appropriate N-deprotected pentapeptide in buffer solution. The water and buffer salts were removed by freeze–drying, redissolving the residue in water (200 mL), and redrying on an Edwards EF03 freeze–drying apparatus as 10^{-1} to 10^{-2} torr.

[(2-Amino-5-hydroxy-2-indanyl)carbonyl]glycylglycyl-L-phenylalanyl-L-leucine methyl ester (2e) was prepared as above from **2d** in 13% yield: mp 173–176 °C; TLC (silica) R_f (chloroform/methanol/acetic acid, 120:90:5) 0.68; IR (KCl) 3395, 3358, 3315, 3280, 3080, 3035, 2960, 2925, 2860, 1750, 1690, 1652, 1635, 1585, 1558, 1540, 1525, 1508 cm^{-1}; NMR ($CDCl_3$, 220 MHz) 0.82 [m, 6 H, leucine δ-$(CH_3)_2$], 1.50 (m, 2 H, leucine β-CH_2), 1.95. (m, 1 H, leucine γ-CH), 2.62 (m, 2 H, phenylalanine β-CH_2), 2.96 (m, 4 H, indan 1- and 3-protons), 3.62 (s, 3 H, leucine OCH_3), 3.65 (br s, replaceable with D_2O, NH_2 and OH), 3.69 (m, 2 H, one of glycine α-CH_2's), 3.75 (m, 2 H, one of glycine α-CH_2's), 4.24 (m, 1 H, leucine α-CH), 4.60 (m, 1 H, phenylalanine α-CH), 6.50–7.16 (m, 8 H, aromatic protons), 8.03 (m, 2 H, replaceable with D_2O, 2 NH), 8.34 (m, 1 H, replaceable with D_2O, NH) 8.42 (m, 1 H, replaceable with D_2O, NH). Anal. ($C_{30}H_{39}N_5O_7$) C, H, N; amino acid (after acidic hydrolysis): **2a**, 0.94; Gly, 2.03; Phe, 1.01; Leu, 1.00.

[(2-Amino-6-hydroxy-2-tetralinyl)carbonyl]glycylglycyl-L-phenylalanyl-L-leucine methyl ester (3e) was prepared as above from **3d** in 34% yield: mp 100–104 °C; TLC (silica) R_f (chloroform/methanol/acetic acid, 120:90:5) 0.70; IR (KCl)) 3270, 3055, 3020, 2950, 2930, 2860, 1740, 1690, 1675, 1645, 1565, 1546, 1500 cm^{-1}; NMR ($CDCl_3$, 300 MHz) 0.80 and 0.85 [2 d, 6 H, leucine δ-$(CH_3)_2$], 1.33 (m, 2 H, leucine β-CH_2), 1.51 (m, 1 H, leucine γ-CH), 1.56 (m, 2 H, tetralin 3-protons), 3.06 (m, 2 H, phenylalanine β-CH_2), 3.07 (m, 4 H, tetralin 1- and 4-protons), 3.65 (s, 3 H, leucine OCH_3), 3.82 (m, 2H, one of glycine α-CH_2's), 3.93 (m, 2 H, one of glycine α-CH_2's), 4.30 (br s, 3 H, replaceable with D_2O, NH_2 and OH), 4.47 (m, 1 H, leucine α-CH), 4.70 (m, 1 H, phenylalanine α-CH), 6.56–7.40 (m, 8 H, aromatic protons), 7.00 (m, 2 H, replaceable with D_2O, 2 NH), 7.42 (m, 1 H, replaceable with D_2O, NH), 8.43 (m, 1 H, replaceable with D_2O, NH). Anal. ($C_{31}H_{41}N_5O_7$) C, H, N; amino acid (after acidic hydrolysis): **3a** no color reaction with ninhydrin; Gly, 2.08; Phe, 1.00; Leu, 1.00.

Pharmacology. Compounds were evaluated for analgesic properties in albino mice (Tuck, TFW strain) by the following procedures: in vitro testing was carried out by measuring the inhibition of electrically stimulated contractions of the guinea pig ileum myenteric plexus muscle using the method of Kosterlitz and Watt[13] and by measuring the inhibition of mouse vas deferens tissue after stimulation wth twin rectilinear pulses 10-ms apart.[14] In vivo evaluation was carried out by using the mouse hot-plate test.[15]

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Registry No. **2a**, 33709-81-8; **2b**·HCl, 84802-81-3; **2c**, 84802-82-4; **2d**, 84802-83-5; **2e**, 73309-72-5; **3a**, 84809-70-1; **3b**·HCl, 84802-84-6; **3c**, 84802-85-7; **3d**, 84802-86-8; **3e**, 73301-07-2; **4**, 68709-94-4; benzyl bromide, 100-39-0; carbobenzyloxy chloride, 501-53-1.

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Antidepressant Activity of 5-Aryl-2,3,5,6-tetrahydroimidazo[2,1-*a*]isoquinolin-5-ols

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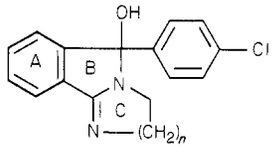
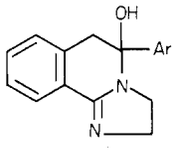
A series of 5-aryl-2,3,5,6-tetrahydroimidazo[2,1-*a*]isoquinolin-5-ols was prepared and evaluated for potential antidepressant activity in the reserpine-induced hypothermia model and selected central nervous system and autonomic activity tests. Several members of the series, notably the 4-chloro- and 4-fluorophenyl analogues, demonstrated pharmacological activity in the range of imipramine. Both compounds provided a marked potentiation of the 5-hydroxytryptophan-facilitated monosynaptic spike in the spinal cat preparation.

During the development of the anorectic agent mazindol (1, Sanorex, Teronac), it was found that the compound produced in animals a profile of CNS activity between that



1, n = 1
2, n = 2
3, n = 3



4

observed with the centrally acting sympathomimetics and the antidepressant agents amitriptyline and imipramine.[1] Evidence for the latter activity was noted from antagonism of reserpine-induced lowering of body temperature in mice and antagonism of tetrabenazine-induced catalepsy in rats.

The six- and seven-member ring C homologues **2** and **3** possess very weak anorectic activity[2] and and appear to be devoid of CNS activity.[3] In an attempt to determine the effect of modifying the size of ring B of mazindol (1), we prepared and evaluated 5-(*p*-chlorophenyl)-2,3,5,6-tetrahydroimidazo[2,1-*a*]isoquinolin-5-ol (**4**, Ar = 4-ClC_6H_4) for anorectic and antidepressant activity. The substance showed minimum anorectic activity in rats but was a potent antagonist of reserpine-induced hypothermia in mice. This finding prompted us to prepare a number of analogues of **4** and evaluate them for potential antidepressant activity.

Chemistry. The synthesis of **4** was carried out by reaction of the recently reported[4] dilithium reagent of 2-

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Table I. Pharmacological Data Obtained with 5-Aryl-2,3,5,6-tetrahydroimidazo[2,1-*a*]isoquinolin-5-ols (**4**)

compd	Ar	res hyp rev:[a] ED_{50} (mice), mg/kg ip 2 h	4 h	DR-VR,[b] mg/kg iv	LD_{50} (mice), mg/kg ip	general CNS and autonomic act. (mice),[d] mg/kg ip: test dose, mg/kg	clon conv:[c] CD_{50}	hyperact.:[e] ED_{50}	hypersen.:[f] ED_{50}	hyperaes.:[g] MD	Str tail.:[h] MD	agg res.:[i] MD	exopht.:[j] MD	piloerect.:[k] MD
4a	C_6H_5	5.0	>9.4		37.5	12.5	NT	12.5	NA	9.4	NA	NA	4.7	NA
4b	2-FC_6H_4	5.1	>11.5		35.5	NT	NT							
4c	3-FC_6H_4	0.7	5.2		21.0	12.5	NT	12.5	WK	9.4	9.4	9.4	9.4	NA
4d	4-FC_6H_4	0.06	10	0.3–1.0	76.9	25.0	75.0	25.0	25.0	18.8	9.4		9.4	18.8
4e	2-ClC_6H_4	6.1	11.5		34.4	25.0	37.5	NA	NA	18.8	25.0	NA	9.4	NA
4f	3-ClC_6H_4	2.1	11.5		37.5	NT	37.5							
4g	4-ClC_6H_4	0.025	6.4	>1.0	75.0	25.0	37.5	25.0	NA	37.5	18.8		18.8	NA
4h	2,4-$Cl_2C_6H_3$	5.4	>25.6	>3.0	81.3	50.0	75.0	NA	NA	NA	NA	NA	NA	NA
4i	3,4-$Cl_2C_6H_3$	1.6	>25.6	0.1–0.3	150.0	150.0	NT	WK	150.0	NA	NA	NA	NA	NA
4j	4-$CH_3C_6H_4$	>25.6	>25.6		84.1	50	75.0	NA	37.5	37.5	37.5	NA	18.8	NA
4k	3-$CF_3C_6H_4$	1.9	>25.6	0.3–1.0	50.0	50	75.0	NA	NA	37.5	NA	NA	37.5	37.5
4l	4-$CH_3OC_6H_4$	8.4	25.6		137.5	50	37.5	NA	50	37.5	18.8	NA	18.8	37.5
4m	3,4-$OCH_2OC_6H_3$	0.1	0.5		10.2	12.5	18.8	NA	12.5	4.7	4.7	NA	4.7	9.4
4n	$C_6H_5CH_2$	5.9	>25.6		37.5	25.0	37.5	NA	25.0	NA	NA	NA	NA	NA
4o	3-pyridyl	7.0	>25.6		68.8	50.0	75.0	NA	NA	NA	NA	NA	NA	NA
4p	4-pyridyl	2.3	3.3		37.9	25.0	37.5	NA	WK	18.8	18.8	NA	18.8	NA
4q	2-thienyl	4.5	>25.6		68.8	25.0	75.0	NA	25.0	18.8	18.8	NA	18.8	25.0
1 (mazindol)		0.05	0.12											
imipramine		6.3	12.8											

[a] Reversal of reserpine induced hypothermia. [b] Dorsal-ventral root preparation in cats. Value is dose that induced enhancement of the 5-hydroxytryptophan-facilitated monosynaptic spike. [c] Clonic convulsions: values are doses at which convulsions occurred in 50% of animals. [d] MD = minimal dose that effect was noted; NA = not active; NT = not tested; WK = weak. NA and WK refer to the values found when the amount of drug given was that listed in the test dose column. [e] Hyperactivity. [f] Hypersensitivity. [g] Hyperaesthesia. [h] Straub tail. [i] Aggressiveness. [j] Exophthalmos. [k] Piloerection.

Table II. Physical Properties of **4**[a]

no.[b]	mp, °C (recrystn solvent)[c]	yield, %	emp formula	anal.[d]
4a	219–221 (A)	28	$C_{17}H_{16}N_2O$	C, H, N
4b	193–194 dec (B)	46	$C_{17}H_{15}FN_2O$	C, H, N
4c	210 dec (C)	23	$C_{17}H_{15}FN_2O$	C, H, N
4d	189–190 (D)	58	$C_{17}H_{15}FN_2O$	C, H, N
4e	177–179 (E)	56	$C_{17}H_{15}ClN_2O$	C, H, Cl, N
4f	206–208 (D)	59	$C_{17}H_{15}ClN_2O$	C, H, Cl, N
4g	199–200 (F)	51	$C_{17}H_{15}ClN_2O$	C, H, Cl, N
4h	201 dec (G)	64	$C_{17}H_{14}Cl_2N_2O$	C, H, Cl, N
4i	212–214 (D)	47	$C_{17}H_{14}Cl_2N_2O$	C, H, Cl, N
4j	181–183 (E)	57	$C_{18}H_{18}N_2O$	C, H, N
4k	194–196 dec (H)	27	$C_{18}H_{15}F_3N_2O$	C, H, N
4l	185 dec (H)	35	$C_{18}H_{18}N_2O_2$	C, H, N
4m	176–178 (E)	36	$C_{18}H_{16}N_2O_3$	C, H, N
4n	163–165 dec (D)	21	$C_{18}H_{18}N_2O$	C, H, N
4o	162–163 (D)	41	$C_{16}H_{15}N_3O$	C, H, N
4p	162–164 (D)	37	$C_{16}H_{15}N_3O$	C, H, N
4q	166–168 (G)	40	$C_{15}H_{14}N_2OS$	C, H, N, S

[a] All compounds in this table gave ^1H NMR and IR spectra consistent with structure **4**. [b] See Table I for definition of Ar in compounds **4**. [c] Recrystallization solvents: A, $CHCl_3$; B, MeOH-EtOH; C, Et_2O-MeOH; D, CH_2Cl_2-EtOH; E, CH_2Cl_2; F, MeOH-C_6H_6; G, EtOH; H, Et_2O-petroleum ether. [d] Unless otherwise stated, the analyses are within ±0.4% of the theoretical values.

(*o*-methylphenyl)imidazoline (**5**) with an aryl, arylalkyl, or heteroaryl ester **6** in THF at −20 °C. With this procedure, the compounds listed in Table II were isolated in yields of 21 to 64%.

Pharmacology. Antagonism of reserpine-induced hypothermia by those imidazo[2,1-*a*]isoquinolin-5-ols described in the present report is given in Table I. The most potent antagonists 2 h after dosing were the 4-Cl (**4g**), 4-F (**4d**), and 3,4-OCH_2O (**4m**) derivatives with ED_{50} values of 0.10 mg/kg or less. Substituting a Cl or F atom in position 3 (**4c,f**) or 4 (**4d,g**) provided relatively good activity, while the 2-isomers (**4b,e**) were weaker. Relative to the 4-Cl isomer (**4g**), placement of a second Cl atom in the 3-position (3,4-Cl_2; **4i**) led to reduced potency, while placement in the 2-position (2,4-Cl_2; **4h**) resulted in a greater loss of potency. The 3-CF_3 derivative **4k** gave activity similar to the 3-Cl derivative (**4f**), while the 4-OCH_3 derivative (**4l**) was weak and 4-CH_3 derivative (**4j**) was inactive up to 25.6 mg/kg. Replacement of the phenyl group at position 5 by a pyridyl (**4o,p**) or thienyl (**4q**) group provided a slight reduction in activity relative to **4g**. In summary, tests in which antagonism of reserpine-induced hypothermia was evaluated 2 h following administration of the test substance led to the following order of activity: 4-Cl > 4-F ≈ 3,4-OCH_2O > 3-F > 3,4-Cl_2 ≈ 3-CF_3 ≈ 3-Cl ≈ 4-pyridyl > 2-thienyl > H ≈ 2-F ≈ 2,4-Cl_2 ≈ $C_6H_5CH_2$ ≈ 2-Cl > 3-pyridyl ≈ 4-OCH_3 ≫ 4-CH_3.

At 4 h the ability of compounds **4** to antagonize reserpine was considerably weaker, indicating that this class of agents was relatively short acting in comparison to mazindol (**1**) or imipramine. Only 5 of the 16 compounds that were studied had ED_{50} values similar to or better than imipramine, while only **4m** approached that of mazindol. In order of decreasing activity these compounds were the 3,4-OCH_2O (**4m**), 4-pyridyl (**4p**), 3-F (**4c**), 4-Cl (**4g**), 4-F

(**4d**), 2-Cl (**4e**), and the 3-Cl (**4f**) derivatives.

The general CNS and autonomic activities of compounds **4** in mice are listed in Table I. At the doses tested the compounds had little or no effect on hypomotility, docility, loss of righting reflex, ataxia, or hind-limb placing. Marked central activity characterized by the behavioral alteration in hypermotility, exophthalmos, piloerection, hypersensitivity, hyperaesthesia, and aggressiveness was observed in the 3-F (**4c**), 4-F (**4d**), and 4-Cl (**4g**) analogues. The other members of the series were either very weak or devoid of these activities.

Toxic signs, as primarily evidence by clonic convulsions (Table I), were widespread with this group of compounds. In addition, tremors and salivation were noted at or slightly below lethal doses for the 3,4-OCH_2O (**4m**) and 3-CF_3 (**4h**) derivatives.

Based on the overall favorable profile exhibited in regards to the reversal of reserpine-induced hypothermia, general CNS and autonomic activity, and a good ratio of LD_{50} to clonic convulsions, the compounds **4d** (4-F) and **4g** (4-Cl) were selected for evaluation in the dorsal root–ventral root (DR–VR) preparation in cats. Both compounds provided a marked potentiation of the 5-hydroxytryptophan-facilitated monosynaptic spike (Table I). Since potentiation in the DR–VR procedure is indicative of a potential antidepressant agent, both agents were recommended for further studies in this area.

Experimental Section

Chemical Synthesis. Melting points were determined in a Thomas-Hoover capillary melting point apparatus and have not been corrected. For compounds **4**, ^1H NMR spectra were obtained on a Varian Associates A-60 spectrometer in $CDCl_3$ or Me_2SO-d_6, and IR spectra (KBr) were determined with a Perkin-Elmer Infracord. In all cases, the spectra were consistent with the assigned structure. The UV spectra for a selected group of compounds were obtained in 95% EtOH or 95% EtOH–2 N HCl (9:1) solvent on a Cary Model 15 spectrophotometer. Thin-layer chromatography (TLC) was carried out on compounds by using glass plates coated with silica gel HF-254 (E. Merck AG) with the solvent system $CHCl_3$–MeOH (9:1) for the purpose of establishing homogeneity.

Pharmacology Testing. Acute Toxicity. Aggregated groups of five Royal Hart Swiss Webster male mice (18-25 g) were placed in 7 × 7 × 14 in. wire cages. All mice were fasted overnight, but a 20% glucose solution was available ad libitum. The test compound was administered at three dose levels, and deaths were recorded at 2, 24, 48, and 72 h after drug administration. LD_{50} values (Table I) were estimated by probit analysis according to Reed and Muench[5] or Miller and Tainter.[6]

Behavioral Analysis. The test procedure is patterned after the general activity and acute toxicity (GAAT) screen described by Irwin.[7] Groups of four male Royal Hart mice (18–25 g) were dosed ip with the test compound in the appropriate vehicle and then observed for toxic signs and gross behavioral response from dose time to 60 min, whereupon a complete behavioral profile was carried out. Scores of 0–4 were assigned to the individual mouse for each parameter, and those scores were averaged to obtain an overall effect for the groups. When possible, the ED_{50} for each parameter was defined as the dose of compound that produces a mean score of 2. Measured parameters are given in Table I.

Reserpine-Induced Hypothermia in Mice. Experiments were performed in a room with an ambient temperature of 20–25 °C. Royal Hart male mice, 18–24 g, were housed in groups of five. In all groups, control rectal temperatures were taken at 2 h and immediately prior to administration of reserpine at 5 mg/kg ip. This dose has been shown in these laboratories to provide a maximum reduction in rectal temperature of 8.4 ± 1.8 (SD) °C after 3 h. One hour after reserpine administration, selected doses (10 animals per dose) of test drugs or saline were administered intraperitoneally, with rectal temperatures being recorded again 2 and 4 h later. The ED_{50} is defined as that dose of the substance that limited the reduction in rectal temperature to a maximum of 50% of what it would normally be at 2 or 4 h after reserpine dosing. The ED_{50} variation for mazindol at 2 h was ± 0.02 mg/kg based on 10 observations and ± 0.12 mg/kg at 4 h based on 12 observations.

5-Hydroxytryptophan-Induced Facilitation of Monosynaptic Spikes Induced in a Spinal Ventral Root by Stimulation of the Dorsal Root (DR–VR Procedure).[8] Male cats (2.2–2.6 kg) were anesthesized with ether, and the trachea was cannulated for subsequent artificial respiration. The left saphenous vein was cannulated for administration of test drug, and the right carotid artery was cannulated for blood pressure recording. The cat was mounted in a stereotaxic frame assembly (1404 David Kopf) and a C-1 section was performed. A priming dose of Flaxedil (gallamine triethiodide, 10.0 mg/kg iv) was injected, and additional doses were injected throughout the experiment when needed. The animal was then put on a Harvard respiration pump, and body temperature was maintained at 37.5 °C by a Thermistemp temperature controller, Model 71. The spinal column was bared from lumbar vertebrate 3 to the approximate distal end of the sacrum. All muscle attachments along both sides of dorsal processes were clamped for at least 1 min and then cut as close to the processes as possible. Rongeur forceps were used to expose the spinal cord by removing neural spinal processes of L-4, L-5, L-6, L-7, and the sacrum, while L-3 was left intact but cleared of all tissue. The exposed spinal cord was then immersed in extra heavy mineral oil maintained at 35 °C. The dura mater was carefully cut along a dorsal anterior–posterior plane, and its edges were pulled upward to raise the spinal cord. The exposed lumbar and sacral roots (L-5 to S-3) on both sides of the cord were either cut or crushed, and the distal end of the spinal cord was severed. The L-7 root was then severed before it exits the cord through the dura and stripped into its dorsal and ventral root components, each of which was draped over a custom-made bipolar platinum-tipped and glass-insulated electrode. The dorsal root was stimulated with a Grass S-4 stimulator via a stimulus isolation unit and the evoked potential from the ventral root was photographed with a Polaroid (Tektronix oscilloscope camera c-12) from a Tektronix Model 564 storage oscilloscope. Dorsal root stimulation was performed at a frequency of 0.2/s, with a duration of 0.1 ms, delay of 0.01 ms, and a voltage of 10 times threshold. The first large spike of the evoked potential represents a monosynaptic spinal reflex, while the succeeding small spikes represent polysynaptic reflexes. At this stage, one of the following procedures is followed: (1) the test drug is injected iv, and its direct effect on the mono- and polysynaptic reflexes is recorded, or (2) 5-hydroxytryptophan (5-HTP) is injected iv (25–75 μg/kg), and the known effect of the facilitation of the monosynaptic spike is recorded, and then the test drug is injected iv and its effect on the 5-HTP-induced facilitation is recorded.

Aryl Esters (6). A solution of substituted benzoic acid (0.25 mol, Aldrich Chemical Co.) and thionyl chloride (0.50 mol) in 400 mL of dry CH_2Cl_2 was refluxed for ca. 5 h and then allowed to stand overnight at room temperature. The solution was evaporated in vacuo, and the crude benzoyl chloride was dissolved in 50 mL of dry C_6H_6 and added dropwise to a freshly prepared solution of sodium methoxide (0.37 mol) in 450 mL of methanol. After standing overnight at room temperature, the mixture was evaporated in vacuo, and the residue was treated with 250 mL of CH_2Cl_2 and 100 mL of H_2O. The CH_2Cl_2 layer was separated, washed with H_2O, dried with anhydrous $MgSO_4$, and filtered, and the filtrate was concentrated in vacuo. The residue was then either distilled or crystallized to give the 2-F [bp 50–52 °C (1.5 mm)], 3-F [bp 72–75 °C (10 mm)], 2-Cl [bp 112–114 °C (16 mm)], 3-Cl [bp 94–95 °C (5 mm)], 4-Cl [mp 40–42 °C (pentane)], 3-CF_3 [bp

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82–84 °C (0.5 mm)], 4-OCH_3 [mp 47–48 °C (pentane)], and 3,4-OCH_2O [mp 49–50 °C (pentane)] methyl benzoate derivatives and the 2,4-Cl_2 [bp 83–85 °C (0.2 mm)] and 3,4-Cl_2 [bp 137–139 °C (10 mm)] ethyl benzoate derivatives.

The purity of these esters was confirmed by GLC and ^1H NMR. The esters used to prepare compounds **4a,d,j,n–q** were obtained from Aldrich Chemical Co.

5-Aryl-2,3,5,6-tetrahydroimidazo[2,1-*a*]isoquinolin-5-ols (4). General Procedure. A stirred solution of 8.0 g (0.05 mol) of 2-(*o*-methylphenyl)imidazoline in 200 mL of dry THF maintained under a N_2 atmosphere was treated dropwise with 105 mL (0.15 mol *n*-BuLi) of 1.6 M *n*-BuLi in hexane and then heated to 35 °C for ca. 4 h. The mixture was then immersed in a dry ice–acetone bath, cooled to an internal temperature of −25 °C, and treated dropwise with 0.10 mol of methyl or ethyl aryl ester **6** at such a rate that the temperature did not exceed −20 °C. After an additional 3 h at −20 °C, the reaction mixture was allowed to warm to 0 °C and then treated with 30 mL of saturated NH_4Cl solution. After standing overnight at room temperature, the mixture was concentrated in vacuo and then treated with 200 mL of CH_2Cl_2 and 100 mL of H_2O. The CH_2Cl_2 layer was separated, washed with H_2O, dried with anhydrous $MgSO_4$, and filtered, and the filtrate was then concentrated to give a solid that was crystallized from the appropriate solvent given in Table II.

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Registry No. **4a**, 56882-45-2; **4b**, 84774-99-2; **4c**, 56882-43-0; **4d**, 56882-41-8; **4e**, 56882-50-9; **4f**, 84775-00-8; **4g**, 56882-42-9; **4h**, 56882-51-0; **4i**, 56882-49-6; **4j**, 56882-46-3; **4k**, 56882-44-1; **4l**, 56882-47-4; **4m**, 56882-48-5; **4n**, 83634-04-2; **4o**, 60151-19-1; **4p**, 60099-37-8; **4q**, 60099-38-9; **5**, 8363-39-9; **6** (Ar = 2-FC_6H_4; R = CH_3), 394-35-4; **6** (Ar = 3-FC_6H_4; R = CH_3), 455-68-5; **6** (Ar = 2-ClC_6H_4; R = CH_3), 610-96-8; **6** (Ar = 3-ClC_6H_4; R = CH_3), 2905-65-9; **6** (Ar = 4-ClC_6H_4; R = CH_3), 1126-46-1; **6** (Ar = 3-$CF_3C_6H_4$; R = CH_3), 2557-13-3; **6** (Ar = 4-$CH_3OC_6H_4$; R = CH_3), 121-98-2; **6** (Ar = 3,4-$OCH_2OC_6H_4$; R = CH_3), 326-56-7; **6** (Ar = 2,4-$Cl_2C_6H_3$; R = CH_2CH_3), 56882-52-1; **6** (Ar = 3,4-$Cl_2C_6H_3$; R = CH_2CH_3), 28394-58-3.

1-[1-[2-[(3-Chlorobenzyl)oxy]phenyl]vinyl]-1*H*-imidazole Hydrochloride, a New Potent Antifungal Agent

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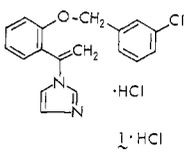
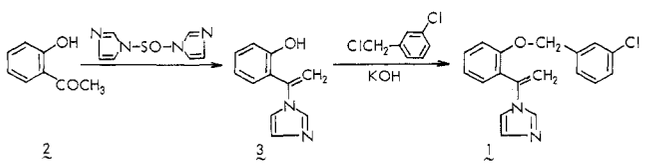
The synthesis and antifungal properties of 1-[1-[2-[(3-chlorobenzyl)oxy]phenyl]vinyl]-1*H*-imidazole hydrochloride (1·HCl) are described. Topical application of cream and gel formulation of 1·HCl showed high efficacy against guinea pig dermatophytosis.

Substances[1] containing the imidazole nucleus are known for their antimycotic activity and fall into two general classes: the poly(aryl)methylimidazoles (e.g., clotrimazole[2]) and the arylethylimidazoles (e.g., miconazole[3]). We describe here the preparation and properties of a potent new antifungal agent based on the 1-vinylimidazole skeleton, namely, 1-[1-[2-[(3-chlorobenzyl)oxy]phenyl]vinyl]-1*H*-imidazole hydrochloride (1·HCl), which is at present undergoing clinical investigation.[4]



1·HCl

Chemistry. The 1-vinylimidazole compound **3** was obtained by reaction of *N,N'*-thionyldiimidazole[5] with *o*-hydroxyacetophenone (**2**) in dichloromethane in good yield. Treatment of **3** with *m*-chlorobenzyl chloride in the presence of potassium hydroxide in dimethylformamide afforded **1**. Formation and purification as the hydrochloride salt gave 1·HCl.



2 3 1

Biological Data. In the agar dilution tests on Sabouraud's glucose agar and Bacto-yeast morphology agar, using inocula[6] of 1×10^6 cells per milliliter of yeasts or 1×10^6 conidia per milliliter of moulds and dermatophytes, 1·HCl exhibited a broad spectrum against a wide variety of fungi. 1·HCl inhibited typical dermatophyte species (seven strains of *Trichophyton mentagrophytes*, six of *Trichophyton rubrum*, two of *Microsporum canis*, one of *Microsporum gypseum*, and three of *Epidermophyton floccosum*) at MIC values 0.16–1.25 μg/mL. *Aspergillus spp.* (five strains) and *Penicillium spp.* (two strains) were sensitive at 0.63–5 μg/mL. However, *Candida* yeasts (eight strains of *Candida albicans*, two of *Candida tropicalis*, and one of *Candida guilliermondii*) and other yeasts (two strains

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