Brit. J. Pharmacol. (1958), **13**, 238.

THE SCHISTOSOMICIDAL AND TOXIC EFFECTS OF SOME αω-DI(*p*-AMINOPHENOXY)ALKANES AND RELATED MONOAMINES

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(RECEIVED FEBRUARY 21, 1958)

An account is given of the results obtained with a number of *p*-aminophenoxyalkanes which were examined for activity against *Schistosoma mansoni* in mice and for the presence of retinotoxicity in cats. The first compound to be found active, 1: 5-di(*p*-aminophenoxy)-pentane dihydrochloride (M & B 968A), was modified in a variety of ways in an attempt to increase its activity and to eliminate its ocular effects. It was found that a *p*-aminophenoxyalkyl group was common to all the active compounds, but that the rest of the molecule could be any of several different groups, including alkoxy, phenoxy, and phenyl groups, without diminishing the activity. Although at least one *p*-aminophenoxyalkyl group was essential for schistosomicidal activity, ocular toxicity was also shown by a *p*-aminophenylalkyl derivative in which the ether linkage was absent.

The standard remedies for schistosomiasis are tartar emetic, stibophen, antimony lithium thiomalate (Anthiomaline) and lucanthone (Miracil D), a thioxanthone derivative first prepared by Mauss (1948). None of these compounds is completely satisfactory because the antimonials must be given at near toxic doses in order to cure the disease, and lucanthone, in addition to its unpleasant side-effects, is inactive against the oriental species *Schistosoma japonicum.*

Over the past few years a large number of compounds has been screened in these laboratories for activity against *S. mansoni* in mice. During the early phases of this investigation some benzthiazole derivatives were prepared by our colleague Mr. S. S. Berg. These proved to be of no biological interest, but an intermediate from this work, 1 : 5-di(*p*-aminophenoxy)pentane dihydrochloride (M & B 968A) (I), was found to be highly active. No compound of this type had previously been shown to possess marked schistosomicidal activity although a related compound, 1 : 5-di(*p*-amidinophenoxy)pentane diisethionate (pentamidine), was found by Boiron and Koerber (1947) to possess slight though transient activity against *S. haematobium* in man.

(I)

This discovery was made in 1952 and led to the initiation of an extensive chemical programme which is still going on (Collins, Davis and Hill, 1954). In the same year, activity was found quite independently by Raison and Standen (1955) in the very closely related compound, 1 : 5-di(*p*-methylaminophenoxy)pentane dihydrochloride. Consequently two groups of workers have quite independently set out from virtually the same chemical starting point and followed paths which have sometimes crossed but more often diverged. Inevitably the two research studies overlap to some extent, especially in the early phases (Raison and Standen, 1955 ; Caldwell and Standen, 1956 ; Standen and Walls, 1956 ; Gorvin, Raison, Solomon, Standen and Walls, 1957).

The present paper therefore deals mainly with compounds similar to those already described by Standen and his colleagues, but it also includes the results of certain toxicological studies in cats to which we attach considerable importance. Some of the compounds studied have been similarly examined by Goodwin, Richards, and Udall (1957). Our therapeutic results with these compounds agree very well with those of Standen, although there are minor differences which are discussed below.

M & B 968A was found by Hill (1956) to be as active as lucanthone against *S. mansoni* in mice and much less toxic, but in monkeys it was almost inactive and produced retinotoxic effects, which have also been observed in cats and dogs, but not in other species (Edge, Mason, Wien, and Ashton, 1956). The histology of the eyes has been studied only in cats (Ashton, 1957), the changes resembling those produced by sodium iodate. Destruction of the visual cells, localized displacement of the outer nuclear layer, and marked degeneration and proliferation of the pigment epithelium occurred ; the bipolar and ganglion cells were unaffected.

It was therefore essential to know if active compounds produced effects on the eye before attempting a clinical trial in man. Consequently many of them were examined in cats to determine whether they produced the initial weakening of the light and blink reflexes which accompany visual impairment.

METHODS

Schistosomicidal Activity in Mice.—The methods employed have been fully described by Hill (1956). Mice infected with *S. mansoni* seven to eight weeks previously were dosed by mouth daily for four days. Fifteen mice were used for each dose ; one group of 15 untreated controls was used in each experiment.

Two types of therapeutic experiment were carried out: (*a*) a preliminary screening test in which a dose equivalent to about one-third of the LD50 was given each day ; and (*b*) a more detailed examination of active compounds in which several doses were given to obtain a dose/response curve.

In the preliminary test, the mice were killed and examined about one week after the end of treatment and the number of living worms recovered from the mesenteric veins, portal vein, and liver was compared with the number from the untreated controls. Compounds which failed to reduce the number of worms significantly (by the " *t* " test, $P=0.01$) were classified as inactive ; a 50% reduction was barely significant ($P=0.05$), whereas a 70% reduction was usually significant ($P=0.01$).

In the second type of experiment, the mice were examined two weeks after the end of treatment and the number cured was determined for each dose as described by Hill (1956), and a dose/response curve was drawn from which the CD50 and the CD95 were obtained graphically. Our methods, like those of Raison and Standen (1955), measured essentially the drift of worms back to the liver after treatment and their subsequent ensheathment and death, but, whereas Raison and Standen expressed their results as the % of worms killed, we expressed ours as the % of mice cured.

The acute oral toxicity of each compound was determined in groups of five mice. The LD50 was obtained graphically. Chronic oral toxicity experiments using 10 mice/dose were carried out with most of the active compounds. The mice were treated daily for four days, as in the therapeutic experiments, and the LD50 and the LD5 were again determined graphically. This enabled therapeutic ratios, LD50/CD50 and LD5/CD95, to be calculated for each compound, although only the LD50 and the CD50 are given here.

Toxicity in Cats.—Healthy, adult cats of both sexes were used. The compounds were administered orally in soluble capsules or sometimes, when sufficiently soluble, by subcutaneous injection. Usually each compound was administered on a single occasion to two cats at a dose of approximately 0.4 g./kg. or less if the compound proved toxic at this dose. The animals were frequently (twice daily) examined for the development of ocular effects and were destroyed immediately such effects were observed. Whereas negative results obtained with two cats are not particularly significant for individual compounds, they do make it possible to distinguish less toxic series where none of the members tested gave a response. On the other hand, a positive response in only two cats could be regarded as a definite effect. Other toxic effects such as ataxia, muscular weakness, and vomiting were seen in some of the cats.

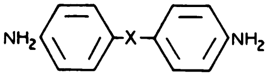
RESULTS

Schistosomicidal Effects

Modification of the Central Chain.—Various modifications of the central chain of M & B 968A are shown in Tables I and II. The methane, ethane, decane and dodecane homologues (Table I) were inactive, but compounds with three to nine carbon atoms in the chain were active, with a peak at about seven carbon atoms. These results accord well with those of Raison and Standen (1955).

TABLE I

DIAMINES, MODIFICATION IN THE NUMBER OF CARBON AND OXYGEN ATOMS IN THE CENTRAL CHAIN

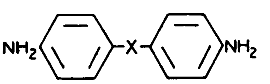


All compounds were tested as the dihydrochlorides except those marked (b) dimethanesulphonates. The following compounds were also therapeutically inactive: $X=O[CH_2]_2O[CH_2]_2O$; $O.CO[CH_2]_3CO.O$; $S[CH_2]_3S$; $O[CH_2]_3NH$; $NH[CH_2]_3NH$; $NAc[CH_2]_3NAc$; CH_2; $[CH_2]_2$; CH_2OCH_2; $CH=CH$; CO; NH; SO_2; SO; SS; S.SO; S; O; single bond.

M & B No.	X	LD50 g./kg.		CD50 g./kg. (Daily Dose)	Ocular Effects
		Single Dose	Daily Dose		
2496	OCH_2O	1·0		Inactive	+
966A	$O[CH_2]_2O$	0·75		,,	+
1113A	$O[CH_2]_3O$	1·0	0·67	0·35	+
2467	$O[CH_2]_4O$	1·0	0·32	0·13	+
968A	$O[CH_2]_5O$	0·75	0·62	0·19	+
2491	$O[CH_2]_6O$	1·5	0·17	0·08	+
2539	$O[CH_2]_7O$	1·5	0·33	0·07	+
2512	$O[CH_2]_8O$	>4·0	0·42	0·08	+
2524	$O[CH_2]_9O$	2 5	0·27	0·1	+
2514	$O[CH_2]_{10}O$	>4·0		Inactive	+
2612	$O[CH_2]_{12}O$ (b)	>8·0		,,	–
2952	$O[CH_2]_5$ (b)	1·5	0·75	0·2	+
2562	$[CH_2]_5$ (b)	0·8		Inactive	+

TABLE II

DIAMINES, REPLACEMENT OF THE CENTRAL CHAIN BY BRANCHED OR UNSATURATED CHAINS OR CARBOCYCLIC RINGS



All compounds were tested as the dihydrochlorides except those marked (a) bases or (b) dimethanesulphonates. The following compounds were also therapeutically inactive: $X = p\text{-}OCH_2C_6H_4CH_2O$; $p\text{-}O[CH_2]_5OC_6H_4O[CH_2]_5O$.

M & B No.	X	LD50 g./kg.		CD50 g./kg. (Daily Dose)	Ocular Effects
		Single Dose	Daily Dose		
2579	$OCH_2CH(OH)CH_2O$ ..			Inactive	
2576	$O[CH_2]_2CHMe[CH_2]_2O$ ..	1·5	0·56	0·33	+
2820	$O[CH_2]_2CMe_2[CH_2]_2O$ ..	0·6		Inactive	
2595	$O[CH_2]_2CHPh[CH_2]_2O$ ..	0·5		,,	
2869	1 : 5-dioxy-3 : 3-pentamethylenepentane	0·75		,,	
2734	$OCH_2C(CH_2OC_6H_4\text{-}p\text{-}NH_2)_2CH_2O$ (b)	3·0		>1·0	
2673	*trans*-$OCH_2CH{=}CHCH_2O$ (a)	2·0	0·65	0·13	+
2676	*cis*-$OCH_2CH{=}CHCH_2O$ (a)	0·75	0·5	0·22	+
2616	$OCH_2C{\equiv}CCH_2O$ (b) ..	1·5		Inactive	
2720	$OCH_2C{\equiv}C.C{\equiv}CCH_2O$ (a)	>4·0		,,	
2451	$p\text{-}OC_6H_4O$	2·0		,,	
2610	1 : 4-dioxy*cyclo*hex-2-ene (b)	0·7	0·3	0·24	
2667	1 : 4-dioxy*cyclo*hexane (b)	0·75	0·29	>0·29	+

Omission of both ether linkages (Table I) resulted in complete loss of activity, but the omission of only one ether linkage had no effect, which demonstrates that only one *p*-aminophenoxyalkyl group is essential for activity.

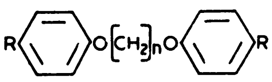
Branched chains (Table II) had a deleterious effect, as Gorvin *et al.* (1957) also found, but compounds with a double bond in the chain were as active as those with a saturated chain. It is doubtful if the apparent difference in activity between the *cis* and *trans* isomers was significant. The two compounds with a triple bond which we examined were completely inactive although Gorvin *et al.* (1957) found activity in some acetylenic compounds, the activity increasing with the distance between one oxygen atom and the triple bond. The replacement of the central chain with a carbocyclic ring was also dystherapeutic, the activity decreasing from *cyclo*hexene through *cyclo*hexane to benzene.

Substitution in the Amino Groups.—A number of secondary and tertiary amines and one quaternary ammonium compound were tested (Table III). Among the secondary amines activity was found in the methyl, ethyl, hydroxyethyl and *n*-propyl derivatives, but not in the *iso*propyl derivative, whereas among the tertiary amines only the methyl, ethyl and hydroxyethyl derivatives were active. The secondary and primary amines were equally effective but some of the tertiary amines were less so, and the quaternary ammonium compound was inactive.

This field was covered thoroughly by Raison and Standen (1955) and Gorvin *et al.* (1957). Our results agree very well with theirs with the single exception of the *iso*propyl derivative, which Raison and Standen (1955) found to be active.

TABLE III

DIAMINES, SUBSTITUTION IN THE AMINO GROUPS



All compounds were tested as the bases except those marked (c) dihydrochlorides or (d) disulphates. The following compounds were also therapeutically inactive: n = 3, R = NHAc; $N{:}CHPh$; n = 5, $R = NH[CH_2]_2NEt_2$; $NHCO_2Et$; $NHC({:}S)NH_2$; $NHC({:}NH)NH_2$; $NHCH_2Ph$; pyrid-2-ylamino; 4-methylthiazol-2-ylamino; pyrrolidin-1-yl; piperidino; morpholino. M & B No. 2592 was tested in one cat.

M & B No.	n	R	LD50 g./kg.		CD50 g./kg. (Daily Dose)	Ocular Effects
			Single Dose	Daily Dose		
2519	3	NHMe (c)	1·5	0·6	0·32	+
2526	5	NHMe (c)	3·0	0·61	0·16	+
2841	8	NHMe (c)	1·8	0·31	0·065	−
2592	3	NMe_2	4·0	0·82	0·39	−
2542	5	NMe_2 (c)	4·0	0·6	0·33	+
2668	8	NMe_2	>4·0		>1·6	−
2507	3	$\overset{+}{N}Me_3I^-$	0·5		Inactive	
2672	5	NHEt	3·0	0·54	0·14	+
2651	5	NEt_2	>4·0	0·55	0·24	−
2694	5	NHPr (*n*)	>4·0	0·73	0·19	+
2658	5	NHPr (*iso*)	>4·0		Inactive	
2714	5	NPr_2(*n*)(d)	>4·0		,,	−
2782	5	$NHCH_2CH_2OH$ ..	4·0	1·1	0·19	+
3346	5	$N(Me)CH_2CH_2OH$ ..	>4·0		<1·0	
2598	5	$N(CH_2CH_2OH)_2$ ..	>8·0	1·7	0·27	+
3001	8	$N(CH_2CH_2OH)_2$ ..	>4·0		<1·0	+
3106	5	$NHCH_2CH_2OMe$ ..	>4·0	0·38	0·37	+
2440	5	$NHCH_2SO_3Na$ ..	>2·0	3·2	0·41	+

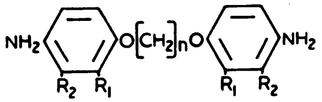
Substitution in the Nucleus.—All the disubstituted compounds of this type (Table IV) were inactive except the *oo'*-dimethoxy derivative, which showed very slight activity at a toxic dose. One monosubstituted compound, 1-(4-amino-2-bromophenoxy)-3-phenoxypropane dihydrochloride, was found to be effective, although less so than the parent compound (M & B 1113A, Table I).

Standen and Walls (1956) also found that nuclear substitution resulted in a great reduction in activity and that the effect was greater when both rings were substituted.

Position and Number of the Amino Groups.—Modification of the position and number of the amino groups demonstrated that activity was dependent on the presence of at least one *p*-amino group since compounds with the amino groups in the *oo'*- or *mm'*-positions were inactive, as was the *op'*-isomer. Slight activity was shown by a compound with the amino groups in the *mp'*-positions. Omission of one of the amino groups increased the toxicity to mice but had little effect on activity. Omission of both amino groups resulted in complete loss of activity.

TABLE IV

DIAMINES, SUBSTITUTION IN THE NUCLEUS



All compounds were tested as bases except those marked (b) dimethanesulphonates or (c) di- or tetra-hydrochlorides. M & B Nos. 2536 and 2623 gave positive ocular responses in cats whereas M & B No. 3927 gave none.

M & B No.	n	R_1	R_2	LD50 g./kg. (Single Dose)	CD50 g./kg. (Daily Dose)
2536	5	Cl (c)	H	3·0	Inactive
2623	5	H (b)	Cl	1·5	,,
3927	5	OMe (b)	H	1·0	>0·8
2563	5	H (c)	CH_3	0·5	Inactive
2492	3	NH_2	H	1·5	,,
2497	5	H	NH_2	1·5	,,
2638	5	H	NHAc	>4·0	,,
2647	3	H	NO_2	>4·0	,,
2446	5	CH_2NEt_2 (c)	H	0·5	,,

Monoamines with Two Phenoxy Groups.—It was at first thought probable that two *p*-aminophenoxy groups were necessary for schistosomicidal activity. However, with the discovery of slight activity, at a toxic dose, in 1-*p*-aminophenoxy-3-phenoxypropane methanesulphonate, it became clear that only one such group was required and hence a new range of compounds was examined. The pentane derivative (M & B 2666, Table V) was tested next and found to be more active than the propane homologue. The effect of various substituents in the phenoxy group of M & B 2666 was then investigated, but unfortunately all of these except a *p*-acetamido substituent reduced the activity (Table V). This latter compound, which was rather more active and only about half as toxic as the parent, was later shown by our colleague Dr. Fraser to be a metabolite of M & B 968A (Table I).

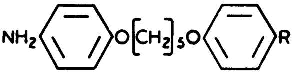
Caldwell and Standen (1956) also studied compounds of this type with substantially similar results, except for the *p*-methyl, *p*-chloro and *p*-carboxy derivatives, which they found to be very slightly active at total doses higher than those we were able to administer owing to the toxicity of the compounds.

Other Monoamines with Two Ether Linkages.—Extending the search for active monoamines, we prepared and tested some analogous alkoxy derivatives (Table VI). Apart from the benzyloxy compound (M & B 3113), however, the order of activity was low throughout this series. Caldwell and Standen (1956) also studied similar compounds and concluded that the activity was only moderate.

Monoamines with One Ether Linkage.—Of several compounds of this type which were tested (Table VII) only the 5-phenylpentyl derivative

TABLE V

MONOAMINES WITH TWO PHENOXY GROUPS

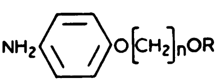


All compounds were tested as bases except those marked (b) methanesulphonates or (c) hydrochlorides. The following compounds were also therapeutically inactive: 1-*p*-aminophenoxy-5-(3:5-xylyloxy)-pentane methanesulphonate; 1-*p*-aminophenoxy-5-*o*-methoxyphenoxypentane; 1-*p*-aminophenoxy-4-phenoxy*cyclo*hexane.

M & B No.	R	LD50 g./kg.		CD50 g./kg. (Daily Dose)	Ocular Effects
		Single Dose	Daily Dose		
2666	H	0·75	0·49	0·21	+
2709	Cl (c)	0·5		Inactive	
2718	Me (c)	1·8		,,	
2735	CH_2NH_2 (b)	0·8		,,	
2730	OH (b)	2·0		,,	
2660	OMe	1·5	0·27	>0·27	+
2967	OEt	3·0		1·0	−
2783	OPh	1·0		Inactive	
2956	Ac	4·0		>1·0	+
2877	CO_2H (c)	0·9		Inactive	
2847	CO_2Et	>4·0		,,	
2818	NO_2	>4·0		>1·0	−
2693	NHAc	>4·0	1·1	0·15	+
3152	$NHCOCH_2OH$	0·5		Inactive	
2997	NHCOEt	>4·0		<1·0	+
3003	NHCOPh	>4·0		1·0	
3041	$NHSO_2Me$	>4·0		<1·0	−
2805	Ph (b)	>4·0		Inactive	

TABLE VI

OTHER MONOAMINES WITH TWO ETHER LINKS



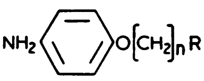
All compounds were tested as methanesulphonates except those marked (a) bases or (c) hydrochlorides.

M & B No.	n	R	LD50 g./kg.		CD50 g./kg. (Daily Dose)	Ocular Effects
			Single Dose	Daily Dose		
2742	3	Me	1·5		>0·4	
2836	5	Me	1·5		>0·5	−
3037	5	Et	0·5		Inactive	+
3048	5	Pr(*n*)	1·5	0·6	0·35	+
3113	5	CH_2Ph	0·75	0·64	0·095	+
3057	5	CH_2CH_2OH (a)	2·0	0·94	0·77	−
3066	5	CH_2CH_2OMe	0·7		Inactive	
3675	5	2-phthalimidoethyl	>4·0		0·6	
2775	5	naphth-1-yl	1·6		Inactive	
2844	5	naphth-2-yl (a)	4·0		,,	
3306	5	pyrid-2-yl (a)	3·0		>0·5	
2770	5	quinol-6-yl (c)	0·6		Inactive	
3026	5	*cyclo*hexyl	0·25		,,	

(M & B 2719) was active. However, this result in conjunction with that found for M & B 2952 (Table I) shows that only one ether linkage is essential for activity. The inactivity of the propane homologue was possibly due to its high toxicity which meant that only a very small dose could be given in the therapeutic experiment. All the compounds of this type which Caldwell and Standen (1956) examined were inactive.

TABLE VII

MONOAMINES WITH ONE ETHER LINK



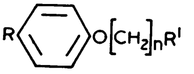
All compounds were tested as bases except those marked (b) methanesulphonates or (c) hydrochlorides.

M & B No.	n	R	LD50 g./kg. Single Dose	LD50 g./kg. Daily Dose	CD50 g./kg. (Daily Dose)	Ocular Effects
2652	0	H	0·75		Inactive	—
2417	1	H (c)	1·5		,,	—
2415	2	H (c)	1·0		,,	—
2839	6	H (b)	0·07		,,	+
2655	10	H	1·5		,,	—
2843	0	*cyclo*hex-2-en-1-yl	0·03		,,	
2817	0	*cyclo*hexyl (b)	0·02		,,	
3837	3	$CH=CH_2$ (b)	0·15		,,	
3933	3	$CH(OEt)_2$	1·5		,,	
2701	3	OH (b)	>4·0		,,	
2729	5	OH	2 0		,,	
2685	3	OAc	1·5		,,	
2754	1	CO_2H	>4·0		,,	
2966	4	CO_2H	1·5		,,	
2857	5	CO_2H	>4·0		,,	
2840	1	$CONH_2$	>4·0		,,	
3039	5	$CONH_2$	>4·0		,,	
3017	0	Ph (c)	0·12		,,	
2926	2	Ph (b)	0·2		,,	
2883	3	Ph	0·08		,,	
2719	5	Ph (b)	1·5	0·37	0·08	+

Monoamines, Substitution in the Amino Group. Only a few of these compounds were examined (Table VIII) and all but two of them were active.

TABLE VIII

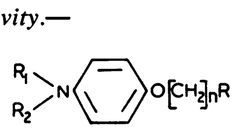
MONOAMINES, SUBSTITUTION IN THE AMINO GROUP



All compounds were tested as bases except the one marked (c) hydrochloride. M & B No. 3011 gave a positive ocular response in cats.

M & B No.	n	R	R^1	LD50 g./kg. (Single Dose)	CD50 g./kg. (Daily Dose)
3568	8	NHMe	OPh	3·0	>0·8
3383	5	NMe_2	p-OC_6H_4NEtAc	1·8	0·4
3506	5	NHEt (c)	Ph	1·5	<0·4
3112	5	$N(CH_2CH_2OH)_2$	Ph	3·0	<1·0
3011	5	$N(CH_2CH_2OH)_2$	p-OC_6H_4NHAc	>4·0	<1·0
2763	5	$NHCH_2CH_2NEt_2$	OPh	0·8	Inactive
2785	5	$N(CH_2CH_2NEt_2)_2$	OPh	0·5	,,

Molecular Features Essential for Schistosomicidal Activity.—



(II)

A very wide range of compounds with the above general formula (II) (where n=3 to 9; R_1 and R_2=H, lower alkyl or hydroxyalkyl; and R= alkoxy, phenoxy, or phenyl, which may be substituted) was found to be active. The *p*-aminophenoxypropyl moiety common to all of them appeared to be essential for activity, since compounds without a *p*-amino group, without an ether linkage, or with less than three carbon atoms in the chain were inactive. This conclusion differs from that of Caldwell and Standen (1956), who considered that two ether linkages were necessary for activity. Our results have demonstrated that only the ether linkage present in the *p*-aminophenoxyalkyl group is essential.

Ocular Effects

Diamines.—All the compounds in Tables I and II except the dodecane compound (Table I) which were examined for ocular effects in cats gave a positive response.

Ten substituted amines (Table III) were retinotoxic, but five others, four of them tertiary amines, failed to produce an effect.

Among the nuclear substituted diamines (Table IV) the *oo'*- and *mm'*-dichloro derivatives both produced ocular symptoms. The *oo*-dimethoxy derivative gave no ocular response, but it produced ataxia and muscular weakness in cats, symptoms which sometimes accompanied the disappearance of ocular effects in other compounds.

Among the tertiary amines we found the hydroxyethyl derivatives of the pentane and octane member to be retinotoxic, although Goodwin *et al.* (1957) found that the corresponding heptane did not possess this property.

Variation in the Position and Number of the Amino Groups in M & B 968A.—Two compounds with amino groups in the *oo*- or *mm*-positions produced no retinal effects in cats, but those with amino groups in the *mp'*-, *op'*- or *p*-positions were retinotoxic.

Monoamines.—Among the monoamines (Tables V, VI, VII, and VIII) the 5-*p*-acetamidophenoxy, 5-benzyloxy and 5-phenyl derivatives showed sufficient schistosomicidal activity to be of interest, but they all produced ocular symptoms in cats, whereas the compounds which gave no response in cats had small therapeutic ratios or were inactive against *S. mansoni.* 1-p-Aminophenoxy-5-methoxypentane and the corresponding 5-ethoxy derivative (Table VI) both produced ataxia and muscular weakness in cats. 1-*p*-Aminophenoxyhexane (Table VII) also produced ataxia and muscular weakness in addition to its effects on the eye. The toxic symptoms due to *p*-aminophenol, *p*-anisidine and *p*-phenetidine (Table VII) consisted in cyanosis of the mouth and tongue, rapid shallow respiration, and oedema of the face and paws.

Molecular Features Essential for the Production of Retinotoxicity.—The molecular features essential for the production of retinotoxicity were not identical with those required to produce schistosomicidal effects since M & B 2562 (Table I), which had no ether linkage and was consequently not schistosomicidal, was nevertheless toxic to the eye. Also M & B 3927 (Table IV), which showed slight schistosomicidal activity, was non-retinotoxic although its unsubstituted parent compound (M & B 968A, Table I) was highly retinotoxic. This suggests that nuclear methoxy substituents may inhibit the production of ocular effects, although chloro substituents do not (Table IV).

As far as can be judged from the present results a *p*-amino group is necessary for both schistosomicidal activity and ocular toxicity.

We wish to thank our colleagues, Drs. J. N. Ashley, H. J. Barber and R. Wien, for their helpful discussions during this investigation, Miss N. E. Sirett for the preparation of some of the compounds, Mr. D. F. J. Mason for carrying out some of the experiments in cats, and Mr. A. D. Speed for his technical assistance.

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