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THE ANTISCHISTOSOMAL AND RETINOTOXIC EFFECTS OF SOME NUCLEAR SUBSTITUTED AMINOPHENOXYALKANES

BY

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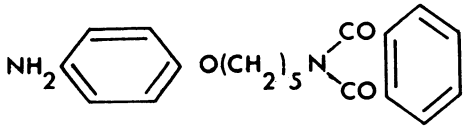
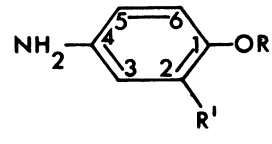
The activity of M&B 2948A(I) against *Schistosoma mansoni* in mice was reported by Collins, Davis, Edge, Hill, Reading & Turnbull (1959), who also found that it produced ocular effects in only a small proportion of the cats tested, in contrast to 1,5-di-(*p*-aminophenoxy)pentane and its homologues, which with the exception of the



(I)



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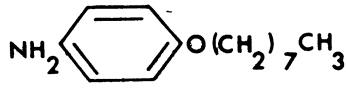

(III)

dodecane were all retinotoxic (Collins, Davis, Edge & Hill, 1958). An account of its first trial against *S. haematobium* in African schoolchildren is given by Alves, Harper & Hill (1961). Although no toxic side effects of any note, and certainly no ocular effects, were observed during this trial, the therapeutic activity of the compound was only

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moderate, and diminution of the visual field was observed subsequently by A. J. S. McFadzean in three patients in Hong Kong (addendum to Alves *et al.*, 1961). The search was therefore continued for a compound completely devoid of retinal toxicity in cats and more active than M&B 2948A against *S. mansoni* in mice.

Collins *et al.* (1958) found that insertion of methoxy groups into 1,5-di-(*p*-aminophenoxy) pentane to give 1,5-di-(4-amino-2-methoxyphenoxy)pentane (described independently by Standen & Walls, 1956) eliminated, or at least reduced the incidence of, the ocular effects of the parent compound which were described by Edge, Mason, Wien & Ashton (1956); Ashton (1957) and Sorsby & Nakajima (1958). Although the antischistosomal activity was also greatly reduced this lead was pursued and many monoamines of the general formula (II) were prepared (Collins & Davis, 1961, 1966a, b, c).

The principal series were those where R = alkyl, phenylalkyl, phenoxyalkyl and phthalimidoalkyl. Most of the nuclear unsubstituted parent compounds (R′ = H) were therapeutically active in the last three series but not in the series of simple alkyl derivatives, where the methane, ethane, hexane and decane homologues were inactive (Collins *et al.*, 1958, Table 7), although the octane member (III) has since been found to possess slight activity (acute oral LD50 = 1.2 g/kg; 90% curative at 0.4 g/kg/day, inactive at 0.1 g/kg/day). This is the simplest aminophenoxyalkane examined so far to exhibit antischistosomal properties.

METHODS

Toxic effects

The oral LD50 after a single dose was determined for each compound, using five mice per dose; and a few of the active ones were further examined for semi-chronic toxicity by giving four daily doses to groups of 10 mice.

Some of the compounds were administered to cats to see if they produced vomiting or the initial weakening of the light and blink reflexes which accompany visual impairment, as described by Collins *et al.* (1958).

Antischistosomal activity

The methods used have been fully described by Hill (1956) and Collins *et al.* (1958). Groups of 12 to 15 mice infected with adult *S. mansoni* were dosed by mouth once daily for four days. They were killed and examined for the presence of worms one to two weeks after the end of treatment. In the preliminary screening test compounds were considered to be effective if they reduced the number of free worms recovered from the mesenteric veins, portal vein, and liver to a significant extent ("t" test, $P = 0.01$) compared with untreated controls. The more active compounds were assessed according to their curative effect. A mouse was regarded as cured if no living male or female worms were recovered at necropsy. Worms which had been at least partially ensheathed by local tissue reaction in the liver were considered to be beyond recovery even if they exhibited some signs of movement at the time of the examination.

The activity is recorded in the tables according to the following scheme:

–	inactive at LD50/4 per day
±	effective at LD50/4 per day
+	25–75% mice cured at LD50/4 per day
++	25–75% mice cured at LD50/8 per day
+++	25–75% mice cured at LD50/16 per day
++++	25–75% mice cured at LD50/32 per day.

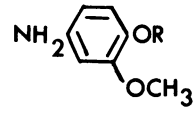
RESULTS

Alkyl and cycloalkyl ethers of 4-aminoguaiacol (Table 1)

The only compound of this type without a nuclear substituent which has been found active is the octane homologue (III), and 2-methoxy substitution increased the activity of this compound whilst having little effect on its toxicity. The toxicity of the hexane and decane homologues (M&B 5313 and 5157) was about half that of the nuclear unsubstituted parent compounds, and some activity became apparent. No conclusion can be drawn about the other active compounds as the unsubstituted parent compounds have not been examined. M&B 5325 was rejected as a candidate for clinical trial because it produced severe vomiting and some locomotor ataxia in cats after four daily oral doses of 0.4 g/kg. No retinotoxic symptoms were observed.

TABLE 1

ALKYL AND CYCLOALKYL ETHERS OF 4-AMINOGUAIACOL (ORAL TOXICITY AND ACTIVITY AGAINST *S. mansoni* IN MICE)



All compounds were tested as the base except those marked (a) hydrochloride or (b) hydrobromide.

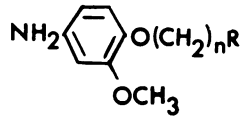
M & B No.	R	Approximate LD50 g/kg (single dose)	Activity
5358	H	0·35	—
1159	CH_3	0·8	—
5279	C_2H_5	0·8	—
5359	n-C_3H_7	0·9	—
5254	n-C_4H_9	0·4	—
5230	n-C_5H_{11}	0·1	—
5313	n-C_6H_{13}	0·15	+
5180	n-C_7H_{15}	0·8	+++
5325	n-C_8H_{17}	1·4	+++
5356	n-C_9H_{19}	2·5	+
5157	n-$C_{10}H_{21}$	3·0	+
5411	n-$C_{11}H_{23}$	>4·0	—
5280	n-$C_{12}H_{25}$	>4·0	—
5379	n-$C_{16}H_{33}$	>4·0	—
5420 (b)	$CH_2CH(C_2H_5)_2$	0·75	+
5326	$(CH_2)_2CH(CH_3)CH_2C(CH_3)_3$	0·8	—
5290 (a)	$CH(CH_3)(CH_2)_5CH_3$	1·2	++
5425 (a)	$(CH_2)_2CH(C_2H_5)(CH_2)_3CH_3$	1·2	++
5608 (a)	$(CH_2)_2CH(CH_3)(CH_2)_3CH(CH_3)_2$	1·5	±
5695 (a)	$CH(CH_3)(CH_2)_6CH_3$	0·9	±
5553	$(CH_2)_2CH=CH(CH_2)_2CH_3$	0·75	++
5430 (b)	$(CH_2)_3CH=CH_2$	0·5	—
5181	$(CH_2)_2$ cyclohexyl	0·08	—
4968	$(CH_2)_5$ cyclohexyl	3·5	+
5215	cyclopentyl	0·4	±

Phenylalkyl ethers of 4-aminoguaiacol (Table 2)

2-Methoxy nuclear substitution to give M&B 4819 and 4717 decreased the toxicity of the inactive parent compounds (Collins *et al.*, 1958, Table 7) and some activity became apparent. It had no effect on the activity or general toxicity of the pentane homologue,

TABLE 2

PHENYLALKYL ETHERS OF 4-AMINOGUAIACOL (ORAL TOXICITY AND ACTIVITY AGAINST *S. mansoni* IN MICE)



All compounds were tested as the base except the one marked (c) methanesulphonate. * The corresponding 2,6-dimethoxy derivative was inactive

M & B No.	n	R	Approximate LD50 g/kg (single dose)	Activity
5070	1	C_6H_5	0·7	+
4819	2	C_6H_5	0·5	+
4717	3	C_6H_5	0·4	+
4583 (c)	4	C_6H_5	1·0	++
3838A*	5	C_6H_5	1·5	++++
4855	6	C_6H_5	2·5	++
4913	7	C_6H_5	3·0	++
4863	8	C_6H_5	4·0	+
4873	5	$C_6H_4 . CH_3$-*p*	>4·0	+++
4899	5	$C_6H_4 . CH_3$-*o*	2·0	++
4874	5	$C_6H_4 . OCH_3$-*p*	4·0	+++
5071	5	$C_6H_4 . NO_2$-*p*	>4·0	+++
5542	1	$C_6H_4 . SO_2CH_3$-*p*	>4·0	+

so that M&B 3838A retained the good antischistosomal activity of M&B 2719 (1-p-aminophenoxy-5-phenylpentane) (Collins *et al.*, 1958, Table 7). In addition, it was apparently free from the retinotoxic symptoms which M&B 2719 exhibited (Table 10). No vomiting was observed in cats although 2/4 dogs vomited when given 0.067–0.1 g/kg by mouth daily for four days. M&B 4789 (Table 9), the NN-dimethyl derivative of M&B 3838A, was devoid of emetic and retinotoxic effects (Table 10), although it was rather less active against *S. mansoni* in mice. M&B 3838A was given a small clinical trial (see Discussion).

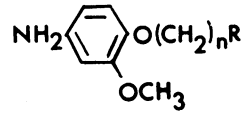
Other substituted alkyl ethers of 4-aminoguaiacol (Tables 3 and 4)

The effect of 2-methoxy nuclear substitution in these compounds was variable, giving an increase in toxicity and activity (M&B 5667), no change in toxicity with increased activity (M&B 4640), no change in toxicity with decreased activity (M&B 3988), a decrease in toxicity with no change in activity (M&B 3589) or a decrease in toxicity and activity (M&B 3593). The activities of the parent compounds are quoted by Collins *et al.* (1958, Tables 1, 5 and 6 or in the text). The retinotoxic effects of some of them are shown in Table 10, where it will be seen that 2-methoxy substitution was beneficial provided that the compound did not contain an unsubstituted *p*-aminophenoxy group, as was the case with M&B 3593.

The most active compound in Table 3 (M&B 4607) was rejected as a candidate for clinical trial because it was very toxic on repeated administration (LD50 = 0.25 g/kg/day over four days) in spite of its low toxicity after a single dose. M&B 3589 and 5227 were not considered active enough, as the rather poor activity of M&B 2948A in the field (Alves *et al.*, 1961) had led us to reject all compounds with a CD50 > 0.1 g/kg/day

TABLE 3

SUBSTITUTED ETHERS OF 4-AMINOGUAIACOL CONTAINING OXYGEN OR SULPHUR LINKAGES (ORAL TOXICITY AND ACTIVITY AGAINST *S. mansoni* IN MICE)

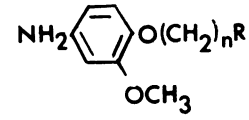


All compounds were tested as the base except those marked (c) mono- or di-methanesulphonate

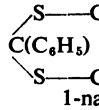
M & B No.	n	R	Approximate LD50 g/kg (single dose)	Activity
5433	1	OCH_3	1·8	−
5667 (c)	5	OCH_3	0·8	±
5282	2	$OCH_2C_6H_5$	0·7	++
3988 (c)	5	$OCH_2C_6H_5$	0·75	+
4767	2	OC_6H_5	0·8	++
4640	3	OC_6H_5	0·75	++
4607	4	OC_6H_5	>4·0	++++
3589	5	OC_6H_5	3·0	+++
4584	6	OC_6H_5	>4·0	±
4587	7	OC_6H_5	1·2	+
4555	8	OC_6H_5	>4·0	++
3593 (c)	5	$OC_6H_4 . NH_2$-*p*	2·0	+
5227	3	$OC_6H_4 . OCH_3$-*p*	3·0	+++
5236	4	$OC_6H_4 . OCH_3$-*p*	>4·0	++
4028	5	$OC_6H_4 . NHCOCH_3$-*p*	2·0	−
5524	5	SCH_3	1·2	++
5668	5	$S(CH_2)_2OH$	1·8	−
5693 (c)	3	$SCH_2C_6H_5$	1·5	+++
5340	3	SC_6H_5	0·75	+
4996	5	SC_6H_5	1·5	+++
5427	5	$SC_6H_4 . Cl$-*p*	2·0	+
5982	5	SO_2CH_3	1·6	−
4988	5	$SO_2C_6H_5$	1·2	+

TABLE 4

OTHER SUBSTITUTED ALKYL ETHERS OF 4-AMINOGUAIACOL (ORAL TOXICITY AND ACTIVITY AGAINST *S. mansoni* IN MICE)



All compounds were tested as the base

M & B No.	n	R	Approximate LD50 g/kg (single dose)	Activity
4750	3	$CH{=}CHC_6H_5$	>4·0	+++
4918	3	$CH{=}CHC_6H_4 . OCH_3$-*p*	>4·0	+
5115	1	$CH(OH)C_6H_5$	0·4	+
5143	4	$CH(OH)C_6H_5$	3·0	+++
4933	6	$CH(OH)C_6H_5$	>4·0	++
5269	4	$CH(OCOCH_3)C_6H_5$	0·9	++
5124	6	$CH(OCOCH_3)C_6H_5$	1·5	+
5378	4	$C(OC_2H_5)_2C_6H_5$	2·0	++
5114	4	COC_6H_5	1·2	++
4911	6	COC_6H_5	3·0	+++
10,763	4		>5·0	−
5249	1	1-naphthyl	1·2	±
10,244	0	$C_6H_4 . C_6H_5$-*p*	>5·0	−

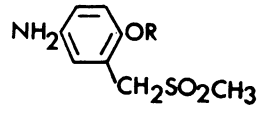
even if of low toxicity (M&B 2948A had a very low toxicity in mice; acute LD50>4.0 g/kg). This also applies to the more active compounds in Table 4. M&B 5693 (Table 3) caused severe ataxia and prostration in cats after a single oral dose of 0.4 g/kg. No retinotoxic symptoms were observed.

Alkyl ethers of 4-amino-2-methylsulphonylmethylphenol (Table 5)

The effect of 2-methylsulphonylmethyl nuclear substitution in the hexane and octane homologues was to decrease the toxicity and increase the activity. Most of the compounds in this series had better therapeutic ratios and were less toxic than the corresponding 2-methoxy compounds (Table 1). Nevertheless, M&B 5881 was rejected for clinical trial because it was not really active enough and because it caused some vomiting in cats at a dose of 0.4 g/kg/day. No retinotoxic symptoms were seen.

TABLE 5

ALKYL ETHERS OF 4-AMINO-2-METHYLSULPHONYLMETHYLPHENOL (ORAL TOXICITY AND ACTIVITY AGAINST *S. mansoni* IN MICE)

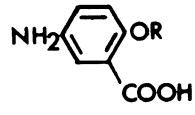


All compounds were tested as the base

M & B No.	R	Approximate LD50 g/kg (single dose)	Activity
7083	n-C_3H_7	1·5	±
6913	n-C_4H_9	1·0	++
6914	n-C_5H_{11}	0·3	+
6385	n-C_6H_{13}	0·2	+
6384	n-C_7H_{15}	0·8	+++
5881	n-C_8H_{17}	>4·0	+++
6915	n-C_9H_{19}	0·75	±

TABLE 6

ALKYL ETHERS OF 4-AMINO-2-CARBOXYPHENOL (ORAL TOXICITY AND ACTIVITY AGAINST *S. mansoni* IN MICE)

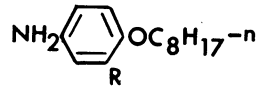


All compounds were tested as the base

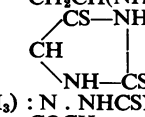
M & B No.	R	Approximate LD50 g/kg (single dose)	Activity
8995	n-C_3H_7	3·2	−
8606	n-C_4H_9	3·2	±
8996	n-C_5H_{11}	3·2	−
8734	n-C_6H_{13}	3·2	+
8910	n-C_7H_{15}	0·5	−
5954	n-C_8H_{17}	1·2	++
8997	n-C_9H_{19}	1·5	+
8766	n-$C_{10}H_{21}$	3·2	±

TABLE 7

EFFECT OF NUCLEAR SUBSTITUTION IN 1-*p*-AMINOPHENOXYOCTANE (ORAL TOXICITY AND ACTIVITY AGAINST *S. mansoni* IN MICE)



All compounds were tested as the base except those marked (a) mono- or di-hydrochloride, (c) methanesulphonate, (e) di-*p*-toluoyl-D-tartrate, or (f) maleate

M & B No.	R	Approximate LD50 g/kg (single dose)	Activity
5927	Cl	1·5	−
9330	CN	1·3	−
5856 (c)	CH_3	1·5	+
5912	CH_2OH	0·75	++
5936 (a)	CH_2OCH_3	0·75	+
6023 (e)	$CH_2OC_2H_5$	3·0	±
6064 (e)	$CH(OC_2H_5)_2$	1·8	−
6153 (e)	$CH_2OC_3H_7n$	3·0	±
6104 (e)	CH_2OCOCH_3	1·8	−
6005 (a)	$CH_2OC_6H_5$	>4·0	−
6076	$CH_2OC_6H_3(OCH_3)NH_2$-1,2,4	0·2	±
5935 (f)	$CH_2N(C_2H_5)_2$	0·3	−
6404	$CH_2NHCOCH_3$	0·3	+
7663 (a)	$CH_2NHCOCH_2N(C_2H_5)_2$	0·15	−
6170	$CH_2NHCOC_6H_5$	>4·0	+
6157	phthalimidomethyl	>4·0	−
7779	$CH_2NHCONH_2$	>4·0	++
7604	$CH_2NHSO_2CH_3$	4·0	+
7640	$CH_2N(CH_3)SO_2CH_3$	>4·0	++
7704	$CH_2NHSO_2C_6H_4 . NH_2$-*p*	>4·0	±
7650	$CH_2NHSO_2C_6H_4 . NHCOCH_3$-*p*	>4·0	−
5885 (c)	CH_2SCH_3	1·5	++
5990 (c)	$CH_2SC_2H_5$	1·8	+++
5991 (a)	$CH_2SC_3H_7n$	3·0	±
5811	$CH_2S(CH_2)_2OH$	1·6	+++
6221	CH_2SCH_2COOH	>4·0	−
5845	$CH_2SCH_2C_6H_5$	>4·0	±
10,842 (a)	$CH_2SC(:NH) . NH_2$	0·3	−
6105 (c)	$CH_2SC_6H_5$	>4·0	−
6916	CH_2SOCH_3	0·5	+
6134	$CH_2SO_2C_2H_5$	>4·0	+++
6406	$CH_2SO_2(CH_2)_2OH$	0·8	++
7400	$CH_2SO_2C_6H_4Cl$-*p*	>4·0	−
6453	$CH_2SO_2C_6H_4 . CH_3$-*p*	>4·0	−
6169	$CH_2SO_2C_6H_4 . NHCOCH_3$-*p*	>4·0	++++
7537	$CH_2SO_2C_6H_3(CH_3) . NHCOCH_3$-1,2,3	>4·0	−
7526	$CH_2SO_2C_6H_3(OCH_3) . NHCOCH_3$-1,2,3	>4·0	−
9408	$CH_2CH(NH_2)COOH$	>4·0	−
9490		>5·0	−
9294	$C(CH_3) : N . NHCSNH_2$	0·8	−
9183 (a)	$COCH_3$	2·3	−
6237	$CONH_2$	0·8	±
8747 (a)	$CON(C_2H_5)_2$	1·3	−
9489 (a)	$CONHCH_2COOH$	2·3	−
8945	$CONH(CH_2)_2N(C_2H_5)_2$	0·06	−
6185	$CONHC_6H_5$	>4·0	−
8998	pyrid-2-ylcarbamoyl	>5·0	−
9203	pyrazin-2-ylcarbamoyl	>5·0	−
9202	pyrimidin-2-ylcarbamoyl	2·7	−
9144	thiazol-2-ylcarbamoyl	>5·0	−
8759	pyrrolidin-1-ylcarbamoyl	1·1	±
9753 (a)	$C(: NH)NH_2$	0·5	−
9363	$NHCOCH_3$	0·5	−
6387	OC_2H_5	3·5	±

Alkyl ethers of 4-amino-2-carboxyphenol (Table 6)

These compounds were of little interest as schistosomicides. M&B 5954 gave rise to sedation and ataxia followed by death in cats, after an oral dose of 0.4 g/kg/day, although there were no retinotoxic symptoms.

Nuclear substitution in 1-p-aminophenoxyoctane (Table 7)

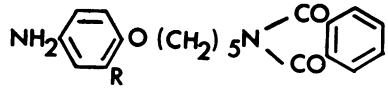
Three of the compounds which could appear in this table (M&B 5325, 5881 and 5954, where R is respectively OCH_3, $CH_2SO_2CH_3$, and COOH) have already been discussed. The most interesting nuclear substituents were those containing a thio or sulphonyl linkage. Nine of the 54 compounds listed showed advantage over the unsubstituted parent compound (formula III), and four of them showed good activity but were not considered for clinical trial because three compounds with an octyl side chain (M&B 5325, 5881 and 5954) were very toxic in cats.

Nuclear substitution in 1-p-aminophenoxy-5-phthalimidopentane (Table 8)

2-Methoxy substitution to give M&B 3530 had little effect on the activity or toxicity of the parent compound (M&B 2948A, I) (Collins *et al.*, 1959), and since M&B 3530 was rather less accessible chemically and unlikely to be more active in man, it was not considered for clinical trial. The most interesting compound in the group, M&B 6354, was retinotoxic in 6/12 cats at a daily dose of 0.4 g/kg given over 6–12 days, and consequently was not considered for clinical trial.

TABLE 8

EFFECT OF NUCLEAR SUBSTITUTION IN 1-*p*-AMINOPHENOXY-5-PHTHALIMIDOPENTANE (ORAL TOXICITY AND ACTIVITY AGAINST *S. mansoni* IN MICE)

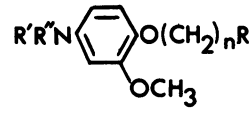


All compounds were tested as the base except those marked (a) hydrochloride or (c) methanesulphonate
N.B. The 3-hydroxy, 3-methoxy and 2,6-dimethoxy derivatives were inactive

M & B No.	R	Approximate LD50 g/kg (single dose)	Activity
3491	Cl	>4·0	−
3555	CH_3	0·4	+
3983	C_2H_5	0·4	−
6354	CH_2OH	1·5	++++
5999	CH_2OCH_3	0·8	+++
6380	$CH_2SO_2CH_3$	1·3	±
7476	$CH_2SO_2C_6H_4 . NHCOCH_3$-*p*	>4·0	−
7474	$CH_2NHCOCH_3$	>4·0	+++
7593	$CH_2NHSO_2CH_3$	>4·0	±
7558 (a)	CH_2OCOCH_3	>4·0	+++
7780	CH_2NHCHO	4·0	++
7971	COOH	3·8	−
8249 (a)	CO_2CH_3	3·0	−
7982	$CONH_2$	>5·0	−
3592 (c)	OH	3·0	−
3530	OCH_3	>4·0	+++
3811	OC_2H_5	>4·0	++
4023	OC_3H_7-n	>4·0	+
3951	OCH_2OCH_3	3·0	+
4024	$OCH_2C_6H_5$	3·0	−
4031	$OCO_2C_2H_5$	>4·0	−

TABLE 9

SELECTED SECONDARY AND TERTIARY AMINES (ORAL TOXICITY AND ACTIVITY AGAINST *S. mansoni* IN MICE)

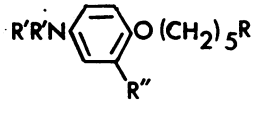


All compounds were tested as the base except those marked (a) hydrochloride, (b) hydrobromide or (c) methanesulphonate

M & B No.	R′	R″	n	R	Approximate LD50 g/kg (single dose)	Activity
5191	CH_3	H	5	C_6H_5	1·5	+++
4789	CH_3	CH_3	5	C_6H_5	>4·0	+++
4850	$(CH_2)_2OH$	H	5	C_6H_5	2·0	+++
4803 (c)	$(CH_2)_2OH$	$(CH_2)_2OH$	5	C_6H_5	1·5	++
5388 (a)	$CO . CH_2N(C_2H_5)_2$	H	5	C_6H_5	2·8	+++
5518 (a)	CH_3	H	7	CH_3	1·5	+++
5448 (b)	CH_3	CH_3	7	CH_3	2·8	+++
5500	$(CH_2)_2OH$	H	7	CH_3	1·2	++
5523	$(CH_2)_2OH$	$(CH_2)_2OH$	7	CH_3	1·6	++
5607	$CO . CH_2N(C_2H_5)_2$	H	7	CH_3	3·0	++

TABLE 10

OCULAR EFFECTS IN CATS



All compounds were tested as the base except those marked (a) mono- or di-hydrochloride or (c) mono- or di-methanesulphonate

* See Collins *et al.* (1958)

† M & B 5191 (Table 9) produced no ocular effects at a daily dose of 0·4 g/kg

M & B No.	R′	R″	R	Solubility in water %	Daily dose g/kg × No. of doses	Route	No. cats treated	Ocular effects
*3113 (c)	H	H	$OCH_2C_6H_5$	>40	0·4 × 1	p.o.	2	+
3988A (c)	H	OCH_3	$OCH_2C_6H_5$	5	0·2 × 1	s.c.	2	—
					0·8 × 1	p.o.	2	—
*2666	H	H	OC_6H_5	< 0·01	0·2 × 1	p.o.	2	+
					0·2 × 1	s.c.	2	—
3589A (c)	H	OCH_3	OC_6H_5	>10	0·4 × 1	p.o.	3	—
					0·2 × 8	p.o.	3	—
*968A (a)	H	H	$OC_6H_4 . NH_2$-*p*	20	0·1 × 1	p.o.	2	+
3593 (c)	H	OCH_3	$OC_6H_4 . NH_2$-*p*	>30	0·2 × 1	s.c.	2	+
*3927 (c)	H	OCH_3	$OC_6H_3(OCH_3) . NH_2$-1,2,4	>10	0·4 × 1	p.o.	2	—
7243A (a)	H	CH_2OH	$OC_6H_3(CH_2OH) . NH_2$-1,2,4	>30	0·4 × 1	s.c.	3	+
*2719	H	H	C_6H_5	0·25	0·2 × 1	p.o.	2	+
3838 (c)	H	OCH_3	C_6H_5	10	0·4 × 1	s.c.	2	—
					0·4 × 4	p.o.	3	—
4789†	CH_3	OCH_3	C_6H_5	< 0·01	0·1 × 65	p.o.	5	—
4789B (a)	CH_3	OCH_3	C_6H_5	2–5	0·4 × 4	p.o.	4	—
					0·4 × 43	p.o.	10	—

Other nuclear substituted compounds

1,5-Di-(4-amino-2-hydroxymethylphenoxy)pentane (M&B 7243) was 62% curative at 1.0 g/kg/day and was therefore less active than the unsubstituted parent compound M&B 968A (Collins *et al.*, 1958, Table 1). The related derivative, 1,5-di-(4-amino-2-methylsulphonylmethylphenoxy)pentane (M&B 8571), was completely inactive.

Effect of N-substitution (Table 9)

The results given here demonstrate that N-substituted compounds were active although they were sometimes less so than the corresponding primary amines, as found by Raison & Standen (1955); Gorvin, Raison, Solomon, Standen & Walls (1957) and Collins *et al.* (1958, 1959).

Retinotoxic effects (Table 10)

All the parent compounds without a 2-nuclear substituent were toxic at the doses given, but the only methoxy substituted compound to exhibit any retinotoxicity was M&B 3593, which still bore one unsubstituted *p*-aminophenoxy group. Di-substitution to give M&B 3927 resulted in loss of retinotoxicity. Hydroxymethyl substitution did not reduce the retinotoxicity as shown by the results with M&B 7243A and M&B 6354 (section 7), nor did chloro substitution (Collins *et al.*, 1958).

DISCUSSION

Standen & Walls (1956), working with di-*p*-aminophenoxyalkanes, reached the conclusion that nuclear substitution reduced the antischistosomal activity and that the reduction was greater when both rings were substituted. This was borne out by the results of Collins *et al.* (1958) and further supported by our more recent findings with 1-(4-amino-2-methoxyphenoxy)-5-*p*-aminophenoxypentane, 1,5-di-(4-amino-2-hydroxymethylphenoxy)pentane, and 1,5-di-(4-amino-2-methylsulphonylmethylphenoxy)pentane (Results). Among the monoamines, however, no such generalization can be made, as our present results demonstrate.

It is clear that 2-methoxy substitution reduces the incidence of retinotoxicity in cats provided no unsubstituted *p*-aminophenoxy group is present. It is true that the number of cats in each group was small, but the results with the various compounds support one another.

As the methanesulphonate of M&B 3838A (Table 2) produced no retinotoxic effects during a preliminary test in cats, further experiments to investigate its general toxicity were carried out, and the base was eventually given a small clinical trial by W. Alves and J. Harper (personal communication) against *S. haematobium* in African schoolchildren from S. Rhodesia. The compound was used in the form of a suspension. A total dose of 60–120 mg/kg over 1–4 days cured 16/44 subjects, compared with 4/20 under the same conditions in an earlier trial with a similar preparation of M&B 2948A at an average total dose of 321 mg/kg, and 51/121 with uncoated tablets of M&B 2948A at a total dose of 250 mg/kg (Alves *et al.*, 1961). It gave rise to no ocular symptoms but it did produce serious vomiting, possibly of central nervous origin, and was therefore considered unsuitable for further trial.

SUMMARY

1. Many nuclear substituted monoaminophenoxyalkanes were tested for activity against *Schistosoma mansoni* in mice by oral administration. The principal nuclear substituents were methoxy, carboxy and methylsulphonylmethyl, all in the *ortho* position to the ether link; and the principal side chains were alkyl, phenylalkyl, phenoxyalkyl and phthalimidoalkyl.

2. Although nuclear substitution among the corresponding diamines reduced the antischistosomal activity, no such generalization could be made about the monoamines, as the effect depended entirely upon the nature of the substituent and the type of side chain. In some compounds nuclear substitution increased the activity considerably.

3. No compounds with an *ortho* methoxy group showed retinotoxicity in cats, but this did not apply to other substituents in the same position.

We wish to thank Miss M. A. Brown, Mrs. M. J. Hughes and Mr. P. D. Anthony for their technical assistance.

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