THE PREPARATION AND ANTIFUNGAL ACTIVITY OF SOME SALICYLIC ACID DERIVATIVES

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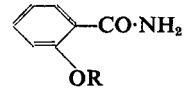
A series of 2-alkoxy derivatives of benzamide, halogenated benzamides, 3-naphthamide, and *N*-substituted benzamides has been prepared and tested *in vitro* as potential antifungal agents. 2-*n*-Amyloxybenzamide, the most active of the derivatives studied, is a slow-acting fungicide of greater fungistatic potency than undecylenic acid, *N*-*n*-butyl-3-phenylsalicylamide, salicylanilide, Nystatin, phenylmercuric acetate, sodium ethylmercurithiosalicylate and 8-hydroxyquinoline.

During routine screening of compounds for chemotherapeutic activity it was observed that 2-*n*-amyloxybenzamide (I,R=$C_5H_{11}{}^n$) and 2-*n*-hexyloxybenzamide (I,R=$C_6H_{13}{}^n$), originally prepared in the course of a search for new analgesics related to salicylamide[1], had fungistatic properties against certain dermatophytes. Many compounds have since been prepared and tested,



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and those more closely related to the active substances are here reported. 2-*n*-Amyloxybenzamide has been found to have *in vitro* fungistatic activity comparable with substances commonly used in the treatment of dermatomycoses.

Experimental

Chemical

Alkyl ethers of salicylamide and its derivatives. The alkyl ethers of salicylamide and of its nuclear and *N*-substituted derivatives were prepared by treatment of the appropriate salicylamide (1 mole) with an alkyl halide (1 mole) in boiling ethanolic sodium ethoxide (1 mole). After the mixture had been refluxed for 24 hours, the ethanol was removed by distillation to give a residue which was washed with 2N sodium hydroxide. The alkyl ether was collected by filtration or ether extraction and purified by either crystallisation or distillation.

N-*Substituted salicylamides.* Mono-substituted amides were prepared by refluxing together methyl salicylate (1 mole) with the corresponding primary amine (2 mole) for 18 hours. Di-substituted amides were prepared by heating phenyl salicylate (1 mole) with the appropriate secondary amine (2 mole) at 140° for 6 hours. The volatile substances were removed under reduced pressure and the residue either recrystallised or distilled *in vacuo* to give the *N*-substituted salicylamide.

Carboxyalkyl ethers. The ethyl esters of the relevant bromo-acids were used to alkylate salicylamide as described above. The corresponding acids were obtained by hydrolysis of the esters with aqueous 2N sodium hydroxide.

3:5-*Diiodosalicylamide.* Hydrogen peroxide (18 ml. of a 30 per cent solution) was slowly added to a mixture of salicylamide (16 g.), iodine (30 g.), sulphuric acid (8 ml.), and ethanol (80 ml.) at 60°. The product that crystallised out on cooling the reaction mixture was collected by filtration and recrystallised (cf. method of Jurd[2]).

4:5-*Dichlorosalicylamide.* Methyl 4:5-dichlorsalicylate (20 g.), ethanol (50 ml.), and aqueous ammonia (100 ml., d. 0·88) were allowed to stand at room temperature for 7 days. The amide obtained on evaporating the solvent from the reaction mixture was recrystallised from ethanol.

N-n-*Butyl-3-phenyl salicylamide.* *N-n*-Butyl-3-phenylsalicylamide was prepared by two methods: (*a*) from methyl 3-phenylsalicylate (b.p. 144 to 148°/1 mm.) and *n*-butylamine by the method described by Jules and others[3]; and (*b*) from phenyl 3-phenylsalicylate (m.p. 95°) by heating with *n*-butylamine at 150 to 160° for five hours. The compounds obtained from methods (*a*) and (*b*) both recrystallised from aqueous methanol or light petroleum to give needles, m.p. and mixed m.p. 49·5 to 50·5°. Found: C, 75·7; H, 7·2; N, 5·5. Calc. for $C_{17}H_{19}NO_2$ C, 75·8; H, 7·1; N, 5·2 per cent. Jules records m.p. 71 to 72° for this compound. Comparison with a sample m.p. 71° to 72° kindly supplied by Dr. J. A. Faust, Director of Organic Research, Sahyun Laboratories, gave no depression of melting point on admixture. The product m.p. 49·5° to 50·5°, after melting and seeding with a crystal of the higher melting form had m.p. 71° to 72°.

The pertinent analytical details for new compounds are shown in Table I.

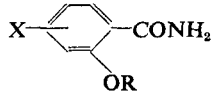
Microbiological

Fungistatic Test. The organisms and media used are shown in Table II. Activity was assayed by the method of Schamberg and Kolmer[4] with the modified inoculation technique devised by Archibald and Reiss[5].

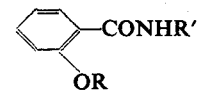
Compounds were dissolved in a 'self-sterilising' solvent consisting of ethanol (70 vols), propylene glycol (5 vols), and distilled water (25 vols), to give a concentration of 1·0 per cent w/v. These solutions were then serially diluted in Sabouraud broth and aliquots transferred to molten malt agar to give final concentrations within the range 50 — 1·5 μg./ml. The highest concentration of ethanol incorporated in the dilution plates was 0·35 per cent v/v which had previously been shown to exert no fungistatic effect. Test plates were inoculated by implanting a small portion of mycelium not exceeding 2 mg. in weight, from a 10 to 17 day old stock culture of the fungus under test. With *M. audouini* and *T. tonsurans* it was necessary to lift the mycelial mat from the agar plate before cutting into small portions. The plates were incubated for 7 days at 25 to 28°,

TABLE I

SUBSTITUTED SALICYLAMIDES



X	R	Physical form	Melting point °C.	Empirical formula	Required per cent			Found per cent		
					C	H	N	C	H	N
H	Bu^{sec}	Prisms[a]	69·5–70·5	$C_{11}H_{15}NO_2$	68·4	7·8	7·3	68·4	7·7	7·4
H	$C_5H_{11}{}^i$	Needles[b]	89	$C_{12}H_{17}NO_2$	69·5	8·3	6·8	69·7	8·2	—
H	$-CH(CO_2H)CH_3$	Prisms[c]	184–185	$C_{10}H_{11}NO_4$	57·4	5·3	6·7	57·5	5·2	6·1
H	$-CH(CO_2H)C_2H_5$	Prisms[c]	179–180	$C_{11}H_{13}NO_4$	59·2	5·8	6·3	59·0	6·0	6·4
H	$-CH(CO_2H)C_6H_7{}^n$	Prisms[c]	156–157	$C_{15}H_{19}NO_4$	60·8	6·3	5·9	60·4	6·3	5·9
5-Cl	Bu^n	Plates[a]	98·5	$C_{11}H_{14}ClNO_2$	58·0	6·2	6·2	58·1	6·1	6·3
5-Cl	$C_5H_{11}{}^n$	Plates[a]	91	$C_{12}H_{16}ClNO_2$	59·6	6·7	5·8	59·4	6·4	5·7
5-Cl	$C_6H_{13}{}^n$	Plates[a]	94	$C_{13}H_{18}ClNO_2$	60·9	7·1	—	61·3	7·2	—
5-Br	$C_6H_{13}{}^n$	Plates[a]	103	$C_{13}H_{18}BrNO_2$	52·0	6·0	4·7	51·9	6·3	4·5
3:5-I_2	H	Needles[c]	199	$C_7H_5I_2NO_2$	21·6	1·3	3·6	22·1	1·5	3·6
3:5-I_2	$C_5H_{11}{}^n$	Needles[c]	147	$C_{12}H_{15}I_2NO_2$	31·4	3·3	3·1	31·5	3·4	2·9
3:5-I_2	$C_6H_{13}{}^n$	Needles[c]	147·5–148	$C_{13}H_{17}I_2NO_2$	33·0	3·6	3·0	33·0	3·6	2·9
4:5-Cl_2	H	Needles[c]	230	$C_7H_5Cl_2NO_2$	40·8	2·4	6·8	40·6	2·6	7·0
4:5-Cl_2	Bu^n	Clusters[a]	137	$C_{11}H_{13}Cl_2NO_2$	50·4	5·0	5·3	50·7	5·2	5·7
4:5-Cl_2	$C_5H_{11}{}^n$	Needles[a]	138	$C_{12}H_{15}Cl_2NO_2$	52·2	5·5	5·1	52·5	5·3	5·1
Benz-*d*	Bu^n	Prisms[a]	144	$C_{16}H_{17}NO_2$	74·1	7·0	5·8	73·8	7·0	6·0
Benz-*d*	$C_5H_{11}{}^n$	Prisms[a]	132	$C_{16}H_{19}NO_2$	74·7	7·4	5·4	74·7	7·3	5·6
Benz-*d*	$C_6H_{13}{}^n$	Needles[d]	123	$C_{17}H_{21}NO_2$	75·3	7·7	5·2	75·2	7·5	5·0



R	R′	Physical form	Melting point	Empirical formula	Required per cent			Found per cent		
					C	H	N	C	H	N
H	$C_6H_{13}{}^n$	Prisms[a]	42·5–43·5	$C_{13}H_{19}NO_2$	70·5	8·7	6·3	70·2	8·8	6·4
Bu^n	Bu^n	Matted needles[a]	40–41	$C_{15}H_{23}NO_2$	72·3	9·3	5·6	72·1	9·4	5·9
$C_5H_{11}{}^n$	Bu^n	Matted needles[a]	39–40	$C_{16}H_{25}NO_2$	73·0	9·6	5·3	73·0	9·8	5·3
$C_5H_{11}{}^n$	$C_6H_{13}{}^n$	Colourless oil[e]	—	$C_{18}H_{29}NO_2$	74·2	10·0	4·8	74·4	10·6	5·0
$C_5H_{11}{}^n$	Ph	Matted needles[b]	44–45	$C_{16}H_{21}NO_2$	76·3	7·5	5·0	76·3	7·6	5·0
$C_6H_{13}{}^n$	Bu^n	Matted needles[a]	36–37	$C_{17}H_{27}NO_2$	73·6	9·8	5·0	73·3	9·7	4·7
$C_6H_{13}{}^n$	Ph	Plates[a]	51	$C_{18}H_{23}NO_2$	76·7	7·8	—	76·3	7·9	—

Analyses by Drs. Weiler and Strauss. M.ps. uncorrected.

[a], Recrystallised from light petroleum; [b], recrystallised from aqueous ethanol; [c], Recrystallised from ethanol; [d], recrystallised from ethyl acetate; [e] (b.p. 172–174°/0·35 mm.).

and the inhibitory level of a compound was taken as the highest dilution which completely prevented fungal development.

An anti-fungal index, being the sum of the minimum inhibitory concentrations divided by the number of dermatophytes tested is incorporated in Tables III and IV.

Antimicrobial activity against yeasts and bacteria was determined by serial dilution of the compounds in the appropriate liquid medium, followed by inoculation and a suitable incubation.

Fungicidal Tests. The method used was similar to that of Golden and Oster[6], except that exposure times were prolonged and the rinsing procedure modified.

TABLE II

Microorganisms	Test medium
Trichophyton mentagrophytes, 6 strains (*a*); *T. rubrum* (*a*); *T. concentricum* (*a*); *Microsporum audouini* (*a*); *T. tonsurans* (*a*); *Sporotrichum schenkii* (*a*); *Epidermophyton floccosum* (*a*); *Allescheria boydii* (*b*); *Hormodendron pedrosoi* (*b*).	Malt agar*.
Rhizopus nigricans (*c*); *Aspergillus niger* (*c*); *Penicillium notatum* (*c*); *Mucor erectus* (*c*); *M. hiemalis* (*c*).	Malt agar*.
Candida albicans (*a*); *Saccharomyces cerevisiae* (*c*).	Sabouraud Maltose Broth (Difco Ltd.).
Staphylococcus aureus (*d*); *Pseudomonas aeruginosa* (*d*); *Escherichia coli* (*d*); *Bacillus subtilis* (*d*).	Nutrient Broth No. 2 (Oxo Ltd.).
Streptococcus pyogenes (*d*); *Diplococcus pneumoniae* (*d*); *Corynebacterium diphtheriae* (*d*); *Actinomyces bovis* (*d*); *Pfeifferella mallei* (*d*).	Todd Hewitt Broth[12].
Mycobacterium tuberculosis H37Rv (*d*); *M. phlei* (*d*).	Proskauer and Beck medium.

* Malt extract B.P. (Muntona Ltd.), 40 g.; Yeast extract (Oxo Ltd.), 5 g.; New Zealand Agar (Oxo Ltd.) 15 g.; Distilled water to 1 litre. The pH adjusted to 5·6–5·8 with lactic acid.

(*a*) Supplied through the courtesy of Dr. J. Walker, Director of Medical Mycology, London School of Tropical Medicine and Hygiene.

(*b*) Generously given by Col. R. Lewis, M.C., Director, 5280th Clinical Laboratory, U.S.A.F.

(*c*) Own isolate.

(*d*) National Collection of Type Cultures.

1 sq. cm. plaques, cut from a 10 day culture of *T. mentagrophytes* on an agar plate, were immersed in sterile horse serum for 15 seconds and then transferred to 5 ml. amounts of dilutions of the compounds in Dubos broth for periods of 1 hour, 24 hours and 5 days. After exposure the fungal plaques were immersed in 30 per cent v/v aqueous acetone for 10 minutes and transferred to 20 ml. of Sabouraud broth. Finally, the plaques were placed aseptically onto malt agar plates which were incubated for 14 days at 25 to 28°.

The results of these tests are shown in Table V.

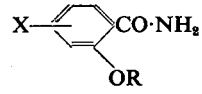
Results and Discussion

A few only of the salicylamide derivatives prepared exhibit high fungistatic activity (Table III). Consideration of the activities of 2-alkoxybenzamides indicates that there is a considerable degree of structural specificity in the activity of this group of compounds. Alkylation of the hydroxyl group of salicylamide by C_3–C_7 alkyl radicals confers activity against the dermatophytes. Maximal antifungal activity occurs with the

n-amyloxy and *n*-hexyloxy derivatives, the former proving significantly more active when the incubation period was extended to 14 days. This fungistatic effect is greatest when the alkyl substituent is unbranched and is no longer apparent with the *n*-octyloxy-derivative. The phenoxyacetic acid derivatives of this series although related to known herbicidal and fungicidal agents[7,8] do not inhibit growth of dermatophytes under the reported test conditions. Activity was not increased by the preparation of either nuclear substituted halogen derivatives or naphthamide

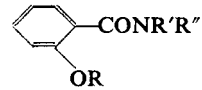
TABLE III

FUNGISTATIC ACTIVITIES OF SUBSTITUTED SALICYLAMIDES



X	R	Minimum inhibitory concentration μg./ml. †T.m.	T.t.	T.c.	T.r.	E.f.	M.a.	Anti-fungal index
H	H	>50	50	50	50	50	50	>50
H	Me^{1b}	>50	—	—	50	>50	—	>50
H	Et^{18}	>50	—	—	50	>50	—	>50
H	Pr^{n1}	>50	50	25	25	25	6	>30
H	Pr^{i19}	>50	—	—	50	>50	—	>50
H	Bu^{n1}	12	25	12	12	12	6	13
H	Bu^{sec}*	>50	>50	>50	>50	>50	>50	>50
H	$C_5H_{11}{}^{n1}$	6	3	3	3	1	1·5	3
H	$C_5H_{11}{}^{i}$*	25	12	6	6	6	6	10
H	$C_6H_{13}{}^{n1}$	12	3	3	3	3	1·5	4
H	$C_7H_{15}{}^{n1}$	50	25	12	12	25	25	25
H	$C_8H_{17}{}^{n1}$; $-(CH_2)_2\cdot CH(CH_3)\cdot CH_2\cdot C(CH_3)_3{}^{1}$; $C_{12}H_{25}{}^{n1}$; $C_{14}H_{29}{}^{n1}$; $-CH_2\cdot CO_2H^{14}$; $-(CH_2)_2\cdot CO_2H^{21}$; $-CH(CO_2H)\cdot CH_3$*; $-CH(CO_2H)\cdot C_2H_5$*; $-CH(CO_2H)\cdot C_5H_7{}^{n}$*; $-(CH_2)_2\cdot N(C_2H_5)_2\cdot HCl.^{21}$ All compounds have M.I.C. >50 against all fungi tested.							
5–Cl	H^{15}	50	50	50	50	50	25	46
5–Cl	Bu^{n}*	50	25	50	50	50	25	41
5–Cl	$C_5H_{11}{}^{n}$*	>50	>50	>50	>50	>50	>12	>43
5–Cl	$C_6H_{13}{}^{n}$*	>50	>50	>50	>50	>50	25	>46
5–Br	$C_6H_{13}{}^{n}$*	>50	>50	>50	>50	>50	25	>46
3:5–Cl_2	H^{15}	50	25	50	50	50	12	39
3:5–I_2	H*	50	25	50	25	25	6	30
3:5–I_2	$C_5H_{11}{}^{n}$*	>50	>50	>50	>50	>50	>50	>50
3:5–I_2	$C_6H_{13}{}^{n}$*	50	50	50	50	50	50	50
4:5–Cl_2	H*	50	25	25	25	25	6	26
4:5–Cl_2	Bu^{n}*	>50	50	50	50	50	50	>50
4:5–Cl_2	$C_5H_{11}{}^{n}$*	>50	>50	50	50	>50	50	>50
Benz·*d*	H^{16}	>50	>50	>50	>50	>50	>50	>50
Benz·*d*	Bu^{n}*	50	50	50	50	50	50	50
Benz·*d*	$C_5H_{11}{}^{n}$*; C_6H_{13}*. M.I.C. >50 against all fungi tested.							

TABLE III—*continued*



R	R'	R"	Minimum inhibitory concentration μg./ml. T.m.†	T.t.	T.c.	T.r.	E.f.	M.a.	Anti-fungal index
H	H	Me^{17}	>50	—	—	>50	>50	—	>50
H	Me	Me^{18}	>50	>50	>50	>50	>50	>50	>50
H	Et	Et^{19}	>50	—	—	>50	>50	—	>50
H	H	Bu^{n20}	50	50	50	50	50	50	50
H	H	$C_6H_{13}{}^{n}$*	25	25	25	25	12	25	23
Bu^n	H	Bu^n*	25	12	12	12	12	12	14
$C_5H_{11}{}^{n}$	H	Bu^n*	25	12	12	12	12	12	14
$C_5H_{11}{}^{n}$	H	$C_6H_{13}{}^{n}$*	>50	>50	>50	>50	>50	>50	>50
$C_5H_{11}{}^{n}$	H	Ph*	>50	>50	>50	>50	>50	>50	>50
$C_6H_{13}{}^{n}$	H	Bu^n*	25	25	50	25	25	25	29
$C_6H_{13}{}^{n}$	H	Ph*	50	>50	>50	50	50	25	>46

* See Table I.
† T.m. = *T. mentagrophytes*, T.t. = *T. tonsurans*, T.c. = *T. concentricum*, T.r. = *T. rubrum*, E.f. = *E. floccosum*, M.a. = *M. audouini*.

analogues. All these latter derivatives were generally inactive at a concentration of 50 μg./ml., although a few halogenated compounds inhibited the growth of one organism, *M. audouini*, at low concentrations. This loss of potency on halogenation is in contrast to the increase in activity shown by the halogenated derivatives of phenol[9], but compares with the decrease in fungitoxicity of halogen substituted 2-phenylphenol derivatives[9]. The lack of fungistatic properties of the 3-alkoxy-2-naphthamides is parallelled by the recently reported[10] low antibacterial activities of naphthol derivatives.

TABLE IV

COMPARISON OF ANTIFUNGAL ACTIVITY OF 2-*n*-AMYLOXY BENZAMIDE WITH KNOWN FUNGISTATIC AGENTS

Compound	Minimum inhibitory concentration T.m.*	T.t.	T.c.	T.r.	E.f.	M.a.	Antifungal index
2-*n*-Amyloxybenzamide	6	3	3	3	1·5	1·5	3
N-*n*-Butyl 3-phenylsalicylamide	>50	25	25	6	>50	3	>26
Salicylanilide	12	6	6	3	6	1·5	6
8-Hydroxyquinoline	15	4	8	8	8	2	7
Undecylenic acid	>50	50	25	50	25	12	>35
Phenylmercuric acetate	25	1·5	25	6	6	6	12
Sodium ethylmercurithiosalicylate ..	12	1·5	12	6	1·5	1·5	6
Nystatin	15	4	8	15	4	4	8

* See footnote to Table III for definitions.

The preceding results prompted the preparation of a number of *N*-substituted and *ON*-disubstituted salicylamides, none of which showed activity comparable with that of 2-*n*-amyloxybenzamide.

The fungistatic activity of 2-*n*-amyloxybenzamide was compared with that of other compounds of known activity (Table IV). The 2-*n*-amyloxy derivative was found to be more active than *N*-*n*-butyl-3-phenylsalicylamide, undecylenic acid, salicylanilide, Nystatin, phenylmercuric acetate, sodium ethylmercurithiosalicylate, and 8-hydroxyquinoline.

TABLE V

COMPARATIVE FUNGICIDAL ACTIVITIES AGAINST *T. mentagrophytes*

Compound	Exposure period	Dilution µg./ml. 1000	100
N-Butyl-3-phenyl salicylamide ..	1 hr.	+	+
	24 hrs.	+	+
	5 days	−	+
2-*n*-Amyloxy benzamide	1 hr.	+	+
	24 hrs.	−	+
	5 days	−	+
Salicylanilide	1 hr.	+	+
	24 hrs.	+	+
	5 days	−	+

+, −, = Growth, or no growth on sub-culture at 14 days.

It seemed logical in considering the use of 2-*n*-amyloxybenzamide for the chemotherapy of dermatophyte infections to compare the fungicidal activity of this compound with other known antifungal agents. Preliminary results (Table V) indicate that it is a slow-acting fungicide comparable with salicylanilide and *N*-*n*-butyl-3-phenylsalicylamide.

Amyloxybenzamide inhibited our test range of fungi, at 25 to 28°, at the following concentrations in µg./ml. *Hormodrendron pedrosoi*, 25, *Sporotrichum schenkii*, *Allescheria boydii*, *Rhizopus nigricans*, *Aspergillus niger*, *Penicillium notatum* and *Mucor hiemalis*, 100, and *Mucor erectus* at >100. Of the yeasts, *Candida albicans* at 37° was inhibited at 62 and *Saccharomyces cerevisiae* at 25 to 28°, at 250. Of bacteria, at 37°, *Mycobacterium tuberculosis* H37Rv was inhibited at 31, *Mycobacterium phlei* at 125, *Corynebacterium diphtheriae*, *Bacillus subtilis*, *Staphylococcus aureus*, *Streptococcus pyogenes*, *Diplococcus pneumoniae* and *Pfeifferella mallei* at 250, *Pseudomonas aeruginosa* at 500, and *Actinomyces bovis* and *Escherichia coli* at >500.

2-*n*-Amyloxybenzamide is an antifungal agent with specificity for dermatophytes commonly responsible for mycotic infections in man. Animal tests have been commenced and these, together with further pharmacological investigations will form the subject of a later communication.

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DISCUSSION

The paper was presented by MR. D. J. DRAIN.

The CHAIRMAN. The authors had not given any solubility data for the most active compound, and data should also be given about partition between non-aqueous and aqueous media.

DR. J. C. PARKINSON (Brighton). Did the fungistatic values alter with temperature? Had any tests been made at 37°?

MR. G. R. WILKINSON (London) asked about the toxicity of the compounds.

DR. G. E. FOSTER (Dartford) enquired about the mechanism of action of the substances.

MR. G. SYKES (Nottingham). It was common amongst the newer antifungal agents to be rather more specific and more active against pathogenic fungi than saprophytic types. What was the virtue of carrying out a fungicidal test at an interval of five days? Was fungistatic or fungicidal activity desirable for clinical use?

MR. T. D. WHITTET (London). There would be little difficulty in obtaining clinical material in man.

DR. B. K. MARTIN (Slough). Lack of success in the treatment of fungal infection was largely due to the use of fungistatic rather than fungicidal agents.

DR. J. B. STENLAKE (Glasgow). Had the solubilities been considered in relation to the size of the alkyl group, because as this was increased there was a steady drop in solubility and then a sudden drop.

MR. D. J. DRAIN replied. The compounds had not been tested at 37°, but the test method was rigorous. The acute LD50's for a number of

alkyl ethers of salicylamide both by oral and interperitoneal routes had been given by the authors in the *Journal of Pharmacy and Pharmacology* in 1952. No sensitising properties of the substances was detected when lotions were applied to animal or human skin. The test substances interfered with the metabolism of the organism. The pharmaceutical preparation of an antifungal substance was as important as the inherent activity of the substance itself, and they had concluded that clinical trials would be necessary. Bushby and Stewart in 1949 were unable to find any correlation between fungicidal activity and the activity in their animals. A marked difference was found in the *in vivo* effects depending on the base used. There was little correlation between relative fungistatic or fungicidal potencies, and there were no clinical results on their substances as yet. They considered that a five-day fungicidal test was different from a fungistatic test. The dissociation constants of the amides had not been determined, but it was certain that they would be very weak bases. The solubility of the amyloxybenzamides in aqueous solution had not yet been determined, but it would probably be about 50 to 100 μg./ml. In alcohol, chloroform and benzene the compounds were readily soluble, and the partition ratios between water and a fatty solvent would be in favour of the organic solvent. The problem of solubilities was being investigated. A sudden drop in solubility probably occurred between the butyl and amyl members of the series.