basis for future design of candidate irreversible inhibitors of phenylalanyl-tRNA synthetase. In addition to the guanidine or amidine function, these shall be characterized by (a) two phenyl rings, one for binding and the other to carry a reactive covalent-bond forming group, and (b) the structural features described here which will determine whether the inhibitor shall bind to the catalytically operative active site or a remote site of the enzyme.

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2-Phenethylimidazole Derivatives. Synthesis and Antimycotic Properties

Erik F. Godefroi,* Jack J. H. Geenen,

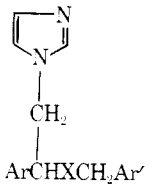
Department of Organic Chemistry, The University of Technology, Eindhoven, The Netherlands

Bert van Klingeren, and Leo J. van Wijngaarden

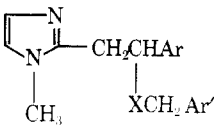
National Institute of Public Health, Bilthoven, The Netherlands. *Received September 24, 1974*

Compounds of type I (X = O, NH; Ar and Ar′ = phenyl or substituted phenyl; ten examples) were prepared and assayed against miconazole (II, X = O; Ar = Ar′ = 2,4-$Cl_2C_6H_3$) as potential antimycotic agents. Optimal activity was noted for I (X = O; Ar = Ar′ = 2,4-$Cl_2C_6H_3$), the direct analog of miconazole. It is about one-tenth as active.

N-Substituted phenethylimidazoles of type I (X = O, NH) have been shown to display potent in vitro and in vivo antifungal properties.[1,2] One of these, namely miconazole[3] (X = O; Ar = Ar′ = 2,4-$Cl_2C_3H_3$), is currently finding use in human medicine as an antimycotic agent. Continued interest in this class of compounds made us turn attention to the preparation and biological evaluation of members of type II, which bear relation to I in that the N-substituent, on having been transposed to C-2, has been replaced by a Me group. The results of these studies are herein reported.



I



II

X = O, NH

Chemistry. Recent work from our laboratories described a facile and high-yield process for transforming 1,2-dialkylimidazoles into N-substituted 2-(2-imidazolyl)acetophenones;[4] the method was therefore utilized to prepare ketones **2a,b.** To this end 1,2-dimethylimidazole (DMI) was treated respectively with *p*-chloro- and 2,4-dichlorobenzoyl chloride in Et_3N-containing MeCN to give enol esters **1a,b;** these were then hydrolyzed to **2a,b.** In its respective reactions with *p*-chloro- and 2,4-dichlorobenzylamine, ketone **2b** furnished solid condensation products in high yields. These were assigned enamine structures **3a,b** rather than those of the corresponding imines on the basis of vinyl proton signals at δ 5.01. Failure of $NaBH_4$ to bring about reduction of these enamines was therefore not surprising. Recourse was then taken to the use of $NaBH_3CN$, a reagent recently shown to be effective in reducing enamines under acidic conditions.[5] Under related circumstances **3a,b** were readily transformed into amines **4a,b** (Scheme I).

$NaBH_4$ reduction of ketones **2a,b** led to carbinols **5a,b.** The latter may formally be considered as stemming from the addition of DMI to aromatic aldehydes and should, in principle, also be accessible in one step from these components. 1,2-Dialkylimidazoles, however, tend to undergo electrophilic processes at C-5. This was shown to be so for hydroxymethylation[6] and also for the BuLi-induced lithiation as demonstrated by isolation of **6** on further treatment of the mixture with C_6H_5CHO.[7] In our group, treatment of DMI successively with C_6H_5Li and C_6H_5CHO gave approximately a 50:50 mixture of **6** and **5c** as shown by NMR data[8] (see Experimental Section). Even though these could be chromatographically separated, the method, not lending itself for indefinite scale up, was abandoned.

Alcohols **5a,b** were anionized (NaH–THF) and were subsequently treated with the appropriate benzyl chlorides to give ethers **7a–h;** these were isolated and assayed as nitrate salts (Table I).

Experimental Section

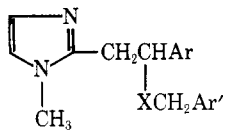
Chemistry. Melting points, taken on a Mettler FP1 apparatus, are uncorrected. Analytical samples had ir and NMR spectra compatible with assigned structures. Combustion data for C, H, and N, obtained by Messrs. P. van den Bosch and H. Eding of these laboratories, were within 0.4% of theory.

Compound 1b. To a solution of 43.2 g (0.45 mol) of DMI and 100 g (1.00 mol) of Et_3N in 400 ml of MeCN was added dropwise and with stirring below 10° 207 g (1.00 mol) of 2,4-Cl_2BzCl. After 1 hr at room temperature, 3 l. of H_2O and 1 l. of Et_2O were added to give, on filtration and recrystallization (C_6H_6–*i*-Pr_2O), 110 g (55%) of **1b,** mp 136–139°. Anal. ($C_{19}H_{12}Cl_4N_2O_2$) C, H, N.

2′,4′-Dichloro-2-[2-(1-methylimidazolyl)]acetophenone (2b). A solution of 67 g (0.15 mol) of **1b** in 450 ml of a 2:1 mixture of AcOH–HCl was refluxed for 3 hr. Solvent removal and repeated trituration of the residue with Me_2CO yielded, on filtration, 36.5 g (78%) of product hydrochloride. A small sample was recrystallized from *i*-PrOH–*i*-Pr_2O: mp 206–207°. Anal. ($C_{12}H_{10}Cl_2N_2O \cdot HCl$) C, H, N.

The main batch, taken up in H_2O and treated with $NaHCO_3$, gave crude, solid **2b.** It was dissolved in CH_2Cl_2 which was washed, dried, and evaporated, leaving **2b,** mp ~85°.

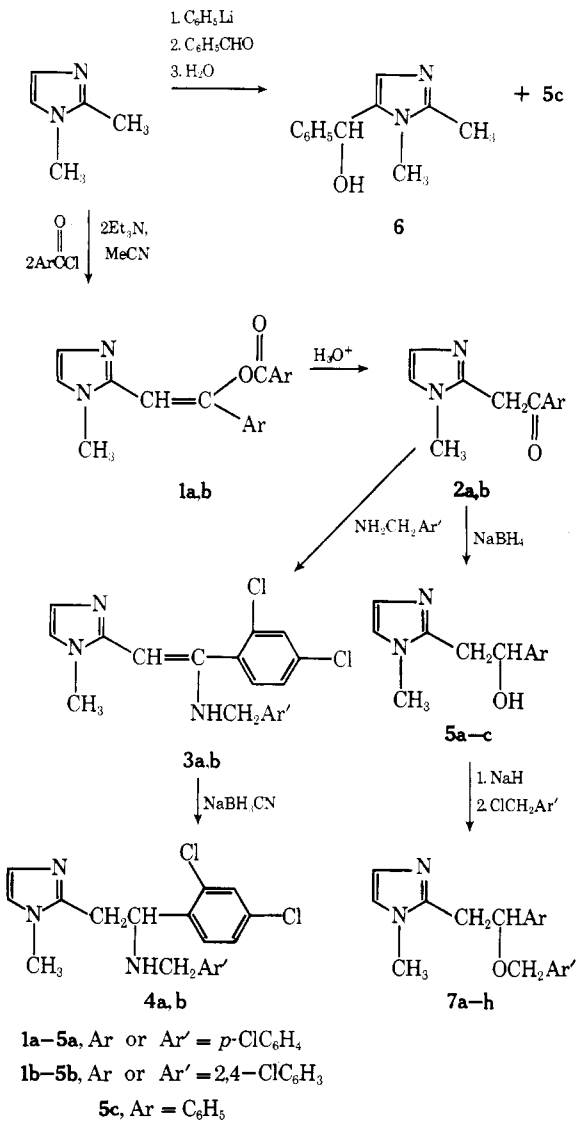
Table I. Compounds **4a,b** and **7a–h**



Compd	X	Ar	Ar′	Mp, °C	Formula[a]
4a	NH	2,4-$Cl_2C_6H_3$	*p*-ClC_6H_4	97–98	$C_{19}H_{18}Cl_4N_3$
4b	NH	2,4-$Cl_2C_6H_3$	2,4-$Cl_2C_6H_3$	89–90	$C_{19}H_{17}Cl_4N_3$
7a	O	*p*-ClC_6H_4	2,4-$Cl_2C_6H_3$	128–129	$C_{19}H_{17}Cl_3N_2O\cdot HNO_3$
7b	O	2,4-$Cl_2C_6H_3$	*p*-ClC_6H_4	127–128	$C_{19}H_{17}Cl_3N_2O\cdot HNO_3$
7c	O	2,4-$Cl_2C_6H_3$	*p*-BrC_6H_4	137–139	$C_{19}H_{17}BrCl_2N_2O\cdot HNO_3$
7d	O	2,4-$Cl_2C_6H_3$	*p*-$CH_3C_6H_4$	124–127	$C_{20}H_{20}Cl_2N_2O\cdot HNO_3$
7e	O	2,4-$Cl_2C_6H_3$	*p*-$CH_3OC_6H_4$	134–135	$C_{20}H_{20}Cl_2N_2O_2\cdot HNO_3$
7f	O	2,4-$Cl_2C_6H_3$	2,4-$Cl_2C_6H_3$	172–173	$C_{19}H_{16}Cl_4N_2O\cdot HNO_3$
7g	O	2,4-$Cl_2C_6H_3$	2,6-$Cl_2C_6H_3$	200–202	$C_{19}H_{16}Cl_4N_2O\cdot HNO_3$
7h	O	2,4-$Cl_2C_6H_3$	3,4-$Cl_2C_6H_3$	125–127	$C_{19}H_{16}Cl_4N_2O\cdot HNO_3$

[a] Analytical data for C, H, and N were within 0.4% of theory.

Scheme I



1a–5a, Ar or Ar′ = *p*-ClC_6H_4

1b–5b, Ar or Ar′ = 2,4-ClC_6H_3

5c, Ar = C_6H_5

4′-Chloro-2-[2-(1-methylimidazolyl)]acetophenone (2a). Hydrolysis of **1a** prepared as described for **1b** gave **2a** (72%), mp 124–126° on recrystallization from *i*-PrOH. Anal. ($C_{12}H_{11}ClN_2O$) C, H, N.

Compound 3b. Ketone **2b**, 6.72 g (0.025 mol), and 5.28 g (0.03 mol) of 2,4-$Cl_2C_6H_3CH_2NH_2$ in 100 ml of xylene containing a trace of toluenesulfonic acid were refluxed in a system allowing for azeotropic H_2O removal. After 3 hr solvent was removed, whereupon trituration of the residue with MeOH gave 7.0 g (65%) of white product, mp 92–95°. Analytical material was obtained from MeOH: mp 95–96°. Anal. ($C_{19}H_{15}Cl_4N_3$) C, H, N.

1-Methyl-2-[(2,4-dichlorobenzylamino)-2,4-dichlorophenethyl]imidazole (4b). A solution of 3.1 g (0.0072 mol) of **3b** in 75 ml of THF was treated with HCl gas until wet pH paper registered pH 3. $NaBH_3CN$, 0.469 g (0.0072 mol), in 5 ml of MeOH was then introduced. The mixture was then stirred at 25° for 1.5 hr while periodically readjusting the pH to 3 by means of HCl gas. Solvent was then removed; water, followed by an excess of 1 *N* NaOH, was added until the solution was strongly alkaline. The product was extracted into Et_2O, which was dried and evaporated. Trituration of the residue with *i*-Pr_2O gave 2.4 g (77%) of amine which was recrystallized from EtOH: mp 89–90°. Anal. ($C_{19}H_{17}Cl_4N_2$) C, H, N.

Compound 3a. Reaction of **2b** with *p*-$ClC_6H_4CH_2NH_2$ as described for **3b** gave **3a** in 81% yield. Analytical material (C_6H_6–*i*-Pr_2O) melted at 159–160°. Anal. ($C_{19}H_{16}Cl_3N_3$) C, H, N.

1-Methyl-2-[β-(*p*-chlorobenzylamino)-2,4-dichlorophenethyl]imidazole (4a). $NaBH_3CN$ reduction of **3a**, under conditions offered for **4b**, provided 70% of **4a**, mp (EtOH) 98–99°.

α-(1-Methylimidazol-2-ylmethyl)-2,4-dichlorobenzyl Alcohol (5b). To a stirred solution of 8.5 g (0.032 mol) of **2b** in 100 ml of MeOH was added portionwise and below 10° 0.7 g (0.018 mol) of $NaBH_4$. After 1 hr, the mixture was refluxed for another 0.5 hr; MeOH (80 ml) was then removed and 150 ml of H_2O was added. The mixture was acidified (concentrated HCl) and was refluxed for 10 min more. Alkalinization gave solid product. It was filtered off and taken up in hot xylene which, on separation from adhering H_2O and addition of petroleum ether, gave 7.7 g (90%) of carbinol: mp 171–172°. Anal. ($C_{12}H_{11}Cl_2N_2O$) C, H, N.

Reaction of DMI with C_6H_5Li and C_6H_5CHO Successively. To a solution of C_6H_5Li in Et_2O, prepared from 1.85 g of Li and 18.05 g of C_6H_5Br, was added in one portion at 0° 8.65 g (0.090 mol) of DMI in 25 ml of C_6H_6. The exchange was allowed to proceed for 30 min at 0°; the temperature was then lowered to −15° and 11.7 g (0.11 mol) of C_6H_5CHO was introduced. After 3 hr at this temperature 200 ml of H_2O was added. Product crystallized out and was removed by filtration; it was taken up in aqueous HCl. The filtrate Et_2O phase was also extracted with dilute HCl. Basification of the combined acidic layers gave the crude basic product components.

Part of this was purified by repeated crystallizations from aqueous DMF to give isomer **6**: mp 194–195°; NMR ($CDCl_3$) δ 3.38 (s, 3, NCH_3). Anal. ($C_{12}H_{14}N_2O$) C, H, N.

Another part of the crude mixture was subjected to column chromatography (silica gel, 10% EtOH in $CHCl_3$ as eluent) to give isomer-free **5c**: mp 141–143°; NMR ($CDCl_3$) δ 3.35 (s, 3, NCH_3). Anal. ($C_{12}H_{14}N_2O$) C, H, N.

NMR examination of the crude mixture and comparison of signals at δ 3.35 and 3.38 showed **5c** and **6** to be present in about equal amounts. Their total yield represented ~60%.

The preparation of ethers **7a–h** will be exemplified by **7f**.

1-Methyl-2-[β-(2,4-dichlorobenzyloxy)-2,4-dichlorophenethyl]imidazole (7f). To a slurry of 0.36 g of 80% NaH in oil (i.e.,

Table II. Antifungal and Antibacterial Activities of Compounds 4a,b and 7a–h[a]

Organism	4a	4b	7a	7b	7c	7d	7e	7f	7g	7h	Miconazole nitrate
Trichophyton rubrum	100	50	50	50	50	50	x	25	25	25	2.5
Trichophyton mentagrophytes	100	50	50	50	50	50	100	25	50	25	2.5
Microsporum gypseum	100	25	50	50	50	50	100	25	50	25	0.1
Epidermopython floccosum	x	100	x	100	x	100	x	50	100	x	0.1
Penicillium notatum	x	x	x	x	x	x	x	100	x	x	2.5
Aspergillus niger	x	100	100	100	100	100	x	50	100	50	2.5
Aspergillus fumigates	x	x	x	x	x	x	x	50	x	x	10
Candida albicans	x	100	100	x	x	x	x	100	100	x	2.5
Torulopsis glabrata	x	x	x	x	x	x	x	x	100	x	1
Saccharomyses cerevisiae	x	10	100	x	100	x	x	100	100	x	10
Staphylococcus aureus H	5	2.5	2.5	10	5	10	25	5	5	5	0.5
Staphylococcus aureus (multiresistent)	2.5	2.5	1	5	5	5	25	2.5	2.5	2.5	0.5
Staphylococcus aureus ATCC 6538	5	2.5	2.5	5	5	10	25	2.5	2.5	2.5	0.5
Staphylococcus epidermidis	10	5	5	25	10	25	50	10	10	10	1
Streptococcus faecalis	5	5	5	25	5	25	50	5	10	5	10
Mycobacterium phlei	5	2.5	5	2.5	2.5	5	10	2.5	2.5	2.5	0.5
Bacillus cereus	5	2.5	2.5	10	5	10	25	5	5	5	1

[a] The figures represent the lowest dose levels causing total inhibition; the symbol "x" denotes total or partial growth at 100 μg/ml.

0.012 mol of NaH) in 25 ml of dry THF was added portionwise 2.36 g (0.0087 mol) of **5b**. The mixture was refluxed until H_2 evolution ceased (1 hr); to it 2.54 g (0.013 mol) of 2,4-$Cl_2C_6H_3CH_2Cl$ was added and refluxing was continued for 18 hr. Solvent was then removed and replaced with Et_2O which was repeatedly scrubbed with H_2O. Drying of the organic phase and addition of concentrated HNO_3 gave 3.3 g (77%) of **7f** nitrate salt. It was recrystallized from MeOH–*i*-Pr_2O to melt at 172–173°. Anal. ($C_{19}H_{16}Cl_4N_2O \cdot HNO_3$) C, H, N.

The salt was taken up in 1 vol of DMF and treated with concentrated NH_4OH and then with H_2O. The resulting base was taken up in Et_2O which, in turn, was dried and evaporated. Solid **7f** was obtained by seeding an *i*-Pr_2O solution of the oily residue; it melted at 87–89°.

Biological Evaluation. Compounds **3a, 4a,b,** and **7a–h** were tested on seven moulds, three yeasts, and ten bacterial strains (see Table II). All strains are in routine use for testing the activity of our antimicrobial substances.

The fungi were maintained on malt extract agar (4°) and the bacteria on horse blood-agar (4°). The media used were Malt Extract Broth (MEB, Oxoid CM 57), Malt Extract Agar (MEA, Oxoid CM 59), tryptone Soya Broth (TSB, Oxoid CM 129), and Nutrient Broth Agar (NBA, pH 7.4), containing 2% peptone and beef extract. Horse blood-agar was prepared by supplementing NBA with 5% horse blood.

Agar dilutions of the imidazoles were prepared in MEA and in NBA to final concentrations ranging from 0.1 to 100 μg/ml. The compounds were dissolved in dimethylformamide (DMF, Merck). The DMF concentration in the media did not exceed 0.5% and was not inhibitory to any of the fungi and bacteria being tested. The MEA dilutions were poured in culture tubes and solidified in slope position. The NBA dilutions were poured in petri dishes.

Molds were grown in MEB for 48 hr (*Aspergillus, Penicillium, Microsporum*) or for 72 hr (*Trichophyton, Epidermophyton*) at 32° (Epidermophyton at 24°). The cultures were vigorously shaken for 30 min (Griffith flask shaker) in flasks containing glass pearls and put aside during 30 min for sedimentation of the debris. The supernatant was used as the inoculum for the MEA dilutions of the imidazoles (0.1 ml per tube), either undiluted for (*Trichophyton, Epidermophyton*) or after dilution (10–400 times) in saline for the other molds. MIC's were usually read after 3 days of incubation at 32°. *Trichophyton* strains were incubated 7 days at 32° and *Epidermophyton floccosum* 3 days at 24°.

Yeasts were grown in MEB for 24 hr at 32°. MEA dilutions were seeded (0.1 ml per tube) with 1–100 dilutions of these cultures in saline. MIC's were read after 24 hr of incubation at 32°.

Bacterial strains were grown in TSB at 32° for 24 hr. The cultures were diluted 1–1000 in saline, prior to inoculating them on the NBA-supplemented media by means of a Steers replicator, ~10^3 cells per drop being applied to the agar surface. The compounds were tested at concentrations of 100, 50, 25, 10, 5, 2.5, 1, 0.5, 0.25, and 0.1 g/ml. Minimum inhibitory concentrations were read after 24 hr of incubation at 32°. Miconazole nitrate was used as reference drug.

Results and Discussion

The biological data are presented in Table II. Although the differences in antimycotic activity are small, compound **7f** appears to be the most active of the series; it is the direct analog of miconazole and possesses 1–10% of its activity against fungi. Systems **7g,h** are isomers of **7f** and resemble it in their antimicrobial action. Compound **7a,** being derived from monochlorocarbinol **5a,** and all monosubstituted benzyl ethers obtained from dichlorocarbinol **5b** (i.e., **7b–e**) are somewhat inferior.

Significant activity was also noted for amines **4a,b.** Compound **4b** is the NH analog of **7f;** it is more active than **4a,** which is related to **7b.** Enamine **3a,** the immediate precursor for **4a,** was totally inactive.

All compounds tested were inactive against the bacteria *Proteus mirabilis, Pseudomonas aeruginosa,* and *Escherichia coli.*

It would appear then that the antimycotic and antibacterial properties peculiar to miconazole and its analogs are, in part at least, derived from location of the benzyloxyphenethyl side chain on N. Our studies clearly demonstrate that transposition of this substituent to C-2 and replacement of it by a Me group (i.e., type II) leads to a decrease in biological potency. Structure–activity correlations, however, emerging from Table II resemble those previously reported for miconazole and its congeners;[1] this would suggest a similarity between types I and II in their modes of action.

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Preparation of [^{18}F]Haloperidol

C. S. Kook, M. F. Reed, and G. A. Digenis*[1]

Divisions of Medicinal Chemistry and Nuclear Medicine, Colleges of Pharmacy and Medicine, University of Kentucky, Lexington, Kentucky 40506. *Received March 18, 1974*

A procedure is described that permits the preparation of [^{18}F]haloperidol in 140 min at specific activities ranging from 4–5 μCi mg^{-1}. A key step in the synthetic route involves the incorporation of ^{18}F into the molecule through a Schiemann-type reaction, which involves the pyrolysis of the diazonium tetrafluoroborate salt of 4-[4-(*p*-chlorophenyl)-4-hydroxypiperidino]-4′-aminobutyrophenone.

In vivo tissue distribution studies with ^{14}C-labeled compounds require serial sacrifice of essentially identical isogenic animals followed by laborious analytical assessment of changes in ^{14}C activity in organs as a function of time after administration. The data obtained from such studies are not only inapplicable to man but also are of limited use in any large mammal where colonies of identical isogenic subjects are unavailable.[2] Human studies with compounds labeled with "short-lived," γ-emitting radionuclides can produce much valuable diagnostic information, such as the organ visualization and function studies of nuclear medicine. Such studies also provide the opportunity to perform tissue distribution determinations and pharmacokinetics in man in a nondestructive manner.

One of the more useful radionuclides for bone scanning is ^{18}F which is now in routine use in many medical centers, including our own, in the form of the simple inorganic fluoride.[3a] ^{18}F is a pure positron emitter (0.635 MeV, β+) and the resulting 511 keV annihilation radiation is easily detected with conventional nuclear medicine instrumentation. Its short physical half-life (110 min) results in a low radiation dose to the patient. ^{18}F-Labeled amino acids such as 4-fluorophenylalanine[3,4] and 6-fluorotryptophan[5] have been prepared and evaluated as specific pancreas scanning agents.[4,6] Recently a method for the preparation of fluorine-18 labeled metal fluorides and organic diazonium tetrafluoroborates has been described.[7] This method has been applied in the synthesis of ^{18}F-labeled amino acids. The synthesis of [^{18}F]-5-fluorouracil[8] and [^{18}F]-5-fluoro-Dopa[9,10] has also been reported. The former has been prepared as a potential tumor localizing agent[8] and the latter as a brain scanner.[9] It is interesting to note that a significant loading dose effect on the localization of both [^{18}F]-4-fluorophenylalanine and [^{18}F]-6-fluorotryptophan has been observed in animals.[11,12] Thus, the pancreas to liver ratio increases with decreasing amounts of ^{18}F-labeled amino acids administered. These observations strongly suggest the necessity for development of synthetic methods which can result in carrier-free products of very high specific activity. It is hoped that the availability of such radiopharmaceuticals would permit studies dealing with organ localization of these agents as a function of their loading dose.

Our interest in obtaining data on tissue distribution and pharmacokinetics of the neuroleptic drug haloperidol (**7**) (the chemistry,[13] pharmacology,[14] distribution, excretion, and metabolism in rats[15] of the drug have been studied) by external scintigraphic techniques has led us to devise a synthetic route (Scheme I) for its rapid preparation in the ^{18}F isotopically labeled form. According to this sequence the incorporation of ^{18}F into the molecule occurs at the last step (**6** to **7**) through a Schiemann-type reaction which involves the pyrolysis of the diazonium tetrafluoroborate salt **6**.

Scheme I