J. Pharm. Pharmacol., 1964, **16**, 400–407 Received December 16, 1963

Antifungal activity of some imidazole derivatives

G. P. ELLIS,* C. EPSTEIN, C. FITZMAURICE, L. GOLBERG† AND G. H. LORD

A series of 4(5)-arylimidazoles and their *N*-alkyl and other derivatives has been synthesised. Some of these compounds possessed good *in vitro* antifungal action, especially against strains of *Trichophyton* and less activity against *Microsporum*, *Aspergillus* and *Candida* strains; their activity against all mycological pathogens was reduced in the presence of serum. The three most active compounds are 1-alkyl-4-(3,4-dichlorophenyl)imidazoles in which the alkyl group is an n-propyl, n-butyl or isobutyl group. 4(5)-(2,3,4-Trichlorophenyl)imidazole is also almost as potent as an antifungal compound. Structure-antifungal activity relations for these compounds are discussed.

THE imidazole ring occurs in several physiologically important compounds such as histamine, histidine and the purines. 4(5)-Aminoimidazole-5(4)-carboxyamide promotes the growth of some microorganisms and may be converted into purines by biological or chemical methods. In view of this and of the widespread chemical attention which has been paid to imidazole derivatives (Hofmann, 1953), it is surprising that few therapeutically useful compounds containing the simple imidazole ring exist. The antibiotic azomycin is 2-nitroimidazole (Nakamura, 1955); imidazole-4,5-dicarboxyamide and its 1-alkyl derivatives have been claimed to be effective against coccidiosis in poultry (Merck and Co., 1959); some imidazole-2-thiols have bacteriostatic activity (Simon & Kovtunovskaya-Levshina, 1957) and the use of metronidazole has been described (Cosar & Jolou, 1959). We have explored and now report the pharmacological and microbiological properties of a range of imidazole derivatives.

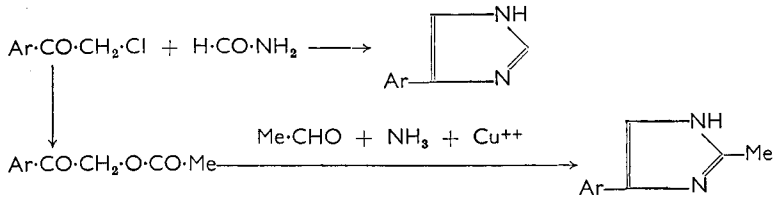
The compounds described consist of imidazoles containing a substituted benzene ring in position 4 or 5 and optionally an alkyl, cyanoalkyl, carboxyalkyl, hydroxyalkyl or pyridylethyl group attached to the ring nitrogen atom. Substituents in the benzene ring included one or more halogen atoms, methyl, cyano, nitro or carboxy groups. A few other related compounds are also included. The synthesis of some typical compounds is described in the experimental section, and the melting- or boiling-point and analysis of the compounds are listed in Table 1, except for those compounds whose analysis is given in the text.

Substituted 4(5)-arylimidazoles were generally prepared by the method of Bredereck & Theilig (1953) in which a phenacyl halide is heated under reflux with formamide. The phenacyl halides were synthesised by a Friedel-Crafts reaction between the aromatic compound and chloroacetyl chloride.

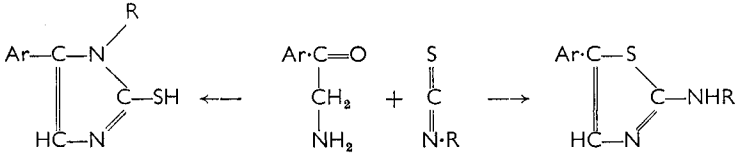
From the Research Department, Benger Laboratories Ltd., Holmes Chapel, Cheshire.

* Present address: Department of Chemistry and Biology, Welsh College of Advanced Technology, Cathays Park, Cardiff.

† Present address: British Industrial Biological Research Association, Radnor House, 93–97 Regent Street, London, W.1.



4(5)-*p*-Chlorophenyl-2-methylimidazole was prepared by heating the phenacyl acetate, acetaldehyde, aqueous ammonia and cupric acetate as described by Weidenhagen & Herrmann (1935) for related compounds. The ring nitrogen atom was alkylated by treatment first with sodium in ethanol and then with an alkyl halide in an autoclave at 100°. Since the formation of two isomeric products (the 4- and 5-arylimidazoles) is possible in this reaction, it was necessary to identify the isomer formed. When a phenacylamine is reacted with an alkyl isothiocyanate two products are formed, a 2-alkylamino-5-arylthiazole and a 1-alkyl-5-aryl-imidazole-2-thiol:



The thiazole, being less soluble in alkali, can be separated from the imidazole-2-thiol, which is then oxidised to the imidazole. When this sequence of reactions was carried out using 3,4-dichlorophenacylamine and methyl isothiocyanate, the dichlorophenylmethylimidazole eventually isolated was not identical with the isomer obtained by the methylation of 4(5)-(3,4-dichlorophenyl)imidazole. Direct alkylation of a 4(5)-aryl-imidazole therefore yields a 4-arylimidazole. A few 4(5)-arylimidazoles in which the imide nitrogen atom carries a 2-(pyrid-2-or-4-yl)ethyl group were prepared by reacting the imidazole with 2- or 4-vinylpyridine respectively. Although there is no direct proof of structure, it is assumed that the products of this reaction are also 4-arylimidazoles. A few nitro-phenyl compounds were obtained as by-products of the nitration of the imidazoles and their preparation will be described in a later paper.

Experimental

4-(3,4-*Dichlorophenyl*)-1-*methylimidazole.* 4(5)-(3,4-Dichlorophenyl)-imidazole (21·4 g) (prepared from 3,4-dichlorophenacyl chloride and formamide) in ethanol (50 ml) was treated with a solution of sodium (2·3 g) in ethanol (50 ml), followed by methyl iodide (14·2 g). The mixture was heated in an autoclave at 100° for 16 hr, then cooled and filtered. The filtrate was diluted with water and extracted with chloroform. After the extracts had been washed and dried (Na_2SO_4), the solvent was removed. The remaining oil distilled at 170–180° at 0·02 mm, and gave the *imidazole* (1·8 g) as crystals, m.p. 84–85° (from ether and light petroleum).

5-(3,4-*Dichlorophenyl*)-1-*methylimidazole*. To a stirred solution of sodium (7·7 g) in ice-cold ethanol (200 ml) was added 3,4-dichloroacetophenone (63 g), followed by the slow addition of butyl nitrite (34 g) in ethanol (50 ml) and ether (50 ml). The mixture was kept in a refrigerator overnight and the sodium salt was collected on a filter, washed with ether and dissolved in water (4 litres). The aqueous solution was filtered and acidified with 33% acetic acid (220 ml), whereupon 3,4-dichloro-α-isonitroso-acetophenone (15 g), m.p. 145°, was precipitated. A solution of this (8·8 g) in ethanol (250 ml) containing concentrated hydrochloric acid (4 ml) was shaken with 10% platinum on charcoal (0·9 g) in an atmosphere of hydrogen until the uptake of hydrogen ceased. Removal of the catalyst and solvent gave 3,4-dichlorophenacylamine hydrochloride (6·4 g), m.p. 210–220°. This hydrochloride (3·6 g), methyl isothiocyanate (1·1 g) and dry pyridine (30 ml) were heated under reflux for 2 hr, then poured into water and left to stand overnight. The solid was collected and stirred with hot 10% sodium hydroxide solution; the solution was filtered, and the filtrate was cooled and acidified to produce 5-(3,4-dichlorophenyl)-1-methyl-imidazole-2-thiol, m.p. 185–188° (decomp.). This was dissolved in ethanol and refluxed for 3 hr with an excess of Raney nickel. Removal of the catalyst and distillation of the solvent left an oil, b.p. 160° at 0·5 mm which solidified to give 5-(3,4-*dichlorophenyl*)-1-*methylimidazole* (0·6 g), m.p. 80–82°. An admixture of this with 4-(3,4-dichlorophenyl)-1-methylimidazole described above melted at 50°.

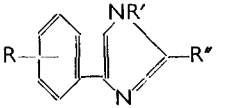
4(5)-(2,4,5-*Trichlorophenyl*)*imidazole*. (*a*) 4(5)-(2-Amino-4,5-dichlorophenyl)imidazole dihydrochloride (1·7 g) was diazotised and converted via a Sandmeyer reaction with cuprous chloride to 4(5)-(2,4,5-*trichlorophenyl*)*imidazole* (0·7 g), m.p. 228–229° (from aqueous methanol).

(*b*) 1,2,4-Trichlorobenzene (19 g), acetyl chloride (15·6 g) and aluminium chloride (25·4 g) were reacted together, first in refluxing carbon disulphide and then, after removal of the solvent, at 130° for 2 hr. 2,4,5-Trichloroacetophenone (4·2 g), b.p. 136–146° at 15 mm, was obtained and was reacted with bromine (3 g) in chloroform to form the phenacyl bromide. The chloroform was distilled off and the residue was heated under reflux for 2 hr with formamide (45 ml). After acidifying, filtering and basifying with ammonia, crystals of 4(5)-(2,4,5-*trichlorophenyl*)-*imidazole* (1·5 g), m.p. 226–227°, were obtained.

4(5)-(4,5-*Dichloro*-2-*cyanophenyl*)*imidazole*. 4(5)-(2-Amino-4,5-dichlorophenyl)imidazole dihydrochloride (7·7 g) dissolved in N hydrochloric acid (60 ml) was diazotised and treated with cuprous cyanide (3·8 g) and sodium cyanide (7 g). The *nitrile* (1·2 g) formed colourless leaflets, m.p. 245–246° (from aqueous ethanol).

1-(3,4-*Dichlorophenyl*)*imidazole*-2-*thiol*. 2,2-Diethoxyethyl isothiocyanate (Easson & Pyman, 1932) (6·6 g) and 3,4-dichloroaniline (6·2 g) were heated together on a steam-bath for 1 hr. The product was then heated under reflux with 5N sulphuric acid (140 ml) for 2 hr, cooled and filtered. The solid was recrystallised from ethanol to obtain the *thiol* (6·1 g),

TABLE 1. ARYLIMIDAZOLE DERIVATIVES



R″ = H except for compound No. 5, where R″ = Me

Compound No.	Position of aryl ring	R	R′	m.p. (or b.p.) °C	Formula	Analysis							
						Found				Required			
						C	H	Cl	N	C	H	Cl	N
1	4 (5)	*p*-NO_2	H	225	—	Grant & Pyman, 1921							
2	4 (5)	*p*-Br	H	140–142	—	Theilig, 1953							
3	4 (5)	*p*-Cl	H	146–147	—	Weidenhagen, Herrmann & Wegner, 1937							
4	4 (5)	*p*-MeO	H	139–140	—	Weidenhagen & Herrmann, 1935							
5	4 (5)	*p*-Cl	H (R″ = Me)	172–174	$C_{10}H_9ClN_2$	61·9	5·0	18·1	14·6	62·3	4·7	18·4	14·5
6	4 (5)	*p*-CN	H	168–169	$C_{10}H_7N_3$	70·7	4·3	—	25·2	71·0	4·2	—	24·8
7	4 (5)	*p*-Ph	H	222–223	$C_{15}H_{12}N_2$	82·3	5·3	—	12·6	81·8	5·5	—	12·7
8	4 (5)	4-Cl-2-NO_2	H	201	$C_9H_6ClN_3O_2$	48·3	2·9	15·9	18·7	48·4	2·7	15·9	18·8
9	4 (5)	4-Cl-3-NO_2	H	245	$C_9H_6ClN_3O_2$	48·1	2·8	16·0	18·6	48·4	2·7	15·9	18·8
10	4 (5)	4-Cl-3-Me	H	140	$C_{10}H_9ClN_2$	—	—	—	17·9	—	—	—	18·4
11	4 (5)	4-Cl-2-NH_2	H	274–275	$C_9H_{10}Cl_2N_3$	—	—	26·4[a]	—	—	—	26·4[a]	—
12	4 (5)	4-Cl-2-CO_2H	H	202–204	$C_{10}H_7ClN_2O_2$	53·4	3·3	16·1	13·1	53·9	3·2	16·0	12·6
13	4	*p*-NO_2	2-(pyrid-2-yl)ethyl	225–227	$C_{16}H_{15}Cl_2N_4O_2$	—	—	18·9	—	—	—	19·4	—
14	4 (5)	3,4-Cl_2	H	181	$C_9H_6Cl_2N_2$	50·8	2·9	33·2	13·4	50·7	2·8	33·3	13·1
15	4 (5)	2,4-Cl_2	H	143–144	$C_9H_6Cl_2N_2$	50·6	3·0	33·3	13·1	50·7	2·8	33·3	13·1
16	4 (5)	2,5-Cl_2	H	237–238	$C_9H_6Cl_2N_2$	50·8	2·7	33·1	12·8	50·7	2·8	33·3	13·1
17	4 or 5	3,4-Cl_2	D-Glucosyl	243–245	$C_{14}H_{16}Cl_2NO_5$	—	—	—	7·2	—	—	—	7·2
18	4	3,4-Cl_2	Me	84–85	$C_{10}H_8Cl_2N_2$	52·8	4·0	31·2	12·1	52·8	3·5	31·3	12·3
19	4	3,4-Cl_2	Et	(158–162/0·03 mm)									
				Picrate 249–250	$C_{17}H_{13}Cl_2N_5O_7$	43·3	2·9	—	14·7	43·4	2·8	—	14·9
20	4	3,4-Cl_2	Pr^n	(170/0·2 mm)									
				Picrate 203–204	$C_{18}H_{15}Cl_2N_5O_7$	44·5	2·9	—	14·7	44·6	3·1	—	14·5
21	4	3,4-Cl_2	Pr^i	(206–210/0·06 mm)									
				Picrate 252	$C_{18}H_{15}Cl_2N_5O_7$	44·5	3·3	—	14·3	44·6	3·1	—	14·5
22	4	3,4-Cl_2	Allyl	(196–200/0·05 mm)									
				Picrate 203	$C_{18}H_{13}Cl_2N_5O_7$	43·5	2·8	—	14·4	44·8	2·7	—	14·5
23	4	3,4-Cl_2	Bu^n	(170–174/0·02 mm)									
				Picrate 206	$C_{19}H_{17}Cl_2N_5O_7$	45·5	3·7	—	13·8	45·7	3·4	—	14·0
24	4	3,4-Cl_2	Bu^i	(210–220/0·06 mm)									
				Picrate 212	$C_{19}H_{17}Cl_2N_5O_7$	45·5	3·4	—	13·7	45·7	3·4	—	14·0

[a] Ionic chlorine.

TABLE 1—*continued*

Compound No.	Position of aryl ring	R	R′	m.p. (or b.p.) °C	Formula	Analysis							
						Found				Required			
						C	H	Cl	N	C	H	Cl	N
25	4	3,4-Cl_2	Bu^s	(210–215/0·05 mm)									
			Picrate	217	$C_{19}H_{17}Cl_2N_5O_7$	45·9	3·4	—	14·1	45·7	3·4	—	14·0
26	4	3,4-Cl_2	n-C_5H_{11}	(188–192/0·05 mm)									
			Picrate	177	$C_{20}H_{19}Cl_2N_5O_7$	46·6	3·9	—	13·8	46·8	3·7	—	13·7
27	4	3,4-Cl_2	n-C_6H_{13}	(192–196/0·05 mm)									
			Picrate	168	$C_{21}H_{21}Cl_2N_5O_7$	47·6	4·1	—	13·1	47·9	4·0	—	13·3
28	4	3,4-Cl_2	n-C_7H_{15}	(200–205/0·05 mm)									
			Picrate	163	$C_{22}H_{23}Cl_2N_5O_7$	48·5	4·4	—	13·0	49·0	4·3	—	13·0
29	4	3,4-Cl_2	n-$C_{16}H_{33}$	51–52	$C_{22}H_{35}Cl_2N$	67·8	8·8	—	6·5	68·7	8·7	—	6·4
30	4	3,4-Cl_2	$CH_2{\cdot}CH_2{\cdot}CN$	113	$C_{12}H_{10}Cl_2N_2$	53·9	3·5	—	15·6	54·1	3·4	—	15·8
31	4	3,4-Cl_2	$CH_2{\cdot}CH_2{\cdot}CO_2H$	187–188	$C_{12}H_{10}Cl_2N_2O_2$	50·3	3·6	—	9·4	50·6	3·5	—	9·8
32	4	3,4-Cl_2	$CH_2{\cdot}CH_2OH$	132–133	$C_{11}H_{10}Cl_2N_2O$	51·2	3·4	27·6	10·7	51·3	3·9	27·6	10·9
33	4	3,4-Cl_2	2-(pyrid-2-yl)ethyl	126	$C_{16}H_{12}Cl_2N_2$	—	—	22·1	—	—	—	22·3	—
34	4	3,4-Cl_2	2-(pyrid-2-yl)ethyl	218–219	$C_{16}H_{15}Cl_4N_2$	48·7	4·0	17·7[a]	—	49·1	3·8	18·1[a]	—
35	4	3,4-Cl_2	2-(pyrid-4-yl)ethyl	235	$C_{16}H_{15}Cl_4N_2$	48·8	3·9	17·9[a]	—	49·1	3·8	18·1[a]	—
36	4 (5)	4,5-Cl_2-2-NO_2	H	225–226	$C_9H_5Cl_2N_3O_2$	42·2	1·9	27·7	16·1	41·9	1·9	27·5	16·3
37	4	4,5-Cl_2-2-NO_2	Me	139–140	$C_{10}H_7Cl_2N_3O_2$	44·3	2·6	25·9	15·5	44·1	2·6	26·1	15·4
38	4	4,5-Cl_2-2-NO_2	2-(pyrid-2-yl)ethyl	220–224	$C_{16}H_{14}Cl_4N_4O_2$	—	—	16·0[a]	—	—	—	16·3[a]	—
39	4	4,5-Cl_2-2-NH_2	2-(pyrid-2-yl)ethyl	240–243	$C_{16}H_{16}Cl_4N_4$	—	—	17·2[a]	—	—	—	17·5[a]	—
40	4 (5)	4,5-Cl_2-2-NH_2	H	171–173	$C_9H_7Cl_2N_3$	46·8	3·2	31·4	17·9	47·3	3·1	31·1	18·4
41	4 (5)	4,5-Cl_2-2-Me	H	214–215	$C_{10}H_8Cl_2N_2$	52·6	4·0	—	12·0	52·8	3·5	—	12·3
42	4 (5)	4,5-Cl_2-2-CN	H	245–246	$C_{10}H_5Cl_2N_3$	50·9	2·5	29·6	16·7	50·4	2·1	29·8	17·6
43	4 (5)	4,5-Cl_2-2-CO_2H	H	283–284	$C_{10}H_6Cl_2N_2O_2$	46·3	2·4	27·4	11·0	46·7	2·3	27·6	10·9
44	4 (5)	2,3,4-Cl_3	H	195–196	$C_9H_5Cl_3N_2$	43·2	1·8	43·2	11·3	43·7	2·0	43·0	11·3
45	4 (5)	2,4,5-Cl_3	H	229–230	$C_9H_5Cl_3N_2$	43·7	2·0	43·2	11·1	43·7	2·0	43·0	11·3
46	4 (5)	2,4-Me_2	H	82–83	$C_{11}H_{12}N_2$	76·6	7·1	—	16·0	76·8	7·0	—	16·2

[a] Ionic chlorine.

m.p. 247–249°; found C, 45·0; H, 2·7; Cl, 28·1; N, 11·4; S, 12·8. $C_9H_6Cl_2N_2S$ requires C, 44·1; H, 2·5; Cl, 28·9; N, 11·4; S, 13·0%.

1-(3,4-*Dichlorophenyl*)*imidazole.* 1-(3,4-Dichlorophenyl)imidazole-2-thiol (5·1 g) was added in portions to hot 10% nitric acid (100 ml). When all the reaction had ceased the liquid was filtered, cooled and basified with ammonia. The precipitate gave crystals of the *imidazole* (3·6 g), m.p. 83–84°, from aqueous ethanol. Found C, 49·3; H, 3·0; Cl, 31·9; N, 12·6. $C_9H_6Cl_2N_2.\frac{1}{2}H_2O$ requires C, 48·6; H, 3·1; Cl, 31·9; N, 12·6%.

Biological methods

In vitro ASSAY OF FUNGISTATIC ACTIVITY

The following pathogenic fungi and yeast were obtained from the National Collection of Type Cultures, Colindale, London, and were used as test organisms: *Trichophyton rubrum* (T 88), *T. mentagrophytes* (T 95), *T. interdigitale* (T 72), *T. verrucosum* (T 97), *Candida albicans* (T 71), *Epidermophyton floccosum* (T 99), *Aspergillus fumigatus* (T 98), *Microsporum canis* (T 90) and *M. audouini* (T 100). The two culture media used were:

(*a*) for growth inhibition, Sabouraud's broth composed of 0·5% w/v pancreatic digest of casein, 0·5% w/v peptic digest of fresh meat and 2% w/v glucose in water at pH 5·7; this was sterilised for 15 min at 15 lb/in².

(*b*) to provide a potential biological antagonist of the growth inhibition provided by the test compound, a supplement of 10% v/v of heat-inactivated horse serum (Oxo) was added to the medium described in (*a*) and was provided in 9 ml and 5 ml quantities in 1 oz bottles.

A concentrated stock solution of the test compound at 1% w/v was prepared in either liquid macrogol (Carbowax 300) or glycerol formal. Neither of these solvents alone at 2% (drug concentrations equivalent to 200 μg/ml) exerted inhibitory activity but the neat solvents served as sterilising agents.

The fungistatic activity of the compounds was determined by a procedure similar to that of Collier, Potter & Taylor (1955), involving two-fold serial dilutions, with test compound concentrations over the ranges of 150–4·5, 100–3 and 10–0·3 μg/ml.

Inocula. (*a*) In tests against *C. albicans*, a heavily grown one-day-old culture of the yeast in Sabouraud's broth was diluted one hundred-fold and 0·1 ml of this suspension was introduced into bottles containing 5 ml of medicated broth as well as a bottle containing drug-free broth as growth control.

(*b*) In tests for fungistatic activity, 0·2 ml suspensions of mycelium and spores were taken from 7–21-days-old broth cultures of the filamentous moulds and added to 10 ml Sabouraud's broth in a screw-capped bottle, shaken well and then allowed to stand at room temperature for 10 min to allow any large fragments to settle. The slightly opalescent supernatants were diluted ten-fold and then 0·1 ml of the respective inoculum

was used to inoculate 5 ml volumes of the serially diluted test compound in Sabouraud's broth.

After inoculation, the bottles were incubated at 28° for 7 days and the degree of inhibition was read by eye, recording after 3 and 7 days the maximum dilution of the drug to give partial growth as compared with the growth control. In addition, the dilution required to give complete visual inhibition of the fungi, that is, the minimum inhibitory concentration in μg/ml was observed.

TABLE 2. ANTIFUNGAL ACTIVITY OF IMIDAZOLE DERIVATIVES

Compound No.	Minimum inhibitory concentration after 7 days at 28° (μg/ml)			
	Trichophyton	*Microsporum*	*Aspergillus*	*Candida*
7	20			
14	25			
18	25			
19	25			
20	4 (15)	15 (45)	20 (40)	25 (50)
21	25			
22	20			
23	5 (12)	12 (25)	18 (35)	25 (50)
24	5	20	—	50
25	25			
26	10	25	—	50
27	7·5	100	—	50
28	20			
29	20			
30	25			
33	8 (22)	60 (100)	50 (75)	100
41	25			
42	12	50	—	50
43	25			
44	6 (15)	12 (25)	—	—
45	25			
Hedaquinium chloride	1 (3)	1 (1)	5 (5)	0·5 (1)
Nystatin	2 (5)	2 (5)	5 (10)	2 (5)
N-Butyl-4-chloro-2-hydroxybenzamide (Jadit)	25 (100)	25 (100)	25 (150)	50 (200)

The figures in parentheses were determined in the presence of serum.

Results

Of the compounds described in this paper, those listed in Table 2 exhibited activity at a concentration of 25 μg/ml or less against at least one of the species mentioned the previous section. The minimum inhibitory concentrations given were determined in medium without serum supplement, except for the values shown in brackets which were determined in the presence of 10% inactivated horse serum.

Discussion

CHEMICAL STRUCTURE—BIOLOGICAL ACTIVITY CONSIDERATIONS

The *in vitro* tests show a distinct relationship between the structure and the antifungal activity of the imidazoles studied. The presence of only one halogen atom in the benzene ring (as in compounds 2 and 3) does not confer fungicidal activity and neither does a pair of chlorine atoms in positions 2 and 4 or 2 and 5 (compounds 15 and 16), but the 3,4-dichlorophenyl derivative does show moderate activity. It is of interest to mention that a clinically used antifungal drug, Dybenal, is

2,4-dichlorobenzyl alcohol (Taylor & D'Arcy, 1961). Alkylation of the ring nitrogen atom had no effect on potency if the alkyl group contained up to three carbon atoms, although the allyl compound (22) showed a marginal improvement. Longer alkyl chains, however, increased the potency until a maximum was reached at the n-hexyl derivative, after which activity rapidly diminished. A similar variation of activity with length of alkyl chain has been demonstrated for a number of 2-alkoxybenzamides (Coates, Drain, Macrae & Tattersall, 1959). It cannot be stated that branching of the alkyl chain has a uniform effect on antifungal activity (compare compounds 20, 21 and 23, 24, 25), neither has increasing the number of halogen atoms in the aryl ring as it depends on their positions, the 2,3,4- orientation (compound 44) giving a higher activity than the 2,4,5- arrangement (compound 45). Difficulties in synthesis prevented further exploration of these trichlorophenyl compounds.

The presence in the aryl ring of a nitro, amino, carboxy or methyl group in addition to the halogens had no appreciable effect on potency, but a nitrile group (compound 42) appeared to double the activity. A nitrile group without the halogen atoms (compound 6) however, had no merit. In the only active compound (7) not containing a halogen atom or nitrile group, the aryl substituent consisted of a *p*-phenyl substituent.

Although the potency of a few of the compounds was high, especially against *T. interdigitale*, the activity was adversely affected by the presence of serum.

Acknowledgements. The authors wish to thank Mr. K. F. Clarke and Mr. P. B. Johnson for experimental assistance and Mr. C. Campbell, B.Sc., F.R.I.C., for analytical results.

References

Bredereck, H. & Theilig, G. (1953). *Chem. Ber.*, **86**, 88–96.
Coates, L. V., Drain, D. J., Macrae, F. J. & Tattersall, K. (1959). *J. Pharm. Pharmacol.*, **11**, 240*T*–249*T*.
Collier, H. O. J., Potter, M. D. & Taylor, E. P. (1955). *Brit. J. Pharmacol.*, **10**, 343–347.
Cosar, C. & Julou, L. (1959). *Ann. Inst. Pasteur*, **96**, 238–241.
Easson, A. P. T. & Pyman, F. L. (1932). *J. chem. Soc.*, 1806–1812.
Grant, R. L. & Pyman, F. L. (1921). *J. chem. Soc.*, **119**, 1893–1903.
Hofmann, K. (1953). *Imidazole and its Derivatives, Part I.* New York: Interscience Publishers Inc.
Merck and Co. (1959). U.S. Patent 2,872,371.
Nakamura, S. (1955). *Pharm. Bull. Japan*, **3**, 379–383.
Simon, I. B. and Kovtunovskaya-Levshina, I. I. (1959). *Tiolovye Soedinen. v. Med. Ukrain. Nauch-Isseldovatel. Sanit. Khim. Inst., Trudy Nauch. Konf. Kiev*, 40–46.
Taylor, E. P. & D'Arcy, P. F. (1961). In *Progress in Medicinal Chemistry*, Volume 1, pp. 220–255; ed. Ellis, G. P. and West, G. B., London: Butterworths.
Theilig, G. (1953). *Chem. Ber.*, **86**, 96–109.
Weidenhagen, R. & Herrmann, R. (1935). *Ber. dtsch. chem. Ges.*, **68**, 1953–1961.
Weidenhagen, R., Herrmann, R. & Wegner, H. (1937). *Ibid.*, **70**, 570–583.