3-Acetamido-4-[*p*-bis(2-chloroethyl)aminoacetamidophenyl]isoquinoline (12). A solution of 500 mg (1.19 mmol) of **5a** in 50 mL of dry CH_3CN was cooled to 4 °C and 0.51 mL (7.20 mmol) of $SOCl_2$ was added immediately producing a coffee-colored precipitate which dissolved after 1 h at 4 °C. The reaction was stored at 4 °C for 16 h and then evaporated to give a solid residue. The residue was dissolved in a mixture of 15 mL of $CHCl_3$ and 3 mL of CH_3OH and vigorously stirred with a solution of 270 mg of $NaHCO_3$ in 20 mL of H_2O for 5 min. The $CHCl_3$ layer was separated and the aqueous solution extracted with more $CHCl_3$. The combined $CHCl_3$ layers were dried (Na_2SO_4), filtered, and evaporated to give 420 mg of a crude solid. Preparative TLC (S_5) yielded 200 mg (37%) of **12** as an off-white solid, mp 200 °C.

4-[*p*-[4-(2-Chloroethyl)piperazino]phenyl]-3-ethylaminoisoquinoline (16). Compound **15** (260 mg, 0.6 mmol) as its free base was heated at 50 °C for 16 h under vacuum to yield 260 mg of a yellow solid, mp 128–130 °C. The solid was then vigorously stirred in 20 mL of $CHCl_3$ and 1 mL of CH_3OH with 20 mL of H_2O containing 200 mg of $NaHCO_3$. The layers were separated and the $CHCl_3$ layer was dried (Na_2SO_4), filtered, and evaporated to yield 250 mg of a brown oil. Preparative TLC (S_8) gave 80 mg (30%) of **16** as a waxy solid, mp 125–127 °C.

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Cannabinoids. Synthesis and Central Nervous System Activity of 8-Substituted 10-Hydroxy-5,5-dimethyl-5*H*-[1]benzopyrano[4,3-*c*]pyridine and Derivatives

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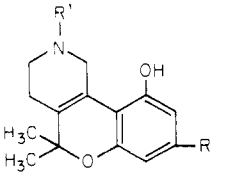
8-(1,2-Dimethylheptyl)- and 8-[5-(4-fluorophenyl)-2-pentyl]-10-hydroxy-5,5-dimethyl-5*H*-[1]benzopyrano[4,3-*c*]pyridines (**2a** and **2b**), their phenolic ester and ether derivatives, and their *N*-oxides were synthesized and evaluated in various CNS pharmacological tests in animals. **2a** was found to be the most potent compound.

In continuation of synthetic work in the cannabinoid field in our laboratories, we have prepared and studied the pharmacological activity of several nitrogen analogues of the tetrahydrocannabinols (THC's). Pars et al.[1] and Winn et al.[2] have found that Ia and Ib are among the most potent compounds in a large series of nitrogen-containing cannabinoids. Because the 2-propynyl group on nitrogen resulted in such outstanding central nervous system (CNS) potency (i.e., simple alkyl-, alkenyl-, or arylalkyl-substituted analogues were clearly less active), and because it is well known that simple 2-propynylamines are 2–3 p*K* units less basic than simple alkylamines, we prepared the pyridine analogues of Ia,b (Table I) to see whether potency could be increased further by incorporation of an even less basic nitrogen atom. The results summarized in Table II clearly show that these pyridine analogues **2a** and **2b** are indeed slightly more potent than their hydroheteroaromatic predecessors (Ia,b) in most tests.

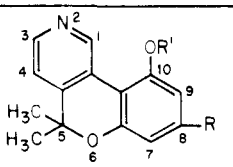
The phenolic hydroxyl group in the THC's is essential for eliciting CNS activity.[3,4] In an attempt to selectively eliminate one of the characteristic cannabinol-like CNS



Ia, R' = $CH_2C{\equiv}CH$; R = $CH(CH_3)CH(CH_3)$-*n*-C_5H_{11}
b, R' = $CH_2C{\equiv}CH$; R = $CH(CH_3)(CH_2)_3$-C_6H_4-*p*-F

effects, i.e., the hyperexcitability reaction to external stimuli produced in animals,[5] we modified the phenolic hydroxyl group by preparing ester and ether derivatives. The esters retained the hyperexcitability reaction and general CNS activity. However, the ethers produced much less hyperexcitability but were also less active as CNS depressants than the esters. Interestingly, the methoxy and 2-propynyloxy derivatives **6** and **9** were found to be active as sedative–hypnotics in cat EEG studies as shown by an increase in sleeping time. To increase the polar character of the nitrogen atom and further decrease basicity, the pyridyl analogues were oxidized to their

Table I. 8-Substituted 10-Hydroxy-5,5-dimethyl-5*H*-[1]benzopyran[4,3-*c*]pyridine and Derivatives



Compd	R	R'	Mp, °C	Yield, %	Purificn solvents	Formula[a]
2a	C_9H_{19}	H	155-157	82	CH_3CN	$C_{23}H_{31}NO_2$
2b	$C_{11}H_{14}F$	H	72-74	71	CH_3CN	$C_{25}H_{26}FNO_2$
3	C_9H_{19}	$COCH_3$	Oil	90	$CHCl_3$ (C)[b]	$C_{25}H_{33}NO_3$
4	C_9H_{19}	$COOC_2H_5$	Oil	85	C_6H_6-Et_2O (C)	$C_{26}H_{35}NO_4$
5	C_9H_{19}	$CO(CH_2)_3$-c-NC_5H_{10}	134-137 (HCl)	76	CH_2Cl_2-Et_2O	$C_{32}H_{46}N_2O_3 \cdot HCl$
6	C_9H_{19}	CH_3	Oil	79	$CHCl_3$ (C)	$C_{24}H_{33}NO_2$
7	$C_{11}H_{14}F$	CH_3	Oil	46	C_6H_6-CH_3OH (C)	$C_{26}H_{28}FNO_2$
8	$C_{11}H_{14}F$	$CH_2CH{=}CH_2$	Oil	50	$CHCl_3$ (C)	$C_{28}H_{30}FNO_2$
9	C_9H_{19}	$CH_2C{\equiv}CH$	Oil	86	$CHCl_3$ (C)	$C_{26}H_{33}NO_2$
10	C_9H_{19}	CH_2-c-C_3H_5	Oil	91	$CHCl_3$ (C)	$C_{27}H_{37}NO_2$
11	C_9H_{19}	$(CH_2)_3$-c-NC_5H_{10}	222-225 (2HCl)	58	*i*-PrOH-Et_2O	$C_{31}H_{46}N_2O_2 \cdot 2HCl$
12	C_9H_{19}	$(CH_2)_3$-c-$N(CH_2CH_2)_2O$	229-232 (2HCl)	64	*i*-PrOH-Et_2O	$C_{30}H_{44}N_2O_3 \cdot 2HCl$
13a	C_9H_{19}	H	193-195 (*N*-oxide)	48	CH_3CN	$C_{23}H_{31}NO_3$
13b	$C_{11}H_{14}F$	H	185-187 (*N*-oxide)	50	CH_3CN	$C_{25}H_{26}FNO_3$

[a] C, H, and N analyses for all compounds were within ±0.4% of the theoretical value except in the case of compound 8. C: calcd, 77.93; found, 78.56. [b] (C) denotes chromatography using Florisil column (60-100 mesh).

Table II. Biological Activity[h]

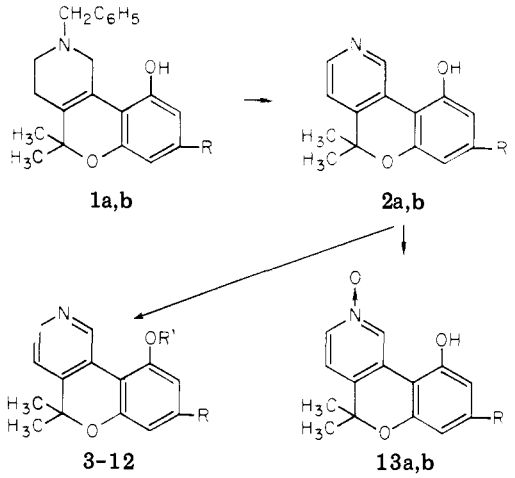
Compd	Dopa,[a] 5 mg/kg	Analgesia,[b] ED_{50}, mg/kg RTF	W	Mouse fighting[c]	Rat motor act.[d]	Dog ataxia[e]	Methamphetamine antagonism,[d] rat	Sedative-hypnotic[f] (TST, cat)	Rat hyperexcitability[g]
2a	+++	3.07	3.3	29 (5) 36 (10)	79 (5)	<1 (++)	61 (5)	225 (0.1) 193 (0.25)	36/48 (10)
2b	+++	5.7	7.1	58 (5)	34 (5)		40 (5)		31/48 (5) 38/48 (10)
3	+		3.3	48 (10)	43 (2) 86 (5)	<5 (++)	46 (5)		40/48 (5)
4	+		5.2	12 (10)	93 (5)		37 (2) 66 (5)		47/48 (10)
5	+		4.0	+3 (5)	43 (5) 63 (10)		40 (5)		29/48 (5) 48/48 (10)
6	+	>200	158	29 (10)	37 (10) 46 (20)	2 (++)	+15 (5) 12 (10)	58 (1) 102 (5)	0/48 (10) 0/48 (80)
7	+	>40		65 (10)		10 (++)	48 (10)	121 (5)	27/48 (20)
8	+	>40		17 (10)			20 (10) 27 (20)		0/48 (20) 24/48 (80)
9	+	>40	>40	6 (10)	27 (5)	2 (++)	31 (10) 42 (20)	82 (1) 114 (5)	0/48 (10) 43/48 (80)
10	+	>40					1 (10)	105 (2.5)	0/48 (20) 0/48 (80)
11	+	>40					15 (10)	-153 (5)	0/48 (20) 0/48 (80)
12	+	>40					+13 (10) +28 (20)	-11 (5)	0/48 (20) 0/48 (80)
13a	++	>40	8.6	44 (10)	14 (5) 40 (10)		+42 (5) +12 (10)	59 (0.5)	0/48 (10) 38/48 (80)
13b	+	>40	>10	24 (10)	18 (5)		16 (5)		0/48 (10)
Ia	+++	13.8	4.3	48 (5)	51 (10)	1 (++)	59 (5)	100 (0.1)	14/48 (5) 34/48 (10)
Ib	+	3.7	5.3	47 (10)	57 (10)	1 (++)	25 (5)	99 (0.5)	29/48 (5) 48/48 (10)
Δ^9-THC	+++	27.2	43	36 (5)	39 (10)	4 (++)	15 (5)	29 (1)	45/48 (10)

[a] In the Dopa test, results are graded as + (slight), ++ (moderate), and +++ (marked) potentiation of *dl*-Dopa effects. [b] RTF = rat tail flick and W = acetic acid writhing tests. [c] In the mouse fighting test, values are percent decrease in fighting; + indicates an increase; three pairs of mice per dose. [d] In the rat motor activity test and methamphetamine antagonism tests, values are percent decrease in motor activity; + indicates as increase. [e] Minimum dose producing ataxia in dogs, two or more dogs per dose. [f] TST is the change in total sleep time (minutes) from paired control experiments, 12 h after drug, two or more cats per dose; (-) indicates a decrease in total sleep time. [g] Hyperexcitability index = sum of responses over maximum score of 48. [h] All doses are oral and in milligrams per kilogram and were given as a suspension in olive oil and 0.5% methylcellulose except for sedative-hypnotic studies in which drugs were mixed with cat food. For the mouse fighting, rat motor activity, methamphetamine antagonism, sedative-hypnotic, and hyperexcitability tests, doses are enclosed in parentheses.

N-oxides, but they were found to be less active.

Chemistry. The 5*H*-[1]benzopyrano[4,3-*c*]pyridines (**2a,b**) were obtained by heating **1a** and **1b** with 10% palladium on carbon in xylene (Scheme I). Reaction of **2a** with acetic anhydride and ethyl chloroformate yielded the acetyl and ethoxycarbonyl derivatives **3** and **4**, re-

Scheme I



a, R = $CH(CH_3)CH(CH_3)$-*n*-C_5H_{11}
b, R = $CH(CH_3)(CH_2)_3$-C_6H_4-*p*-F

spectively. Condensation of **2a** with 4-piperidinobutyric acid hydrochloride in the presence of dicyclohexylcarbodiimide (DCC) in methylene chloride gave a water-soluble basic ester derivative **5**.[6] The phenolic ethers **6–10** were prepared by alkylation of **2a** and **2b** with the appropriate halides and sodium methoxide in dimethylformamide. The basic phenolic ethers **11** and **12** were obtained by heating 10-(3-chloropropyloxy)-5,5-dimethyl-8-(1,2-dimethylheptyl)-5*H*-[1]benzopyrano[4,3-*c*]pyridine with piperidine or morpholine in the presence of potassium iodide in 2-butanone. Compounds **2a,b** were converted to the *N*-oxides **13a,b** by *m*-chloroperbenzoic acid in chloroform.

Pharmacology. These compounds were studied in selected pharmacological tests (Table II) in mice, rats, and dogs, using methods previously described.[6]

Antidepressant Activity. Compounds were tested in the mouse Dopa potentiation test. Compounds **2a** and **2b** were the most active; **13a** was only moderately active; and the remaining were only slightly active.

Analgesic Activity. Compounds were evaluated by using the tail-flick method in the rat and the writhing method in the mouse. Compounds **2a** and **2b** were also the most active in both tail-flick and writhing tests; **3**, **4**, **5**, and **13a** were active in the writhing test; **13a** was relatively inactive in the tail-flick test.

Tranquilizer Activity. The tests for tranquilizer or antianxiety activity included the mouse fighting, rat motor activity, and dog ataxia tests. The most active compound in the mouse fighting test was **2b**. Compounds **2a**, **3**, **6**, **7**, and **13a** were moderately active. In rat motor activity, **2a**, **3**, **4**, and **5** were the most potent, whereas **2b** was much less active. In the dog ataxia test, **2a** was the most active.

Antipsychotic Activity. Activity in this test was determined by measuring the reduction of methamphetamine (Desoxyn)-induced hyperactivity in the rat. Compounds **2a** and **4** had the best activity in this series; **2b**, **3**, and **5** were moderately active.

Sedative–Hypnotic Activity. Sleep-inducing properties were evaluated in cats implanted with chronic indwelling electrodes for continuous measurement of EEG, neck muscle, and eye movement potentials. Compound **2a** was the most potent in the series; however, **6**, **7**, **9**, **10**, and **13a** also had moderate activity.

Hyperexcitability Studies. Compounds in the cannabinoid series produce a characteristic hyperexcitability reaction (increased sensitivity to tactile sensory stimuli) in several animal species.[5] The hyperexcitability studies were carried out in male, Long–Evans, black-hooded rats (Simonsen), weighing between 90 and 120 g. The animals were randomly divided into groups of four and, after oral drug administration, were placed in individual containers in a sound-attenuated room. At intervals of 1, 2, 3, and 4 h, each animal was observed for three types of behavioral responses to tactile stimulation with a wooden rod consisting of (1) an exaggerated motor reaction, (2) squeaking, and (3) biting. A maximum score of 16 could be obtained for each of the responses (four animals × four time periods = 16). A hyperexcitability index was calculated by dividing the sum of the three behavioral response scores by the maximum possible score of 48.

Discussion

Compound **2a** was generally the most active in this series with **2b** being only slightly less active, indicating that the potency of nitrogen-containing heterocyclic cannabinoids can be maintained or even increased slightly by aromatizing the hydroheteroaromatic ring to a pyridine ring. By modifying the phenolic hydroxy group with an ester linkage, compounds such as **3**, **4**, and **5** lost antidepressant activity but retained analgetic properties, rat motor depressant activity, and rat methamphetamine antagonism activity. However, with the formation of an ether linkage on the phenolic hydroxy, compounds **6–12** invariably lost most of their CNS depressant properties. Surprisingly, **6**, **7**, **9**, **10**, and **13a** retained moderate sedative–hypnotic activity; **6** and **9** have been identified as potentially useful sedative–hypnotic agents because of their sleep-inducing properties in cats, coupled with a lack of cannabinoid-like hyperexcitability in rats.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting apparatus and are uncorrected. IR and NMR were determined for most of the compounds.

10-Hydroxy-5,5-dimethyl-8-(1,2-dimethylheptyl)-5*H*-[1]benzopyrano[4,3-*c*]pyridine (2a). A mixture of 2.23 g (0.005 mol) of 2-benzyl-10-hydroxy-5,5-dimethyl-8-(1,2-dimethylheptyl)-1,2,3,4-tetrahydro-5*H*-[1]benzopyrano[4,3-*c*]pyridine (**1a**),[1] 0.8 g of 10% Pd/C, and 100 mL of xylene was stirred and refluxed for 24 h. The warm mixture was filtered to remove the catalyst and the filtrate was evaporated in vacuo; the residue was recrystallized.

8-[5-(4-Fluorophenyl)-2-pentyl]-10-hydroxy-5,5-dimethyl-5*H*-[1]benzopyrano[4,3-*c*]pyridine (2b). The procedure for the preparation of **2a** was followed using **1b**.[2]

10-Acetoxy-5,5-dimethyl-8-(1,2-dimethylheptyl)-5*H*-[1]benzopyrano[4,3-*c*]pyridine (3). A mixture of 3.53 g (0.01 mol) of **2a**, 1.22 g (0.012 mol) of acetic anhydride, and 5 mL of pyridine was stirred at room temperature for 24 h. The mixture was evaporated in vacuo, and the residue was taken up with ether. The ether solution was washed with H_2O, dried over sodium sulfate, and evaporated to give a gum which was purified by chromatography.

10-Ethoxycarbonyloxy-5,5-dimethyl-8-(1,2-dimethylheptyl)-5*H*-[1]benzopyrano[4,3-*c*]pyridine (4). Redistilled ethyl chloroformate (4.34 g, 0.04 mol) was added dropwise to a stirred solution of 3.53 g (0.01 mol) of **2a** in 100 mL of pyridine. After stirring at room temperature for 20 h, the solution was evaporated in vacuo. The residue was taken up in $CHCl_3$, washed with H_2O, and dried over sodium sulfate. After removal of the solvent, the residue was chromatographed.

5,5-Dimethyl-8-(1,2-dimethylheptyl)-10-[4-(piperidino)butyryloxy]-5*H*-[1]benzopyrano[4,3-*c*]pyridine Hydrochloride (5). A mixture of 3.53 g (0.01 mol) of **2a**, 2.07 g (0.01 mol) of γ-piperidinobutyric acid hydrochloride, 2.16 g (0.0105 mol) of dicyclohexylcarbodiimide, and 160 mL of CH_2Cl_2 was stirred at room temperature for 20 h. The mixture was cooled and filtered, and the filtrate was concentrated to give a gummy residue which was dissolved in 12.5 mL of CH_2Cl_2–50 mL of cyclohexane. After cooling overnight, the solution was filtered to remove a small

amount of insoluble material. The filtrate was evaporated in vacuo, and the residue was crystallized.

10-Methoxy-5,5-dimethyl-8-(1,2-dimethylheptyl)-5*H*-[1]benzopyrano[4,3-*c*]pyridine (6). A solution of 3.53 g (0.01 mol) of **2a** in 100 mL of DMF containing 0.59 g (0.011 mol) of freshly prepared sodium methoxide was warmed on a steam bath for 5–10 min. After cooling to room temperature, the stirred solution was treated dropwise with 1.7 g (0.012 mol) of methyl iodide. The mixture was stirred at room temperature for 18 h, diluted with 100 mL of H_2O, and extracted with petroleum ether (bp 30–60 °C). The combined extracts were washed with H_2O, dried over sodium sulfate, and concentrated. The residue was purified by chromatography.

Compound **7** was prepared as above; **8** and **9** were obtained by using the appropriate bromides.

10-(Cyclopropylmethoxy)-5,5-dimethyl-8-(1,2-dimethylheptyl)-5*H*-[1]benzopyrano[4,3-*c*]pyridine (10). A mixture of 4.95 g (0.014 mol) of **2a**, 0.96 g (0.02 mol) of NaH (50% suspension in oil), and 5 mL of DMF was heated, with stirring, at 80 °C for 2 h. The solution was allowed to cool and 0.5 g (0.003 mol) of KI and 1.81 g (0.02 mol) of cyclopropylmethyl chloride were added. The mixture was stirred at 80 °C for 3 h and then at room temperature overnight. To the mixture was added 75 mL of H_2O which was extracted with petroleum ether (bp 30–60 °C). The combined extracts were washed with H_2O, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by chromatography.

10-(3-Chloropropyloxy)-5,5-dimethyl-8-(1,2-dimethylheptyl)-5*H*-[1]benzopyrano[4,3-*c*]pyridine. A mixture of 7.06 g (0.02 mol) of **2a**, 1.01 g (0.024 mol) of NaH (57% suspension in oil), and 150 mL of DMF, under N_2, was warmed to effect solution. After cooling to room temperature, the stirred solution was treated dropwise with a solution of 3.77 g (0.024 mol) of 1-bromo-3-chloropropane in 5 mL of DMF. After stirring for 17 h, the mixture was diluted with H_2O and extracted with petroleum ether (bp 30–60 °C). The combined extracts were washed with H_2O, dried over sodium sulfate, and concentrated in vacuo. The residue was purified by chromatography using a Florisil column and $CHCl_3$. Anal. ($C_{26}H_{36}ClNO_2$) C, H, N.

5,5-Dimethyl-8-(1,2-dimethylheptyl)-10-(3-piperidinopropyloxy)-5*H*-[1]benzopyrano[4,3-*c*]pyridine (11). A mixture of 3.01 g (0.007 mol) of 10-(3-chloropropyloxy)-5,5-dimethyl-8-(1,2-dimethylheptyl)-5*H*-[1]benzopyrano[4,3-*c*]pyridine, 1.79 g (0.021 mol) of piperidine, 1.16 g (0.007 mol) of powdered KI, and 35 mL of 2-butanone was stirred and refluxed under N_2, for 42 h. The mixture was evaporated in vacuo, and the residue was triturated with H_2O and extracted with $CHCl_3$. The extracts were washed with H_2O, dried over sodium sulfate, and concentrated. The residue was purified by chromatography on a Florisil column using graded CH_3OH–$CHCl_3$ mixtures for elution. The dihydrochloride was prepared by passing HCl gas to the ether solution of the base, filtering, and recrystallizing.

Compound **12** was prepared in the same manner.

10-Hydroxy-5,5-dimethyl-8-(1,2-dimethylheptyl)-5*H*-[1]benzopyrano[4,3-*c*]pyridine *N*-Oxide (13a). A solution of 3.05 g (0.015 mol) of 85% *m*-chloroperbenzoic acid in 40 mL of $CHCl_3$ was added dropwise to a stirred, ice-cooled solution of 3.53 g (0.01 mol) of **2a** in 50 mL of $CHCl_3$. After stirring at room temperature for 72 h, the mixture was shaken twice with aqueous $NaHCO_3$, washed with H_2O, and dried over sodium sulfate. After removal of the solvent, the residue was crystallized.

Compound **13b** was similarly prepared.

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Antimycotic Imidazoles. 2. Synthesis and Antimycotic Properties of 1-[2-(Arylalkyl)-2-phenylethyl]-1*H*-imidazoles

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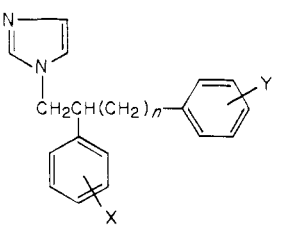
Synthesis of 1-[2-(arylalkyl)-2-phenylethyl]-1*H*-imidazoles was accomplished starting from the corresponding phenylacetonitriles. Via successive alkylation, conversion to the corresponding ester, and sodium borohydride–lithium iodide reduction, β-phenylalcanols were obtained. These alcohols were mesylated and then refluxed with imidazole in dimethylformamide to yield the title compounds, which were active in vitro against dermatophytes, yeasts, other fungi, and gram-positive bacteria. Some were also active in vivo against *Candida albicans*.

In a previous paper[1] the synthesis and antimycotic activity was described of a series of 1-(2-alkyl-2-phenylethyl)-1*H*-imidazoles. The present paper deals with the antimycotic activity of the analogous 1-[2-(arylalkyl)-2-phenylethyl]-1*H*-imidazoles (I). This class of compounds was synthesized by the same pathway described before.[1] In this case also the use of DMF–PhH mixtures prevented the formation of bis-alkylated phenylacetonitriles. Sterically hindered phenylacetonitriles in this case also had to be converted to the corresponding esters by a two-step pathway via the carboxylic acid (Scheme I). The new compounds are summarized in Tables I–V. The title compounds were tested against a large number of microorganisms by the procedure described by Godefroi et al.[2]



I

Fungi used in preliminary in vitro experiments are