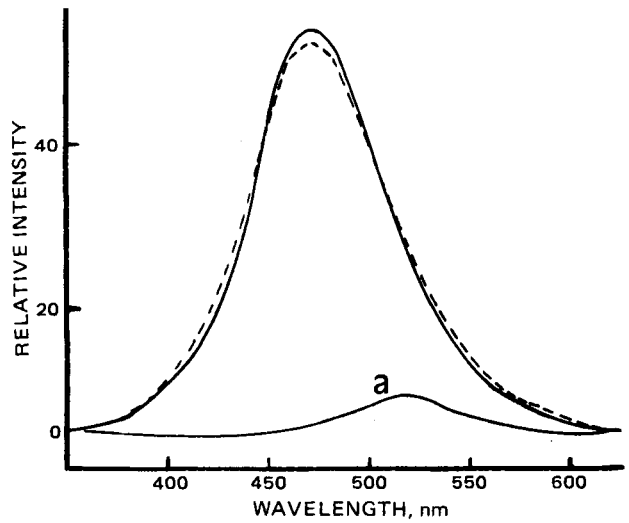

Figure 3—*Fluorescence emission spectra of the probe in pH 7.0 phosphate buffer (curve a) and when bound to imipramine (—) and to desipramine (- - -). The excitation maximum was set at 387 nm.*

solvents, it exhibited a large hypsochromic shift and increased fluorescence intensity (9–12). A direct correlation between the hydrophobicity of the solvent and the degree of spectral changes was found. It was suggested that hypsochromic shifts and enhanced fluorescence intensity were due to the conservation of excited energy in environments of decreasing polarity. The effects of potassium chloride and urea, which are known to bring about salting-out and salting-in effects, respectively, on the fluorescence properties of the I–chlorpromazine and I–imipramine complexes (Table I) provided additional evidence of the hydrophobic nature of the interaction.

Comparison of curves b and c in Fig. 1 suggested that chlorpromazine forms a stronger complex with I than does trimeprazine. The 2-chloro substituent in one aromatic ring of chlorpromazine appears to increase hydrophobic binding over the latter compound, which contains no chlorine substituents in its phenothiazine ring system. The greater ability of chlorpromazine to lower surface tension in aqueous solution relative to trimeprazine also was attributed to the greater hydrophobic effect of the 2-chlorophenothiazine ring of chlorpromazine (13). It was suggested that hydrophobic binding of these and related drugs to bovine serum albumin involved principally the phenothiazine moiety, with substituents attached to its nitrogen atom being of little significance in this regard (14). In accordance with this theory, the phenothiazine ring of chlorpromazine and, to a somewhat lesser extent, that of trimeprazine interact hydrophobically with the anilinonaphthalene ring of I, which causes the spectral changes.

The spectra of solutions of I in the presence of imipramine and desipramine exhibited similar emission spectra (Fig. 3). These compounds are structurally dissimilar only in the lack of a one side-chain methyl group in desipramine. Each contains a dibenzazepine ring system, which is presumably involved principally in hydrophobic binding with I, as in the case of the drugs containing a phenothiazine ring. This finding supports the suggestion (14) that side-chain substitution does not contribute to hydrophobic binding, since its participation in these otherwise structurally identical compounds would be expected to cause spectral differences.

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Synthesis of Antifungal 2-Substituted Phthalimidines

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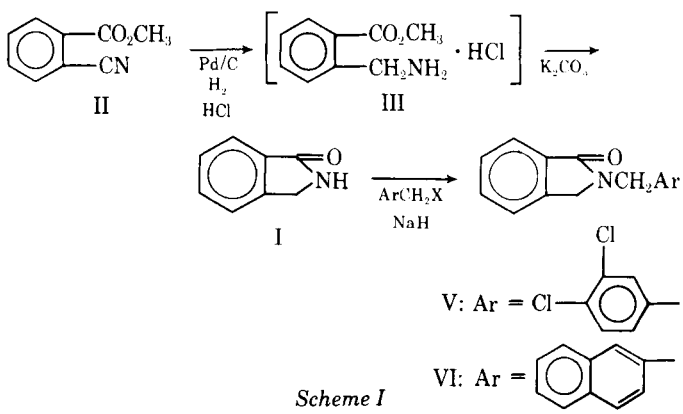
Received August 19, 1977, from the *Research and Development Department, Norwich-Eaton Pharmaceuticals Division of Morton-Norwich Products, Inc., Norwich, NY 13815.* Accepted for publication September 16, 1977.

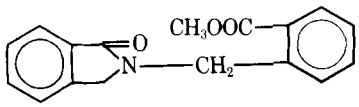
Abstract □ An improved synthesis of phthalimidine is reported. Two *N*-substituted phthalimidines were synthesized by alkylation of the parent compound, and they showed complete inhibition of *Microsporum* and *Trichophyton* species at 10–100 μg/ml in an agar dilution test. Both compounds were inactive against *Candida albicans* at 100 μg/ml or *Aspergillus niger* at 250 μg/ml.

Keyphrases □ Phthalimidines, substituted—synthesized, evaluated for antifungal activity □ Antifungal activity—various substituted phthalimidines evaluated □ Structure–activity relationships—various substituted phthalimidines evaluated for antifungal activity

Several *N*-substituted phthalimidines were desired for antifungal screening, so a convenient route to the parent compound I (Scheme I) was sought.



Scheme I



IV

Target compound I was prepared in a yield of 88% by the palladium-on-carbon hydrogenation of methyl 2-cyanobenzoate (II) and subsequent cyclization of the resultant amine (III). This method is a variation of that originally reported by Velluz and Amiard (1), who obtained 46–67% yields of I contaminated with *N*-(2-methoxycarbonylbenzyl)phthalimidine (IV) when Raney nickel was employed in the hydrogenation. No trace of IV was evident in the present work.

Alkylation of I with the appropriate halo compound gave the 3,4-dichlorobenzyl compound V and the 2-naphthylmethyl compound VI. That alkylation occurred on nitrogen rather than oxygen was ascertained by carbonyl absorption in the IR spectra of V and VI.

Compound VI was slightly more active than V when challenged by six dermatophytic organisms in an agar dilution test (Table I). Neither compound was active against *Candida albicans* at 100 μg/ml or *Aspergillus niger* at 250 μg/ml.

EXPERIMENTAL[1]

Chemistry—*Phthalimidine (I)*—A mixture of 48.6 g (0.302 mole) of II, 2.0 g of 5% palladium-on-carbon (50% moisture), 500 ml of methanol, and 500 ml of ethanol saturated with hydrogen chloride was shaken with hydrogen on a Parr apparatus until the theoretical quantity of hydrogen was consumed (24 hr).

The catalyst was filtered and washed with 2 × 100 ml of methanol. To the filtrate and combined washings was added 40 g of potassium carbonate. The mixture was stirred and refluxed for 20 hr and concentrated to dryness *in vacuo*, and the solid residue was stirred with 150 ml of water for 2.0 hr.

The solid was filtered, and the filtrate was extracted with 2 × 150 ml of chloroform. The extracts were combined, dried (magnesium sulfate), and concentrated to dryness. The residue was combined with the original solid.

Recrystallization from 235 ml of acetonitrile gave, in two crops, 35.4 g (88%) of the product, mp 151–152.5°. Further recrystallization from water gave an analytical sample, mp 148–151° [lit. (1) mp 149°]; IR: 3.11 (NH), 5.88–5.97 (C=O), and 6.25 (C=C) μm.

Anal.—Calc. for C_8H_7NO: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.42; H, 5.23; N, 10.61.

N-(3,4-Dichlorobenzyl)phthalimidine (V)—A mixture of 13.3 g (0.100 mole) of I, 8.0 g of sodium hydride 60% in mineral oil (4.80 g, 0.200 mole), and 19.5 g (0.100 mole) of 3,4-dichlorobenzyl chloride in 175 ml of toluene was stirred and refluxed for 18 hr. Methanol (25 ml) was added to destroy excess sodium hydride, and the mixture was concentrated to dryness *in vacuo*. The residue was partitioned between 200 ml of water and 200 ml of chloroform. The chloroform layer was separated, and the aqueous layer was extracted with 2 × 100 ml of chloroform. The combined extracts were washed with 200 ml of water, dried (magnesium sulfate), and concentrated to dryness *in vacuo* to give 33.5 g of an oil; this oil was washed with 75 ml of cold hexane.

Crystallization from 125 ml of toluene gave 13.1 g of material, which was boiled with 325 ml of heptane. The heptane solution was combined with the toluene filtrate, and the mixture was concentrated to dryness. Crystallization of the residue from 30 ml of toluene gave 5.1 g (17%) of the product, mp 92–105°. Further recrystallization from heptane gave an analytical sample, mp 105–106°; IR: 5.97 (C=O), 6.29, and 6.40 (C=C) μm; NMR (deuterochloroform): δ 4.30 (s, 2, phthalimidine CH_2), 4.76 (s, 2, NCH_2Ar), and 7.05–8.00 (m, 7, phenyl CH) ppm.

Anal.—Calc. for $C_{15}H_{11}Cl_2NO$: C, 61.66; H, 3.80; N, 4.80. Found: C, 61.71; H, 3.92; N, 4.70.

N-(2-Naphthylmethyl)phthalimidine (VI)—A mixture of I (16.1 g, 0.121 mole), 30.94 g (0.140 mole) of 2-(bromomethyl)naphthalene, and 8.0 g of sodium hydride 60% in mineral oil (4.80 g, 0.20 mole) in 150 ml of toluene was stirred and refluxed for 16 hr and cooled. Then 3.0 ml of methanol was added. After dilution with 250 ml of water, the mixture was stirred for 1 hr. The toluene layer was separated, and the aqueous layer was extracted with 100 ml of toluene. The combined organic extracts were washed with 150 ml of water, dried (magnesium sulfate), and concentrated to dryness *in vacuo*. Crystallization from 40 ml of toluene gave 12.6 g (46%) of the product, mp 97–102°. Further recrystallization from toluene gave an analytical sample, mp 103–106°; IR: 5.92 (C=O) and 6.20 (C=C) μm; NMR (deuterochloroform): δ 4.23 (s, 2, phthalimidine CH_2), 4.93 (s, 2, NCH_2Ar), and 7.00–8.00 (m, 11, aryl CH) ppm.

Anal.—Calc. for $C_{19}H_{15}NO$: C, 83.49; H, 5.53; N, 5.13. Found: C, 83.76; H, 5.67; N, 4.94.

Mycology—The antifungal activity of the compounds was determined by a minimum inhibitory concentration procedure (2) for *C. albicans* and by an agar dilution procedure (3) for *Aspergillus, Trichophyton,* and *Microsporum* species. In the latter procedure, with incubation at 25°, complete inhibition of growth for 10 days is the criterion for an active compound.

Table I—MIC [a] by Agar Dilution Method in Sabouraud's Dextrose Agar

Test Organism [b]	V	VI
Microsporum canis (M-4)	100	100
Microsporum audouini (M-17)	100	10
Microsporum gypseum (M-108)	100	100
Trichophyton mentagrophytes (M-93)	100	100
Trichophyton tonsurans (M-76)	100	100
Trichophyton rubrum (M-107)	10	10

[a] Minimum inhibitory concentration, micrograms per milliliter of medium. Compounds were dissolved in dimethylformamide (2). [b] The numbers in parentheses are Norwich-Eaton Pharmaceuticals culture numbers.

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[1] Melting points were determined on a Mel-Temp apparatus, and those below 230° are corrected. IR spectra were determined as mineral oil mulls using a Perkin-Elmer 137B spectrophotometer. NMR spectra were obtained on a Varian A-60A instrument and were compared with tetramethylsilane as an internal standard.