RELATION OF CHEMICAL STRUCTURE TO FUNGISTATIC ACTIVITY*

HERMAN I. CHINN, PH.D., ROLAND B. MITCHELL, PH.D. AND ANNA C. ARNOLD, B.A.

Many workers have shown that the introduction of a halogen into the nucleus of a phenolic compound increases its bactericidal and fungicidal potency. Klarmann and co-workers (1, 2) demonstrated that halogenation in para position to the hydroxyl group was more effective than the ortho-substitution and that introduction of alkyl groups further increased the potency of the compounds. The relative effect of bromination and chlorination has been a controversial point. The monobromo derivatives were less effective than the chlorinated compounds against typhoid and paradysentery organisms but more so against staphylococcus and streptococcus (1). Marsh et al. (3) found that brominated bisphenols were less fungistatic than the corresponding chlorinated compounds. Other investigators (4) claimed that bromine substitution produced a more potent bactericide and fungicide than did chlorine while iodine gave an even more effective preparation. The most promising of a series of halogenated salicylaldehydes against *Trichophyton mentagrophytes* was the dibromo derivative (5). Fluoro-phenol, however, differed but little in its germicidal action from phenol itself (6).

The recent demonstration that certain antihistaminic drugs have significant fungistatic action (7) stimulated interest in this pharmacologic group. It was noted that members of this group containing chlorine were more active than their parent compound (8). These compounds were nonphenolic in nature, thus differing from those already reported. It was thought important to extend this series and to include other halogenated derivatives as well as chlorine. Since all compounds tested containing the phenothiazine nucleus inhibited fungous growth, additional compounds of this type were also included in the study.

MATERIALS AND METHODS

The structures of the compounds tested† are shown in Table I. Since many of these compounds are not available commercially and have no common name, reference will be made to them by our own number, as indicated in the first column. A few fungistats were tested which were neither antihistaminic, their halogenated derivatives, nor phenothiazine preparations. These were included for comparative purposes. The test cultures employed were *Trichophyton mentagrophites*, *Microsporum canis*, *Monosporium apiospermum*, *Sporotrichum Schenkii*, *Phialophora verrucosa*, and *Candida albicans*. The method of testing for fungistatic activity was the same as described in our previous report (8). It consisted essentially of determining the zones of partial and complete inhibition of fungal

* From the Departments of Pharmacology and Microbiology, USAF School of Aviation Medicine, Randolph Field, Texas.

Received for publication August 12, 1952.

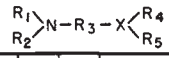
† We wish to thank the manufacturers who made liberal quantities available to us.

growth surrounding a sensitivity paper disc impregnated with various concentrations of the test compound.

All compounds were dissolved in 70 per cent alcohol and made up to the appropriate concentration (0.0001 to 0.1 M).

A limited series of these compounds was also tested in the same manner against *Coccidioides immitis*. This culture was chosen as a typical example of a systemic mycotic infecting agent.

TABLE 1 – STRUCTURE OF COMPOUNDS STUDIED



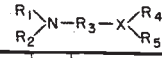
	TRADE OR CHEMICAL NAME	MANUFACTURER	R_1–	R_2 –	>N–	–R3–	–X	–R4	–R5	SALT FORM
1	PYRIBENZAMINE	CIBA	CH_3–	CH_3 –	>N–	$-CH_2-CH_2-$	–N<	$-CH_2-C_6H_5$	$-C_6H_5$	HYDROCHLORIDE
2	CI 216–109–215	AMERICAN CYANAMID	CH_3–	CH_3 –	>N–	$-CH_2-CH_2-$	–N<	$-CH_2-C_6H_5$	$-C_6H_4-Br$	HYDROCHLORIDE
3	CI 216–113–169	AMERICAN CYANAMID	CH_3–	CH_3 –	>N–	$-CH_2-CH_2-$	–N<	–H	$-C_6H_4-Br$	HYDROCHLORIDE
4	CI 216–114–116	AMERICAN CYANAMID	CH_3–	CH_3 –	>N–	$-CH_2-CH_2-$	–N<	$-CH_2-C_6H_4-F$	$-C_6H_5$	HYDROCHLORIDE
5	CI 216–118–66	AMERICAN CYANAMID	CH_3–	CH_3 –	>N–	$-CH_2-CH_2-$	–N<	$-CH_2-C_6H_4-I$	$-C_6H_5$	HYDROCHLORIDE
6	NEOHETRAMINE	NEPERA	CH_3–	CH_3 –	>N–	$-CH_2-CH_2-$	–N<	$-CH_2-C_6H_4-OCH_3$	$-C_6H_5$	HYDROCHLORIDE
7	1158	NEPERA	CH_3–	CH_3 –	>N–	$-CH_2-CH_2-$	–N<	$-CH_2-C_6H_4-OCH_3$	$-C_6H_4-Cl$	HYDROCHLORIDE
8	1157	NEPERA	CH_3–	CH_3 –	>N–	$-CH_2-CH_2-$	–N<	$-CH_2-C_6H_5$	$-C_6H_4-Cl$	HYDROCHLORIDE
9	1168	NEPERA	CH_3–	CH_3 –	>N–	$-CH_2-CH_2-$	–N<	$-CH_2-C_6H_4-Cl$	$-C_6H_5$	HYDROCHLORIDE
10	HISTADYL	LILLY	CH_3–	CH_3 –	>N–	$-CH_2-CH_2-$	–N<	$-C_5H_4N$	$-CH_2-C_5H_4N$	HYDROCHLORIDE
11	TAGATHEN	LEDERLE	CH_3–	CH_3 –	>N–	$-CH_2-CH_2-$	–N<	$-C_5H_4N$	$-CH_2-C_5H_4N-Cl$	CITRATE
12	CI 216–86–184	AMERICAN CYANAMID	CH_3–	CH_3 –	>N–	$-CH_2-CH_2-$	–N<	$-C_5H_4N$	$-CH_2-C_5H_4N-Cl$	METHIODIDE
13	BROMOTHEN	LEDERLE	CH_3–	CH_3 –	>N–	$-CH_2-CH_2-$	–N<	$-C_5H_4N$	$-CH_2-C_5H_4N-Br$	HYDROCHLORIDE
14	ISOBROMOTHEN	AMERICAN CYANAMID	CH_3–	CH_3 –	>N–	$-CH_2-CH_2-$	–N<	$-C_5H_4N$	$-CH_2-C_5H_3N-Br$	HYDROCHLORIDE
15	FORALMIN	EATON	CH_3–	CH_3 –	>N–	$-CH_2-CH_2-$	–N<	$-C_5H_4N$	$-CH_2-C_5H_4N$	FUMARATE
16	F180	EATON	CH_3–	CH_3 –	>N–	$-CH_2-CH_2-$	–N<	$-C_5H_4N$	$-CH_2-C_5H_4N-Br$	FUMARATE
17	BENADRYL	PARKE–DAVIS	CH_3–	CH_3 –	>N–	$-CH_2-CH_2-$	$-O-\overset{H}{\underset{}{C}}<$	$-C_6H_5$	$-C_6H_5$	HYDROCHLORIDE
18		PARKE–DAVIS	CH_3–	CH_3 –	>N–	$-CH_2-CH_2-$	$-O-\overset{H}{\underset{}{C}}<$	$-C_6H_5$	$-C_6H_4-Cl$	HYDROCHLORIDE
19		PARKE–DAVIS	CH_3 –	CH_3 –	>N–	$-CH_2-CH_2-$	$-O-\overset{H}{\underset{}{C}}<$	$-C_6H_4-Cl$	$-C_6H_4-Cl$	HYDROCHLORIDE
20	AMBODRYL	PARKE–DAVIS	CH_3 –	CH_3 –	>N–	$-CH_2-CH_2-$	$-O-\overset{H}{\underset{}{C}}<$	$-C_6H_5$	$-C_6H_4-Br$	HYDROCHLORIDE
21	DECAPRYN	MERRELL	CH_3–	CH_3 –	>N–	$-CH_2-CH_2-$	$-O-C(=O)-CH_3$	$-C_6H_5$	$-C_6H_5$	SUCCINATE
22	278R–255	MERRELL	CH_3–	CH_3 –	>N–	$-CH_2-CH_2-$	$-O-C(=O)-CH_3$	$-C_6H_4-Cl$	$-C_6H_5$	HYDROCHLORIDE
23	358R–66	MERRELL	CH_3–	CH_3 –	>N–	$-CH_2-CH_2-$	$-O-C(=O)-CH_3$	$-C_6H_3Cl_2$	$-C_6H_5$	HYDROCHLORIDE
24	354R285A 163ID2	MERRELL	C_2H_5	C_2H_5	>N–	$-CH_2-CH_2-$	$-O-C(=O)-CH_3$	$-CH_3$		HYDROCHLORIDE

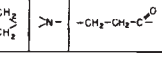
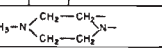
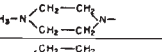
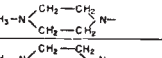
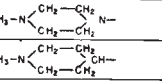
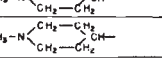
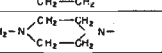
RESULTS AND DISCUSSION

The effectiveness in completely inhibiting growth of the various fungi is summarized in Table II, and the extent of partial inhibition similarly listed in Table III. Members of each family of compounds are grouped in Tables II and III to facilitate comparison. The halogenated series are not as complete as would be desirable since relatively few derivatives of the antihistaminics were available. This is especially true of the fluorinated and iodinated derivatives. Pyribenzamine is the only antihistamine for which either derivative could be obtained. The fluorine derivative shows little superiority over the parent compound. Partial

inhibition of *M. canis* is affected at a slightly lower concentration, but all other fungi respond identically to either Pyribenzamine or its fluorine derivative. Substitutions of iodine, however, significantly improve the fungistatic action. Thus, Pyribenzamine inhibits none of the fungi completely even at 0.1 M concentrations and gives partial inhibition only to *T. mentagrophytes* and *M. canis*.

TABLE 1 (CON'T) STRUCTURE OF COMPOUNDS STUDIED



	TRADE OR CHEMICAL NAME	MANUFACTURER	R_1–	R_2–	>N–	–R_3–	–X<	–R_4	–R_5	SALT FORM
25	ASTEROL	HOFFMAN LA ROCHE	C_2H_5–	C_2H_5–	>N–	$-CH_2-CH_2-$		$-CH_3$	$-CH_3$	HYDROCHLORIDE
26	LISERGAN	RHONE-POULENC	CH_3–	CH_3–	>N–	$-CH_2-CH_2-$				HYDROCHLORIDE
27	LERGIGAN *	RECIP	CH_3–	CH_3–	>N–	$-CH_2-CH(CH_3)^*-$				HYDROCHLORIDE
28	PHENERGAN *	WYETH	CH_3–	CH_3–	>N–	$-CH(CH_3)^*-CH_2-$				HYDROCHLORIDE
29	DIPARCOL	RHONE-POULENC	C_2H_5–	C_2H_5–	>N–	$-CH_2-CH_2-$				HYDROCHLORIDE
30	MULTERGAN	RHONE-POULENC	CH_3–	CH_3–	$>N^+(CH_3)$–	$-CH(CH_3)-CH_2-$				METHYL SULFATE
31		ASTRA	C_2H_5–	C_2H_5–	>N–	$-CH(CH_3)-C(=O)-$				HYDROCHLORIDE
32		ASTRA			>N–	$-CH_2-CH_2-C(=O)-$				HYDROCHLORIDE
33	47-83	BURROUGHS-WELLCOME								HYDROCHLORIDE
34	PERAZIL	BURROUGHS-WELLCOME								HYDROCHLORIDE
35	48-166	BURROUGHS-WELLCOME								HYDROCHLORIDE
36	48-239	BURROUGHS-WELLCOME								HYDROCHLORIDE
37	DIPHENYLPYRALINE	NATIONAL OIL PRODUCTS COMPANY								HYDROCHLORIDE
38	1718	NATIONAL OIL PRODUCTS COMPANY								CITRATE
39	19DA	NATIONAL OIL PRODUCTS COMPANY								CITRATE
40	5062	UNION CHIMIQUE BELGE								HYDROCHLORIDE
41	G20714	GEIGY								
42	G21772	GEIGY								

* Exact positioning of CH_3 is questionable. Lergigan and Phenergan may be identical.

The iodine-containing preparation, on the other hand, inhibits all cultures completely except *P. verrucosa* which it inhibits partially at 0.05 M concentration. Approximately the same inhibition is obtained with the 2 bromine derivatives (2 and 3) and with a chlorinated derivative reported previously.

In practically all cases, the bromine or chlorine-containing compounds average a greater activity than the parent compound. No distinction can be made on the

TABLE II

Minimal molar concentration required to inhibit fungous growth completely

NO.	NAME	HALOGENS PRESENT	T. MENTAGROPHYTES	M. CANIS	M. APIOSPERMUM	S. SCHENKII	PH VERRUCOSA	C. ALBICANS
1	Pyribenzamine	O	>0.1	>0.1	>0.1	>0.1	>0.1	>0.1
2	Cl 216-109-215A	Br	0.05	0.05	0.1	0.075	>0.1	0.075
3	Cl 216-113-169	Br	>0.1	>0.1	>0.1	>0.1	>0.1	>0.1
4	Cl 216-114-116	F	>0.1	>0.1	>0.1	>0.1	>0.1	>0.1
5	Cl 216-118-66	I	0.05	0.05	0.1	0.05	>0.1	0.05
6	Neohetramine	O	>0.1	>0.1	>0.1	>0.1	>0.1	>0.1
7	1158	Cl	>0.1	>0.1	>0.1	>0.1	>0.1	>0.1
8	1157	Cl	>0.1	>0.1	>0.1	>0.1	>0.1	>0.1
9	1168	Cl	>0.1	>0.1	>0.1	>0.1	>0.1	>0.1
10	Histadyl	O	>0.1	>0.1	>0.1	>0.1	>0.1	>0.1
11	Tagathen	Cl	>0.1	>0.1	>0.1	>0.1	0.075	0.075
12	Cl 216-86-184	Cl	>0.1	0.075	>0.1	>0.1	0.05	0.075
13	Bromothen	Br	0.075	0.075	0.1	0.05	>0.1	0.075
14	Isobromothen	Br	0.1	0.075	>0.1	>0.1	>0.1	>0.1
15	Foralmin	O	>0.1	>0.1	>0.1	>0.1	>0.1	>0.1
16	F 180	Br	>0.1	>0.1	>0.1	>0.1	>0.1	>0.1
17	Benadryl	O	>0.1	>0.1	>0.1	>0.1	>0.1	>0.1
18	—	Cl(2)	0.025	0.025	0.05	0.025	0.05	0.025
19	—	Cl(2)	0.025	0.05	0.05	0.025	0.075	0.025
20	Ambodryl	Br	0.05	0.05	0.1	0.075	0.075	0.075
21	Decapryn	O	>0.1	>0.1	>0.1	>0.1	>0.1	>0.1
22	278 R-255	Cl	>0.1	>0.1	>0.1	>0.1	>0.1	>0.1
23	358 R-66	Cl	>0.1	>0.1	>0.1	>0.1	>0.1	>0.1
24	354R 285a 163102	O	0.0075	0.025	0.075	0.05	0.1	0.1
25	Asterol	O	0.001	0.005	>0.1	>0.1	>0.1	>0.1
26	Lisergan	O	0.05	0.075	0.1	0.075	0.075	0.05
27	Lergigan	O	0.025	0.05	0.05	0.05	0.075	0.05
28	Phenergan	O	0.05	0.05	0.05	0.075	0.075	0.05
29	Diparcol	O	0.05	0.075	0.075	>0.1	0.075	0.05
30	Multergan	O	>0.1	>0.1	0.1	0.05	>0.1	0.075
31	—	O	>0.1	>0.1	>0.1	>0.1	0.05	>0.1
32	—	O	0.025	0.025	0.075	0.025	0.025	>0.1
33	47-83	O	>0.1	>0.1	>0.1	>0.1	>0.1	>0.1
34	Perazil	Cl	0.01	0.025	0.075	0.05	0.05	0.05
35	48-166	Cl(2)	0.025	0.01	0.025	0.05	0.025	0.025
36	48-239	Cl(2)	0.025	0.01	0.025	0.05	0.025	0.05
37	Diphenylpyraline	O	0.075	>0.1	>0.1	>0.1	>0.1	0.075
38	171B	Cl	0.075	>0.1	>0.1	>0.1	>0.1	0.05
39	190A	Br	0.075	>0.1	>0.1	>0.1	>0.1	0.075
40	Postafene	Cl	>0.1	>0.1	>0.1	>0.1	0.075	>0.1
41	G20714	O	0.0075	0.005	0.025	0.025	0.01	0.0075
42	G21772	O	0.0005	<0.0001	0.05	0.025	0.01	<0.0001

TABLE III

Minimal molar concentration required to inhibit fungous growth partially

NO.	NAME	HALOGENS PRESENT	T. MENTAGROPHYTES	M. CANIS	M. APIOSPERMUM	S. SCHENKII	PH VERRUCOSA	C. ALBICANS
1	Pyribenzamine	O	0.025	0.025	>0.1	>0.1	>0.1	>0.1
2	Cl 216-109-215A	Br	0.005	0.025	0.05	0.05	0.05	0.05
3	Cl 216–113–169	Br	0.075	0.075	>0.1	>0.1	0.075	>0.1
4	Cl 216–114–116	F	0.025	0.01	>0.1	>0.1	>0.1	>0.1
5	Cl 216-118-66	I	0.005	0.005	0.05	0.05	0.05	0.05
6	Neohetramine	O	0.075	0.075	>0.1	>0.1	>0.1	>0.1
7	1158	Cl	0.0075	0.0075	0.1	>0.1	0.1	>0.1
8	1157	Cl	0.0075	0.0075	>0.1	>0.1	>0.1	>0.1
9	1168	Cl	0.05	0.075	>0.1	>0.1	>0.1	>0.1
10	Histadyl	O	0.025	0.025	>0.1	>0.1	>0.1	>0.1
11	Tagathen	Cl	0.005	0.005	0.075	>0.1	0.025	0.05
12	Cl 216-86-184	Cl	>0.1	0.025	0.075	0.025	0.05	0.025
13	Bromothen	Br	0.005	0.005	0.05	0.05	0.075	0.05
14	Isobromothen	Br	0.01	0.0075	0.05	0.075	0.075	0.1
15	Foralmin	O	0.075	>0.1	>0.1	>0.1	0.075	>0.1
16	F180	Br	0.01	0.01	0.1	>0.1	0.05	>0.1
17	Benadryl	O	0.01	0.01	>0.1	>0.1	>0.1	>0.1
18	—	Cl(2)	0.001	0.0025	0.025	0.025	0.025	0.025
19	—	Cl(2)	0.0025	0.0025	0.05	0.01	0.05	0.025
20	Ambodryl	Br	0.0075	0.0025	0.075	0.05	0.05	0.05
21	Decapryn	O	0.1	>0.1	>0.1	>0.1	>0.1	>0.1
22	278R-255	Cl	0.05	0.025	>0.1	>0.1	>0.1	>0.1
23	358 R-66	Cl	0.05	0.025	>0.1	>0.1	>0.1	>0.1
24	354R 285a 163102	O	0.001	0.005	0.075	0.05	0.05	0.05
25	Asterol	O	0.0001	0.001	0.025	>0.1	0.075	0.1
26	Lisergan	O	0.005	0.005	0.075	0.05	0.025	0.05
27	Lergigan	O	0.005	0.01	0.05	0.05	0.05	0.025
28	Phernergan.	O	0.025	0.005	0.05	0.05	0.05	0.05
29	Diparcol	O	0.0025	0.0075	0.05	>0.1	0.05	0.05
30	Multergan	O	0.1	0.1	0.075	0.05	>0.1	0.05
31	—	O	0.025	0.01	>0.1	>0.1	0.025	>0.1
32	—	O	0.025	0.005	0.0075	0.025	0.0075	>0.1
33	47-83	O	0.025	0.01	0.1	>0.1	0.05	>0.1
34	Perazil	Cl	0.005	0.0025	0.05	0.025	0.01	0.05
35	48-166	Cl(2)	0.0025	0.0025	0.025	0.025	0.01	0.025
36	48-239	Cl(2)	0.0025	0.005	0.025	0.025	0.0075	0.025
37	Diphenylpyraline	O	0.01	0.0075	0.1	0.075	0.075	0.075
38	171B	Cl	0.0025	0.005	>0.1	>0.1	0.05	0.05
39	190A	Br	0.0025	0.0025	0.1	>0.1	0.05	0.075
40	Postafene	Cl	>0.1	>0.1	>0.1	>0.1	0.05	0.05
41	G20714	O	0.0075	0.005	0.005	0.001	0.01	0.0025
42	G21772	O	0.0005	<0.0001	0.01	0.0025	0.0025	<0.0001

basis of the present data between chlorine or bromine. The only preparations which are less active for any fungus than the corresponding non-halogenated compounds are numbers 3, 12, 38, and 39. Compounds 3 and 12 cannot strictly be compared with the non-halogenated compounds since they differ slightly in other respects as well as the possession of a halogen. Compound 3 differs from Pyribenzamine in the absence of a benzyl group and compound 12 has a different salt form. Diphenylpyraline shows a slightly greater activity against *S. Schenkii* than either the chlorinated or brominated compound (38 and 39). It is also slightly more effective against *M. apiospermum* than compound 38. These differences are questionable since they represent only a single dilution. Furthermore, against the remaining fungi the halogenated compounds are more effective.

Except for the questionable exceptions just discussed, in no case is the fungistatic activity of the non-halogenated compound higher than the halogen derivatives. In many instances the superiority of the latter compounds is especially striking. Thus, Benadryl is unable to inhibit any of the 6 fungi completely at a concentration of 0.1 M and only 2 of the 6 even partially at this concentration. Each of the halogenated derivatives, however (18, 19, 20), gives complete fungistasis of every fungus in these concentrations and partial inhibition at levels as low as 0.001 M. Similarly, brominated Pyribenzamine (2) inhibits completely all fungi at 0.1 M concentrations except *P. verrucosa* whereas Pyribenzamine itself can inhibit none at this concentration.

The data suggest that the introduction of 2 chlorine atoms into the molecule is more effective than a single chlorine. Compounds 35 and 36, containing 2 chlorines, are slightly more active than compound 34 which contains only 1, which, in turn, is more active than number 33 which contains none.

As in the previous report, the phenothiazine derivatives show good fungistatic activity. Lisergan, Phenergan,* and Lergigan* inhibit all fungi completely at concentrations of 0.1 M or less. The remaining compounds have fair activity but fail to inhibit at least one of the fungi employed.

The greatest activity over the widest spectrum is afforded by the phenanthroline compounds (41 and 42) which inhibit all fungi at concentrations from <0.0001 to 0.05 M.

The importance of obtaining an effective agent against systemic mycotic infections prompted the testing of the active agents listed in Tables II and III against *Coccidioides immitis*. The results are shown in Table IV. The zone of inhibition was read after 10 days' growth. Inhibition roughly parallels that observed with other fungi, although many differences are apparent. The most striking inhibition is given by the commercial fungistats (41, 42, and 24). To our knowledge, no previous report of their activity against *Coccidioides immitis* has been made. Five of the 15 compounds showing unequivocal inhibition are phenothiazine derivatives. Halogenated derivatives again show greater activity than their non-halogenated parents. Two of the most active compounds (35 and 36) each contain two chlorine atoms. Perazil (34) containing one chlorine atom gave significant inhibition, while 33 with no chlorine was completely ineffective. Simi-

* Recent data (9) suggest that these 2 compounds may be identical.

larly, compounds 18 and 19, the dichlorinated derivatives of Benadryl, gave excellent inhibition; Ambodryl (20), the mono bromo derivative, had questionable activity and Benadryl itself has little effect.

There seems little doubt that chlorination, bromination, and probably iodination, increase the activity against most fungi. Also, the substitution of a second chlorine apparently produces still more active compounds. It would be highly

TABLE IV

Effectiveness of various compounds (0.1M) in inhibiting growth of coccidioides immitis

NO.	NAME	HALOGENS PRESENT	DIAMETER OF ZONES INHIBITION	
			Complete	Partial
			cm.	*cm.*
41	Geigy 20704	O	6.2	8.0
42	Geigy 21772	O	5.4	6.8
24	Merrell 354R-285a 063002	O	4.2	7.0
27	Lergigan	O	3.4	Entire plate
35	Burroughs Wellcome 48-166	Cl(2)	3.4	6.3
36	Burroughs Wellcome 48-239	Cl(2)	3.4	5.8
32	—	O	3.4	4.4
26	Lisergan	O	3.0	8.4
18	—	Cl(2)	2.9	7.4
34	Perazil	Cl	2.8	7.0
19	—	Cl(2)	2.8	5.5
29	Diparcol	O	2.3	Entire plate
28	Phenergan	O	2.0	8.4
5	American Cyanamide Cl-216-118-66	I	1.8	7.2
2	American Cyanamide Cl-216-109-215A	Br	1.5	6.4
25	Asterol	O	0	Entire plate
11	Tagathen	Cl	0	7.4
20	Ambodryl	Br	0	7.4
13	Bromothen	Br	0	7.0
14	Isobromothen	Br	0	7.0
7	Nepera 1158	Cl	0	7.0
8	Nepera 1157	Cl	0	5.7
37	Diphenylpyraline	O	0	5.5
4	American Cyanamide 216-114-116	F	0	4.7
17	Benadryl	O	0	4.3
16	Eaton F 180	Br	0	4.2
38	Nopco 171B	Cl	0	4.0
33	Burroughs Wellcome 47-83	O	0	3.5
31	—	O	0	0

desirable to study the anti-fungus spectrum of a large number of such compounds and to test the most promising *in vivo*, especially against systemic infections. Further screening of additional preparations is planned, as are the indicated clinical studies.

SUMMARY

A total of 42 compounds were tested against *Trichophyton mentagrophytes*, *Microsporum canis*, *Monosporium apiospermum*, *Phialophora verrucosa*, *Sporo-*

richum Schenkii, and *Candida albicans*. Their relative effectiveness against each fungus is tabulated. The most effective of these compounds were tested against *Coccidioides immitis*.

Chlorination and bromination increase the fungistatic activity against most fungi. In the only instance tested, iodination increased the effectiveness but fluorination did not. The substitution of 2 chlorine atoms seemed to increase activity still further.

Additional phenothiazine derivatives were tested and were found active in most cases.

The most active fungistats against *Coccidioides immitis* were 1, 10 phenanthroline; 2, 9 dimethyl 1, 10 phenanthroline; and beta diethylamino ethyl 1 methyl 3 isopropyl cyclopentane-carboxylate hydrochloride.

REFERENCES

1. KLARMANN, E., GATES, L. W., AND SHTERNOV, V. A.: Halogen derivatives of monohydroxydiphenyl methane and their antibacterial action. J. Am. Chem. Soc., **54**: 3315, 1932.
2. KLARMANN, E., SHTERNOV, V. A. AND GATES, L. W.: Alkyl derivatives of halogen phenols and their bactericidal action. I. Chlorophenols. J. Am. Chem. Soc., **55**: 2576, 1933.
3. MARSH, P. B., BUTLER, M. L., AND CLARK, B. J.: Fungicidal activity of histophenols. Indust. & Engin. Chem., **41**: 2176, 1949.
4. WOODWARD, G. J., KINGERY, L. B. AND WILLIAMS, R. J.: Fungicidal power of phenol derivatives. I. Effect of introducing alkyl groups and halogens. J. Lab. & Clin. Med. **19**: 1216 1934.
5. FELTON, L. C. AND BREWER, J. H.: Action of substituted salicylaldehydes on bacteria and fungi. Science **105**: 409 1947.
6. HARRINGTON (cited by Suter, C. M.—Structures and Bactericidal Action of Phenols) Chem. Rev. **28**: 269 1941.
7. CARSON, L. E., AND CAMPBELL, C. C.: The inhibitory effects of three antihistaminic compounds on the growth of fungi pathogenic for man. Science **111**: 689 1950.
8. MITCHELL, R. B., ARNOLD, A. C. AND CHINN, H. I.: Fungistatic action of antihistaminic and anticholinergic compounds. J. Am. Pharm. A. (Scient. Ed.) **41**: 472 1952.
9. CHINN, H. I., HANDFORD, S. W., SMITH, P. K., CONE, T. E., REDMOND, R. F., MALONEY, J. V. AND SMYTHE, C. M.: Unpublished data.