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THE ACTIVITY OF *p*-AMINOPHENOXYALKANE DERIVATIVES AGAINST *SCHISTOSOMA MANSONI*

BY

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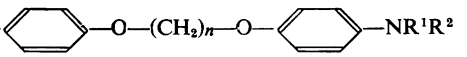
In recent publications, Raison and Standen (1954, 1955) have described the schistosomicidal activity of di-(*p*-aminophenoxy)alkane derivatives of formula



where R^1 and R^2 are H or alkyl.

The present communication is concerned with the schistosomicidal activity of related *p*-aminophenoxyalkane derivatives in which one of the *p*-aminophenyl groups is retained and the other is replaced by a differently substituted phenyl group or an alkyl group. These investigations have shown that schistosomicidal activity is found in many compounds of this general type and have provided further information on the relationship between structure and activity.

MATERIALS AND METHODS

All the compounds in this present series were tested against an Egyptian strain of *S. mansoni* passaged through *Australorbis glabratus*. The white mouse was used in all instances as host for the parasites. The mice were infected by the percutaneous route, each mouse being exposed to 130 cercariae (Standen, 1949, 1953). Determination of infection in mice was made by the identification of viable eggs in the faeces 56 days after exposure to the cercariae. At the time of treatment the infections were 63–70 days old.

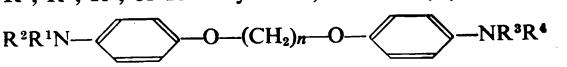
The drugs were given orally as aqueous solutions of their hydrochlorides (except for the non-basic compounds) twice daily for 5 days, and the mice were autopsied 7 days after completion of treatment. The hepatic portal system of each mouse was examined and the worms were removed from mesenteric, portal, and intrahepatic veins to determine numbers, sex, and proportional distribution in these organs. In addition to the indication of schistosomicidal activity provided by the degree of worm shift to the liver (Schubert, 1948; Standen, 1953), the final assessment of dose-response was made upon the proportion of dead worms found. Ten mice were used in each test, and the activity of a drug was estimated in terms of the proportion of dead worms found in relation to the total worms recovered in the group. Worms were considered dead only when completely ensheathed with inflammatory tissue and in process of disintegration.

The compounds mentioned in this paper were prepared by established chemical methods, and most of them have been described elsewhere (Wellcome Foundation, Ltd., 1954).

RESULTS

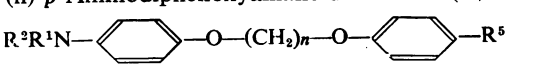
The compounds discussed in this paper may be divided conveniently into four types:

(i) Di-(*p*-aminophenoxy)alkane derivatives where the amino-groups are differently substituted (I; R^1, R^2, R^3, or R^4 may be H, Me or Et) (Table I).



(I)

(ii) *p*-Aminodiphenoxyalkane derivatives (II).

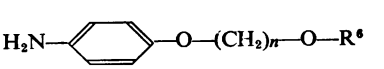


(II)

In this series, R^5 includes the following groups: H, CH_3, Cl, Br, OMe, OH, CH_2NH_2, NO_2, CN, $CONH_2$, CO_2Et, CO_2H, $COCH_3$, SO_2CH_3, $NH.COCH_3$, $NMe.COCH_3$, $NH.COC_4H_9$, $NHCO_2Et$, $NMe.CO_2Et$, $NH.CO_2C_5H_{11}$, $NHCONH_2$, and $NH.SO_2Me$, and the group $NR^1R^2 = NH_2$ (Table IIA), NHMe (Table IIB), and NMe_2 (Table IIC).

A few compounds of this type, but with one of the substituent groups in the *o*- or *m*-position, are listed in Table III.

(iii) *p*-Aminophenoxyalkoxyalkanes (III; R^6 = CH_3, $(CH_2)_2CH_3$, $(CH_2)_5CH_3$, *cyclo*hexyl) (Table IV).



(III)

(iv) Miscellaneous inactive compounds related to the above types (Table V).

The term " unit dose " in the Tables refers to the dose given orally twice daily for 5 days and is thus one-tenth of the total dose.

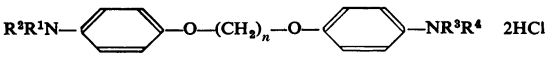
The Tables define the limits of activity for each compound in terms of worm kill. Since the relationship of hepatic shift to worm kill has previously been described (Raison and Standen, 1955), details of worm distribution are not included.

The compounds were well tolerated at the doses used. Toxicity studies on these and related compounds will form the subject of a separate report.

TABLE I

ACTIVITIES OF UNSYMMETRICAL DI-(*p*-AMINOPHENOXY)-ALKANE DERIVATIVES AGAINST *SCHISTOSOMA MANSONI*

For explanation of " unit dose " see Results



Compound No.	NR^1R^2	NR^3R^4	*n*	Unit Dose (mg./kg.)	Worms Killed %
241C53	NH_2	NHMe	5	100 50 25	100 78 36
242C53	NH_2	NHMe	6	50 25	100 83
524C54	NH_2	NHMe	7	50 25	100 93
158C55	NH_2	NMe_2	4	50 25	84 0
382C53	NH_2	NMe_2	5	50 25 12·5	99 90 7
383C53	NH_2	NMe_2	6	50 25 12·5	100 93 31
384C53	NH_2	NMe_2	7	25 12·5	98 42
385C53	NH_2	NMe_2	8	50 25 12·5	95 78 11
15C54	NHMe	NMe_2	6	50 25	100 53
49C54	NHMe	NMe_2	7	25	98
50C54	NHEt	NHMe	6	50 25	82 59

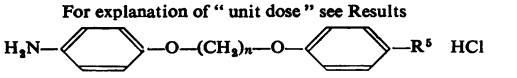
DISCUSSION

(i) *Di-(p-aminophenoxy)alkanes* (I).—In general, these compounds have the high activities which would be expected from their close resemblance to the symmetrical diamino-compounds (Raison and Standen, 1955). In the series where $NR^1R^2 = NH_2$ and $NR^3R^4 = NMe_2$, which was investigated over the range $n = 4$–8, the pattern of activity may

TABLE IIA

ACTIVITIES OF *p'*-SUBSTITUTED *p*-AMINODIPHENOXY-ALKANES AGAINST *S. MANSONI*

For explanation of " unit dose " see Results



Compound No.	R^5	*n*	Unit Dose (mg./kg.)	Worms Killed %
75C51	H	5	200 50	100 16
85C53	H	6	200 50	98 0
107C53	CH_3	5	200 50	51 0
108C53	CH_3	6	200 100 50	96 23 0
109C53	Cl	5	200 100	56 0
110C53	Cl	6	200 50	91 0
38C54	Br	6	200 50	96 0
111C53	OCH_3	5	200 100	64 0
112C53	OCH_3	6	200	0
181C53	OH	5	200	0
182C53	OH	6	200	0
269C53	CH_2NH_2	6	200 50	75 0
99C55	NO_2	3	200 50	78 2
325C54	NO_2	4	200 50	100 76
76C51	NO_2	5	200 50	87 0
86C53	NO_2	6	100 50	96 22
254C53	NO_2	7	200 50	97 0
267C53	NO_2	8	200	5
191C55	CN	3	200 50	100 7
326C54	CN	4	50 25 15	97 78 40
191C53	CN	5	200 50	62 0
192C53	CN	6	200 50 25	95 62 14
270C53	CN	7	200 50	81 0
284C53	CN	8	100 50	100 59
192C55	CN	9	200 50	96 8
303C53	$CONH_2$	5	200 50 25	100 50 0

TABLE IIA—*continued*

Compound No.	R^5	*n*	Unit Dose (mg./kg.)	Worms Killed %
304C53	$CONH_2$	6	200 50 25	80 36 5
136C53	CO_2Et	5	200 50	0 0
137C53	CO_2Et	6	200	2
138C53	CO_2H	5	200 50	36 1
139C53	CO_2H	6	200 50	52 0
119C54	$COCH_3$	6	200	0
13C54	SO_2CH_3	6	200 50	74 2
14C54	SO_2CH_3	7	200 50	94 72
102C55	$NH.COCH_3$	3	200 50	82 0
525C54	$NH.COCH_3$	4	200 50	94 5
349C53	$NH.COCH_3$	5	200 50	100 75
350C53	$NH.COCH_3$	6	200 50	100 19
526C54	$NH.COCH_3$	7	50 25	100 80
103C55	$NH.COCH_3$	8	200 50	97 53
648C54	$NH.COC_4H_9$	7	200 50	99 64
304C54	$NH.CO_2Et$	3	200 50	93 0
305C54	$NH.CO_2Et$	4	200 50	60 2
306C54	$NH.CO_2Et$	5	200 50 25 12·5	99 78 30 0
46C54	$NH.CO_2Et$	6	50 25 12·5 6·25	97 92 30 0
307C54	$NH.CO_2Et$	7	200 50 25	97 41 14
308C54	$NH.CO_2Et$	8	200 50	71 2
319C54	$NH.CO_2C_5H_{11}$	6	200 50	28 0
314C54	$NMe.CO_2Et$	3	200 50	67 0
245C54	$NMe.CO_2Et$	4	50 25 12·5	92 51 0
246C54	$NMe.CO_2Et$	5	50 25	80 13
143C54	$NMe.CO_2Et$	6	25 12·5 6·25	98 10 3

TABLE IIA—*continued*

Compound No.	R^5	*n*	Unit Dose (mg./kg.)	Worms Killed %
247C54	$NMe.CO_2Et$	7	50 25 12·5	98 56 3
248C54	$NMe.CO_2Et$	8	200 50 25	100 61 0
611C54	$NHCONH_2$	6	50 25	96 0
649C54	$NH.SO_2Me$	5	50	41

be compared with that of the symmetrical diamino- and bis-dimethylamino compounds. In the unsymmetrical compounds the graph of *n* against activity is similar to that for the symmetrical diamines, in that at 25 mg./kg. there is a rather broad spread of high activity ($n=5$–8 compared with $n=$ 6–9 for the symmetrical diamines), with peak activity at $n=7$ ($n=7$–8 for the symmetrical diamines), but there is no sign of the alternation in activity with *n* which is characteristic of the bis-dimethylamino-compounds.

(ii) p-*Aminodiphenoxyalkanes* (II).—In this series, some activity at 200 mg./kg. is found where NR^1R^2 is an amino-, methylamino- or dimethylamino-group and R^5 is any of a wide variety of different groups, including H. With $NR^1R^2=NH_2$, where $R^5=H$, CH_3, Cl, Br, OMe, OH, CH_2NH_2, CO_2Et, CO_2H, or $COCH_3$, activity was low with $n=5$ or 6, and further values of *n* were not studied. Similarly, low activity was found when $NR^1R^2=NMe_2$ and $R^5=H$, CH_3, Cl, or OMe and $n=5$ or 6. With $NR^1R^2=NH_2$, the following substituents in R^5 appeared to confer greater activity than those mentioned above, namely NO_2, CN, $CONH_2$, SO_2Me, $NH.COCH_3$, $NMe.COCH_3$, $NH.CO_2Et$, $NMe.CO_2Et$, $NHCONH_2$ and $NH.SO_2Me$. Several of these have been studied in corresponding methylamino- and dimethylamino- compounds, particularly in relation to changes in the value of *n*. Compounds where R^5 is $NH.COCH_3$, $NMe.COCH_3$, $NH.CO_2Et$ or $NMe.CO_2Et$ include some with very high activity.

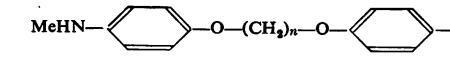
The changes in activity resulting from changes in either NR^1R^2, R^5 or *n* are not regular and predictable, except in a limited sense, but it is possible to make certain generalizations from those series which have been studied in sufficient detail, and to make some comparisons of the activity of these unsymmetrically substituted compounds with that of the previously studied symmetrical diamines.

Variation of Activity with n.—In the diamino-

TABLE IIB

ACTIVITIES OF *p'*-SUBSTITUTED *p*-METHYLAMINODIPHENOXYALKANES AGAINST *S. MANSONI*

For explanation of "unit dose" see Results



Compound No.	R^5	n	Unit Dose (mg./kg.)	Worms Killed %
285C53	H	6	200 50	100 29
100C55	NO_2	3	200 50	99 31
101C55	NO_2	4	200 50	100 33
217C53	NO_2	5	200 50	77 0
218C53	NO_2	6	200 50 25	100 75 19
255C53	NO_2	7	200 50	59 4
268C53	NO_2	8	200 50	55 54
193C55	CN	3	50 25	70 23
327C54	CN	4	25 12·5	98 18
336C53	CN	5	200 50	99 48
286C53	CN	6	100 50	91 21
287C53	CN	7	100 50	100 54
337C53	CN	8	200 50	97 22
645C54	$NH.COCH_3$	3	200 50	100 0
315C54	$NH.COCH_3$	4	25 12·5	97 16
316C54	$NH.COCH_3$	5	25 12·5	94 0
317C54	$NH.COCH_3$	6	25 12·5	100 22
318C54	$NH.COCH_3$	7	25 12·5	98 38
646C54	$NH.COCH_3$	8	50 25 12·5	98 87 7
329C54	$NMe.COCH_3$	4	25 12·5	95 6
209C55	$NMe.COCH_3$	7	50 25	100 80
168C54	$NH.CO_2Et$	4	200 50 25	100 58 3
552C54	$NH.CO_2Et$	5	50 25	100 83
553C54	$NH.CO_2Et$	6	25	95
554C54	$NH.CO_2Et$	7	50 25	86 27
169C54	$NMe.CO_2Et$	4	50 25 12·5	97 90 42
609C54	$NMe.CO_2Et$	5	50 25	99 44
144C54	$NMe.CO_2Et$	6	25 12·5	98 25
610C54	$NMe.CO_2Et$	7	25 12·5	95 12

diphenoxyalkanes studied by Raison and Standen (1955) it was observed that for a given series activity reached a peak for one or more values of n. A similar phenomenon, but with certain differences, is found in the present series, in which there are three types of activity/n relationship:

(a) *With one peak.* In the more active series showing this type of activity/n relationship, peak activity is usually at $n=6$ (e.g., II; $NR^1R^2=NH_2$ or NHMe; $R^5=NH.CO_2Et$) (Fig. 1, A), but may appear at $n=7$ (II; $NR^1R^2=NMe_2$; $R^5=NH.COCH_3$). In the symmetrical diamino-compounds showing this pattern of activity, peak activity is at $n=7$ or 8.

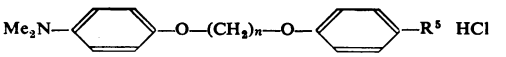
(b) *With two peaks.* Some of the most active series of compounds show a type of response providing one main peak and a second subsidiary one. Good examples are the series (II; $NR^1R^2=NH_2$; $R^5=NMe.CO_2Et$) (Fig. 1, B) with the main peak at $n=6$ and a smaller peak at $n=4$, and (II; $NR^1R^2=NHMe$; $R^5=NH.COCH_3$) in which the main peak is at $n=7$ and the minor one again at $n=4$. In some series, however, the peak at $n=4$ has become the major one, e.g., in (II; $NR^1R^2=NHMe$; $R^5=NMe.CO_2Et$), where the peak at $n=4$ is slightly higher than that at $n=6$, and in (II; $NR^1R^2=NHMe$; $R^5=CN$) where the peak at $n=4$ is very high in relation to the general level of activity of the series, and in comparison with the subsidiary peak at $n=7$. This pattern of activity is strikingly similar to that found in some of the symmetrical bis-alkylamino-compounds, in which the second peak is usually at $n=4$ and may be the higher peak or subsidiary to the main peak at $n=7$–8, according to variation in alkyl substitution.

(c) *Alternation.* This phenomenon, with activity alternately rising and falling for successive values of n, appears in two series (II; $NR^1R^2=NH_2$; $R^5=CN$) (Fig. 1, C) and, less clearly, (II; $NR^1R^2=NHMe$; $R^5=NO_2$). In the former, activity is higher for even values of n (4, 6, 8) and

TABLE IIC

ACTIVITIES OF *p'*-SUBSTITUTED *p*-DIMETHYLAMINO-DIPHENOXYALKANES AGAINST *S. MANSONI*

For explanation of " unit dose " see Results

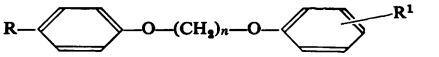


Compound No.	R^5	*n*	Unit Dose (mg./kg.)	Worms Killed %
91C53	H	5	200 50	100 5
92C53	H	6	200 50	62 0
130C53	CH_3	5	200 100	60 36
131C53	CH_3	6	200 100	82 16
132C53	Cl	5	200 100	88 35
133C53	Cl	6	200	7
134C53	OCH_3	5	200 50	96 0
135C53	OCH_3	6	200	0
157C55	NO_2	4	200 50	29 0
93C53	NO_2	5	100 50	44 0
94C53	NO_2	6	100	25
351C53	NO_2	7	200 50	61 9
352C53	NO_2	8	200 50	0 0
334C53	CN	5	200 50	81 26
335C53	CN	6	200 50 25	73 53 8
405C54	$NH.COCH_3$	4	50 25	96 6
406C54	$NH.COCH_3$	5	50 25	99 44
407C54	$NH.COCH_3$	6	50 25	100 45
408C54	$NH.COCH_3$	7	25 12·5	100 26
647C54	$NH.COCH_3$	8	50 25	92 0
47C54	$NMe.COCH_3$	6	50 25	100 55
235C55	$NMe.COCH_3$	7	25	99
527C54	$NH.CO_2Et$	4	200 50 25	87 75 4
528C54	$NH.CO_2Et$	5	50 25	100 24
529C54	$NH.CO_2Et$	6	50 25 12·5	94 64 18
530C54	$NH.CO_2Et$	7	200 50 25	100 84 65
555C54	$NMe.CO_2Et$	4	200 50 25	100 90 15
556C54	$NMe.CO_2Et$	6	50 25 12·5	98 83 84

TABLE III

ACTIVITIES OF SUBSTITUTED AMINODIPHENOXY-ALKANES AGAINST *S. MANSONI*

For explanation of " unit dose " see Results



Compound No.	R	R^1	*n*	Unit Dose (mg./kg.)	Worms Killed %
612C54	NH_2	*m*-NH_2	6	200 50	97 0
613C54	NH_2	*m*-$NH.CO_2Et$	6	200 50	99 32
614C54	$NH.CO_2Et$	*m*-NH_2	6	200 50	6 0
615C54	$NH.COCH_3$	*m*-NH_2	6	200 50	24 0
650C54	NH_2	*o*-$NH.CO_2Et$	7	200 50	36 0

lower for odd values of *n* (3, 5, 7, 9), and at low doses there is a marked peak at $n=4$. The only symmetrical type showing this behaviour is the bis-dimethylamino-series, but here the odd values of *n* give higher activity than even values, with peak activity at $n=7$.

Variation of Activity with NR^1R^2.—In general, for a single group R^5, the level of peak activity is not very different whether NR^1R^2 is NH_2, NHMe or NMe_2, although there may be marked differences in the shapes of the graphs of activity against *n*. For example, in the acetamido-series (II ; $R^5 = NH.COCH_3$), at 25 mg./kg., the methylamino-compounds have very high activity over the whole range $n=3$ to $n=8$, whereas the amino- and dimethylamino-compounds have peaks at $n=7$, but at 12.5 mg./kg. peak activity at $n=7$ is very similar in the amino-, methylamino- and dimethylamino-series.

Variation of Activity with R^5.—The fact that the group R^5 in compounds of type (II) is capable of such wide variation without loss of schistosomicidal

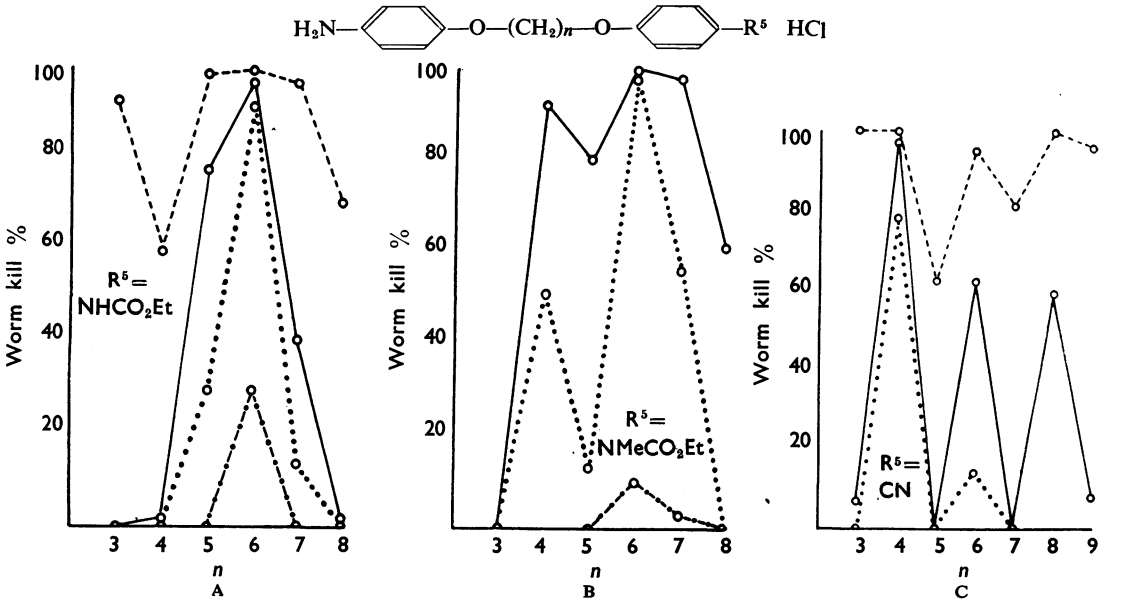


FIG. 1.—The types of relationship between structure and schistosomicidal activity of *p*-aminodiphenoxyalkanes. ----200 mg./kg. ——— 50 mg./kg. .... 25 mg./kg. -·-·-· 12.5 mg./kg.

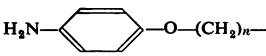
activity indicates clearly that only one *p*-amino-group in the diphenoxyalkane structure is essential for schistosomicidal activity. However, the nature of R^5 has a powerful influence on the degree of activity, which is completely lost when R^5=OH (as in 181C53 and 182C53, Table IIA), but is very high when, for instance, R^5=NH.CO_2Et (as in 46C54, Table IIA). The generally high activity of compounds where R^5=NH.$COCH_3$, NMe.$COCH_3$, NH.CO_2Et and NMe.CO_2Et is striking, since these groups are all capable of hydrolysis to amino-groups, and it is interesting to consider whether the activity of these compounds is attributable to the formation of the active diamino-compounds by hydrolysis in the body. High activity is also encountered, however, when R^5 is not a potential amino-group, as in the compound 326C54 (Table IIA), where R^5=CN.

The di-(*p*-acetamidophenoxy)alkanes and di-(*p*-ethoxycarbonamidophenoxy)alkanes are inactive, but this could be due to the prevention of their absorption and hydrolysis in the body by their unsuitable physical properties—such as lack of water solubility. The bis-(*m*-aminophenoxy)-alkanes are also inactive (Raison and Standen, 1955), but the presence of one *m*- and one *p*-aminophenoxy group (as in 612C54, Table III) gives moderate activity similar to that found in the monoamino-compound 85C53 (Table IIA), as might be expected if only the *p*-aminophenoxy group conferred the activity. The compound 614C54 (Table III), with a *m*-amino and a *p'*-

TABLE IV

ACTIVITIES OF *p*-AMINOPHENOXYALKOXYALKANES AGAINST *S. MANSONI*

For explanation of " unit dose " see Results

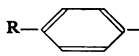


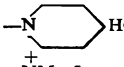
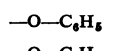
Compound No.	R^6	*n*	Unit Dose (mg./kg.)	Worms Killed %
328C54	CH_3	4	200 50	92 0
35C55	CH_3	5	200 50	83 0
369C53	CH_3	6	200 50	98 8
11C54	CH_3	7	200 50 25	97 82 0
121C54	CH_3	8	100 50 25	100 69 0
182C54	$(CH_2)_2CH_3$	6	100 50 25	98 22 4
183C54	$(CH_2)_2CH_3$	7	100 50 25	98 34 2
313C53	$(CH_2)_5CH_3$	5	200 50	98 0
314C53	$(CH_2)_5CH_3$	6	200 50	77 0
301C53	*cyclo*hexyl	5	200 50 25	92 91 12
302C53	*cyclo*hexyl	6	100 50	100 21

TABLE V

PHENOXYALKANE DERIVATIVES INACTIVE AGAINST *S. MANSONI* AT A UNIT DOSE OF 200 MG./KG.

For explanation of " unit dose " see Results



R	R^1	*n*
	$-O-C_6H_5$	6
$-\overset{+}{N}Me_3\ I^-$	$-O-C_6H_5$	5; 6
$-\overset{+}{N}Me_3\ I^-$	$-O-C_6H_4-NO_2\ (p)$	5; 6
$-NO_2$	$-O-C_6H_5$	6
$-NH.COCH_3$	$-O-C_6H_4-NO_2\ (p)$	6
$-H$	$-O-(CH_2)_5.CH_3$	6
$-CH_2.NH_2\ HCl$	$-OMe$	6
$-NH_2\ HCl$	$-OH$	6; 7
$-NH_2\ HCl$	$-O.COCH_3$	6
$-NH_2\ HCl$	$-H$	3; 4; 6; 12
$-NH_2\ HCl$	$-CO_2H$	5; 6
$-NH_2\ HCl$	$-CO_2Et$	5; 6
$-NH_2\ HCl$		5; 6

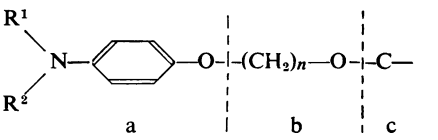
ethoxycarbonamido group, has physical properties similar to those of the active *p*-amino-*p'*-ethoxycarbonamido compound 46C54 (Table IIA), but it is very much less active than the *m*-*p'*-diamino compound, 612C54, which would result from hydrolysis of the ethoxycarbonamido group. Similarly, the *m*-amino-*p'*-acetamido-compound 615C54 (Table III) is much less active than the *m*-*p'*-diamine. These results suggest that the high activity of compounds where $R^5 = NH.COCH_3$ or $NH.CO_2Et$ is not accounted for simply on the basis of their hydrolysis *in vivo* to the diamino-compounds.

(iii) p-*Aminophenoxyalkoxyalkanes* (III).—The general level of activity in this series, as far as it has been studied, is only moderate, but shows features already observed in other types. When $R^6 = CH_3$ and *n* is varied, activity rises sharply to a peak at $n=7$ and decreases again at $n=8$. For a constant value of $n=6$, there is little change in activity whether $R^6 = CH_3$, $(CH_2)_2CH_3$, $(CH_2)_5CH_3$, or *cyclo*hexyl.

The most interesting aspect of this series of compounds is the demonstration that for schistosomicidal activity only one ring is necessary, and this provides a further simplification of the structure required to exhibit schistosomicidal activity.

Structural Requirements for Schistosomicidal Activity.—The foregoing investigations have shown that schistosomicidal activity is found in a very large range of compounds, some of which represent considerable modifications of the original diaminodiphenoxyalkane structure. On the basis of the present results, and those of Raison and Standen (1955), it is possible to attempt a definition of the minimum structural requirements for activity to appear. Such a definition will serve the dual purpose of summarizing the large amount of information already obtained, and of indicating other points requiring investigation. It will clearly be subject to modification in the light of further work which is proceeding and will be described in future communications.

The active compounds so far described all have the partial structure (IV) in common, and the inactivity of the compounds listed in Table V suggests that all the features present in this structure must be combined to produce a schistosomicidal compound. The variations which are permissible in the different portions of the basic structure (IV) may be summarized as follows:



(IV)

(a) The *p*-aminophenoxy-group may be varied with respect to the H or alkyl groups R^1 and R^2, but activity soon diminishes with increasing size of these alkyl groups (Raison and Standen, 1955).

(b) The value of *n* in the central carbon chain may be varied over the range about 3–9, but the values most often found in the most active compounds are 4 and 6–8.

(c) The carbon atom may be part of a wide variety of alkyl or substituted phenyl groups, certain of the latter giving highest activity.

In the light of these conclusions, it is interesting to speculate further on the possibility, suggested by Raison and Standen (1955), that the observed schistosomicidal activity of these compounds might represent a summation of intrinsic schistosomicidal activity and some property which determines the behaviour of the compounds in the host and the parasite. It seems reasonable to suppose that the intrinsic activity might reside in the portion (a) of (IV), since this appears to be the part of the molecule susceptible to least alteration without loss of activity. The parts (b) and (c) of (IV) might then be thought to be responsible for facilitating the attack on the parasite by their influence on absorption and metabolism in the host and parasite. To follow the idea further, it seems possible that the active compounds could all be converted in the body into *p*-aminophenol or a simple derivative by hydrolysis of the ether linkages and

conversion of the group $-NR^1R^2$ into NH_2, for it is known that fission of alkyl aryl ethers (Williams, 1947a) and demethylation of aromatic dimethylamino-groups (Williams, 1947b) may occur in the animal.

p-Aminophenol itself, however, has shown no schistosomicidal activity at non-toxic doses, whether administered orally or parenterally. The same is true of some other possible metabolites which could arise by partial breakdown of the structure (IV)—for example, the alcohols and carboxylic acids in Table V. It may be, of course, that such compounds do not reach the appropriate site of action in the parasite because of their lack of the structures which it is suggested are concerned with absorption. It is clear that such questions can be settled only by investigations into the mode of action of these compounds and their fate in the animal, and work on these lines is in progress.

Summary

1. Diphenoxyalkanes with different primary, secondary or tertiary amino-groups in the *p*-positions have schistosomicidal activity similar to that of the symmetrical *p : p'*-diaminodiphenoxyalkanes.

2. Diphenoxyalkanes, having a *p*-amino group in only one ring, and any of a variety of substituents in the other ring, also have schistosomicidal activity, although this is in general lower than that of the diaminodiphenoxyalkanes. However, where the other group is acetamido-, acetmethylamido-, ethoxycarbonamido-, ethoxycarbonmethylamido-, or cyano-, high activity appears.

3. *p*-Aminophenoxyalkoxyalkanes have moderate schistosomicidal activity.

4. An attempt is made to define the minimum structural features necessary for activity in this series, and the relationship between structure and activity is briefly discussed.

5. *p*-Aminophenol, and a few of its derivatives which are possible metabolites of these compounds, have shown no schistosomicidal activity.

We are indebted to Dr. C. G. Raison, of the Wellcome Research Laboratories, for the provision of some of the compounds mentioned in this paper. We are pleased to acknowledge the valuable technical assistance of Mr. W. E. King with the chemical work, and Mrs. Rosemary Richards and Mr. K. A. Fuller with the biological work.

References

Raison, C. G., and Standen, O. D. (1954). *Trans. roy. Soc. trop. Med. Hyg.*, **48**, 446.

—— —— (1955). *Brit. J. Pharmacol.*, **10**, 191.

Schubert, M. (1948). *Amer. J. trop. Med.*, **28**, 137.

Standen, O. D. (1949). *Ann. trop. Med. Parasit.*, **43**, 268.

—— (1953). Ibid., **47**, 26.

Wellcome Foundation, Ltd. (1954). British Pat. Appln. 7731/54.

Williams, R. T. (1947a). *Detoxication Mechanisms*, p. 83. London: Chapman and Hall.

—— (1947b). Ibid., p. 144.