-5; 4-(trifluoromethyl)benzoyl chloride, 329-15-7; trifluoroacetic anhydride, 407-25-0; cyclopropanecarbonyl chloride, 4023-34-1; cyclobutanecarbonyl chloride, 5006-22-4; cyclopentanecarbonyl chloride, 4524-93-0; *o*-fluorobenzoyl chloride, 393-52-2; *m*-fluorobenzoyl chloride, 1711-07-5; *p*-fluorobenzoyl chloride, 403-43-0; 2,4-difluorobenzoyl chloride, 72482-64-5; 3,4-difluorobenzoyl chloride, 76903-88-3; *p*-cyanobenzoyl chloride, 6068-72-0; 3,4,5-trimethoxybenzoyl chloride, 4521-61-3; 2-naphthoyl chloride, 2243-83-6; 2-quinoxalinecarboxylic acid chloride, 54745-92-5; cyclohexanecarbonyl chloride, 2719-27-9; acetohydrazide, 1068-57-1; benzohydrazide, 613-94-5; 4-ethoxybenzohydrazide, 58586-81-5; 2-pyridinecarboxylic acid hydrazide, 1452-63-7; 3-pyridinecarboxylic acid hydrazide, 553-53-7; 4-pyridinecarboxylic acid hydrazide, 54-85-3; 2-pyrazinecarboxylic acid hydrazide, 768-05-8; methyl pyrazinecarboxylate, 6164-79-0; *N*-methylpiperazine, 109-01-3; 4-nitro-2-picoline *N*-oxide, 5470-66-6; 2-methyl-3-nitro-4-pyridinol, 18614-66-9; cyclohexanone, 108-94-1; 1-phenyl-2-butanone, 1007-32-5; 2-chloro-3-nitropyridine, 5470-18-8; 1-fluoro-2-nitrobenzene, 1493-27-2; benzoic acid 2-(2-aminophenyl)hydrazide, 6299-88-3; 4-hydrazino-3-nitroquinoline, 23589-54-0; nitromethane, 75-52-5.