A New Series of Antifungal Compounds*

By E. B. HODGE, JOSEPHINE R. DAWKINS,† and ELEANORE KROPP‡

Compounds of the type ArCH(OR)CBr-(NO_2)R′ have been found to possess strong antifungal activity. The preparation, properties, and antifungal activities of a number of compounds of this formula are described. 2-Bromo-1-methoxy-2-nitro-1-phenylpropane has been further tested and ointments containing it have been prepared and submitted for clinical trial. Results from one of these trials have been published.

THE PREPARATION of five compounds of the type ArCH(OR)CX(NO_2)R′, where R and R′ are alkyl radicals and X is chlorine or bromine, has been described by Senkus (1). In a routine screening program one of the compounds, 2-bromo-1-methoxy-2-nitro-1-phenylpropane, (P–594) was found to be a very effective antifungal agent. Preparation of several analogous compounds indicated that for high antifungal activity the halogen should be bromine rather than chlorine. A number of compounds of this type were prepared and tested for antifungal activity. The compounds prepared, with their analyses, antifungal activities, and boiling or melting points, are shown in Table I which demonstrates that the presence of substituents on the aryl group in general lowered the antifungal activity.

The two compounds under No. 3 were separated by repeated crystallization from petroleum ether. They are believed to be the two diasteroisomeric mixtures which are possible for this compound. All of the other compounds also have two asymmetric carbon atoms and theoretically should exist in two such forms, but in no other case were the diasteroisomeric mixtures separated.

Because 2-bromo-1-methoxy-2-nitro-1-phenylpropane was about as effective as any of the other compounds, and also because this compound is perhaps more convenient to prepare than any other in the series, it was selected for further study. Additional antifungal data were obtained on this compound and these results are shown in Table II.

Formulated at one per cent in either a petrolatum or vanishing cream base this compound was

TABLE I.—COMPOUNDS OF THE TYPE ArCH(OR)CBr(NO_2)R′

No.	Ar	R	R′	M. P. or B. P., °C.	Yield, %	N, % Calc.	N, % Found	Br, % Calc.	Br, % Found	Min. Inhib. Concn. (μg./ml.) Against *Aspergillus niger*	Against *Trichophyton metagrophytes*	Against *Candida albicans*
1[a]	Phenyl	Me	Me	45–46	93	..	..	...	...	20	1	30
2	*p*-Chlorophenyl	Me	Me	96–98	88	4.54	4.34	25.90	25.85	100	5	>100
3	2,4-Dichlorophenyl	Me	Me	54–55.5	..	4.08	3.61	...	...	50	1	5
				92–94.5	..	4.08	3.77	...	...	5	1	1
4	2,4-Dichlorophenyl	Me	Et	130–140[b]	..	3.92	3.70	22.38	22.44	50	5	>100
5	*p*-Anisyl	Me	Et	144–147[b]	51	4.40	4.36	25.11	25.63	100	5	>100
6	*p*-Anisyl	Me	Me	74–75	55	4.61	4.41	26.28	27.36	<1	50	100
7	*p*-Chlorophenyl	Me	*n*-Propyl	107–108	45	4.16	4.23	...	...	10	10	>100
8	Phenyl	2-Hydroxyethyl	Me	...	79	4.61	4.52	...	...	100	5	100
9	Furyl	Me	Me	92–97[b]	23	5.30	5.59	...	...	10	1	25
10	*o*-Chlorophenyl	Me	Me	120[b]	57	4.54	4.44	...	...	25	<1	50
11	*o*-Chlorophenyl	Et	Me	122[b]	61	4.34	3.96	...	...	25	5	25
12	*o*-Chlorophenyl	Et	Et	128[b]	28	4.16	3.93	...	...	10	5	100
13	*o*-Chlorophenyl	Me	Et	128[b]	38	4.34	3.97	...	...	10	5	>100
14	*p*-Chlorophenyl	Me	Et	104.5–106	44	4.34	4.03	...	...	25	<1	100
15	3,4-Dichlorophenyl	Me	Me	67–70	66	4.08	3.69	...	...	25	5	50
16	Phenyl	Et	Et	113–115[b]	45	4.63	4.85	...	...	<1	<1	100

[a] Prepared by Senkus.
[b] B. p. at 1–2 mm. of mercury.

* Received November 5, 1953, from the Pharmaceutical Research Division of Commercial Solvents Corporation, Terre Haute, Ind.
The authors are indebted to G. L. Lafferty for formulation work, and to Dr. J. N. Spencer for pharmacological testing. Analyses were performed under the direction of Dr. J. A. Riddick.
† Present address: Mrs. P. F. Krouse, 416 Bilbo Street, De Ridder, La.
‡ Present address: Mrs. Glenn La Baw, 425 East Park Place, Park Plaza, Jeffersonville, Ind.

found to cause little or no irritation when applied daily for seven days to the intact skin of twelve rabbits. Preliminary clinical trials of this compound in one per cent concentration in a vanishing cream base have been carried out by several physicians and the results of one of them have been published (2). The conclusions reached in the cited reference were as follows: "This compound possesses low toxicity, little irritancy, an apparent low sensitizing index and a high degree of efficiency in the treatment of mycotic lesions of glabrous skin. It is considered of particular value in the treatment of infections caused by *T. rubrum*."

EXPERIMENTAL

Preparation of Compounds.—The preparation of all of these compounds was carried out essentially as described in reference (1), examples II and IV.

The preparation of the two forms of 2-bromo-1-(2,4-dichlorophenyl)-1-methoxy-2-nitropropane was carried out as follows: A mixture of 46.4 Gm. of 1-(2,4-dichlorophenyl)-2-nitro-1-propene, 200 cc. of methanol, 75 cc. of water, and 10 Gm. of sodium hydroxide was stirred to give an almost clear solution and then filtered. The filtrate was stirred and cooled in an ice bath and 10.2 cc. of bromine was added dropwise at not over 20°, causing the formation of an oil which slowly solidified. This was filtered to give 60.4 Gm. of a solid, melting from 55–70°. This was recrystallized twice from petroleum ether and the filtrates were combined. From them was isolated 17 Gm. of the lower melting product. The precipitate from the second crystallization was recrystallized twice more to give 12.6 Gm. of the higher melting product.

TABLE II.—ACTIVITY OF P-594 AGAINST YEASTS AND FUNGI

Culture	Minimum Inhibitory Concentration (μg./ml.)
M. audouini, 10216	1
S. schenckii, 10212	25–50
E. floccosum, 10227	1
T. mentagrophytes, 10270	1–5
T. rubrum, 10218	1–5
B. dermatitidis, 10225	1
A. fumigatus, 6285	5–10
C. albicans	10–25
A. boris, 10048	10–25
Schizosacharomyces pombe ATCC, 2476	5–10
Endomyces magnusii ATCC, 2105	5–10
Saccharomyces lactis ATCC, 8635	10–25
Saccharomyces cerevisiae Sc31	10–25
Zygosaccharomyces mandshuricus NRRL, Y-301	10–25
Torulaspora rosei NRRL, Y-1567	10–25
Debaryomyces matruchoti NRRL, Y-833	5–10
Endomyces jaronensis NRRL, Y-1483	1–5
Mycoderma cererusuae NRRL, Y-932	5–10
Kloeckera brevis NRRL, Y-915	1–5
Brettanomyces anamalus NRRL, Y-1415	5–10
Candida guilliermondia NRRL, Y-324	25–50
Rhodotorula mucilaginosa var. *ruhrorugosa* ATCC, 4559	50–100
Hansenula saturnos NRRL, Y-12	10–25
Candida keusei NRRL, Y-301	10–25
Aspergillus niger	10–20

Antifungal Testing.—Stock solutions of the compounds being tested were prepared at 1% concentration using a suitable solvent. In initial testing only the concentration 100 μg./ml. was used. This was obtained by diluting the stock solution 1:10 with water and adding a 2-cc. aliquot to 18 cc. of Sabouraud's agar with 0.5% Difco Malt extract. The agar and agent were then steamed for thirty to forty-five minutes. Plates were poured, allowed to solidify, and streaked with suspensions of cells contained in a 7-mm. bacteriological loop. The suspension was prepared from a fresh slope washed into saline and should show about 50% of the light transmission of a saline control using 15- to 16-mm. (i. d.) tubes and a red filter. The fungi used in the initial series of tests were *Aspergillus niger*, *Trichophyton mentagrophytes*, and *Candida albicans*. Plates were checked after five days at 25°. If no growth occurred, the process was repeated at lower concentrations.

SUMMARY

1. A class of antifungal compounds of the type $ArCH(OR)CBr(NO_2)R'$ has been studied and sixteen members of it have been prepared.

2. The compound 2-bromo-1-methoxy-2-nitro-1-phenylpropane has been found to be fungistatic at low concentrations toward a number of yeasts and fungi.

3. This compound, formulated in an ointment at one per cent concentration, has been submitted for clinical trial.

REFERENCES

(1) Senkus, M., U. S. pat. 2,562,151, July 24, 1951.
(2) Wooldridge, W. E., *J. Investigative Dermatol.*, **21**, 121 (1953).