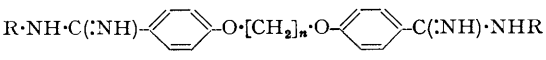
565. *Antituberculous Compounds. Part II. Di-*(p-N-*arylamidinophenoxy*)*alkanes.*

By M. W. Partridge.

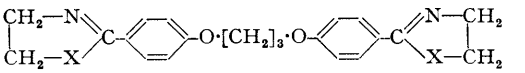
A series of di-(*p-N*-arylamidinophenoxy)alkanes and certain analogues have been prepared for a study of the relation between structure and activity against *Mycobacterium tuberculosis*. Although high activities were observed *in vitro* in several examples, no activity could be demonstrated *in vivo* in guinea-pigs; this may have been due to the high toxicity of the compounds. Di-(*p-N*-phenylamidinophenoxy)alkanes containing three or five methylene groups exhibit high activity *in vitro*, whereas homologues having two, four, or six methylene groups are inactive.

The observation that, in contrast to propamidine [1 : 3-di-(*p*-amidinophenoxy)propane (I; R = H, *n* = 3)], 1 : 3-di-(*p-N*-phenylamidinophenoxy)propane (I; R = Ph, *n* = 3) (Oxley, Partridge, and Short, *J.*, 1947, 1110) exhibited considerable activity *in vitro* against *Myco-*

bacterium tuberculosis, both in the presence and absence of serum, indicated that an examination of analogous compounds might be of interest. Homologues, in which R = Ph and n = 2, 4, 5, and 6, were prepared by orthodox methods from the corresponding dicyanides. Attempts to prepare the first member of this series, in which n = 1, were unsuccessful. Analogues of (I) in which R was *p*-tolyl, *p*-chlorophenyl, *p*-hydroxyphenyl, and *p*-alkoxyphenyl, and n = 3 or 5 were also prepared. Data relating to these compounds are summarised in the table. These *N*-substituted diamidines are weak bases which form sparingly water-soluble



(I.)



(II.)

salts; their dilactates are, however, moderately soluble in water. The substituted arylammonium benzenesulphonates, required as intermediates, are described in the Experimental section, together with other benzenesulphonates prepared before experiments on this series of amidines were discontinued. This preparative work afforded little new of chemical interest.

1 : 3-*Di*-(p-4 : 5-*dihydro*-2-*glyoxalinylphenoxy*)*propane* (II; X = NH) was prepared by the method of Oxley and Short (*J.*, 1947, 497), and the corresponding *bisoxazoline* (II; X = O) was obtained by a replacement reaction of 1 : 3-di-(*p*-*N*-phenylamidinophenoxy)propane with ethanolamine (Oxley and Short, B.P. 615,006).

The biological results will be described in detail elsewhere. Attention is directed here to certain features of chemical interest which appear to be deducible from the *in vitro* activities recorded in the table. The activity of 4-aminosalicylic acid, determined under the same conditions, is included for comparison.

There is a noteworthy relation between the length of the polymethylene chain and the activity of the short series of di-(*p*-*N*-phenylamidinophenoxy)alkanes described; when the number of methylene groups is even, the compounds are inactive whereas, when the number is odd, high activities appear. In this series, the presence of serum does not appreciably affect the *in vitro* activity. This specific effect of the length of the polymethylene chain is unusual and, as far as is known, no strictly analogous case has previously been recorded, although some indication of a similar effect was noted by Ashley *et al.* (*J.*, 1942, 103) for the trypanocidal activites of the corresponding unsubstituted diamidines. In this respect, the di-(*p*-*N*-phenylamidinophenoxy)alkanes differ strikingly from other homologous series of compounds known to exhibit activity against *M. tuberculosis*. *p*-Alkoxyanilines and 2-alkoxy-5-aminopyridines (Friedman *et al.*, *J. Pharm. Exp. Ther.*, 1947, **89**, 153; *J. Amer. Chem. Soc.*, 1947, **69**, 1204, 1795; Forrest, D'Arcy Hart, and Walker, *Nature*, 1947, **160**, 94) and the *p*-alkoxy-*N*-arylbenzamidines, to be described in a later paper in this series, show a gradual change in activity with increase in chain length. Further examples showing this feature have been reported by Bloch *et al.* (*Helv. Chim. Acta*, 1947, **30**, 539) and by Drea (*J. Bact.*, 1946, **51**, 507). The introduction of a *p*-methyl group into the *N*-phenyl substituents of the amidine groups (I; R = *p*-tolyl, n = 3) has no effect on the activity, whereas similarly placed *p*-chloro- and *p*-hydroxy-groups cause a marked decrease. The full activity of the parent compound is restored by methylation of the *p*-hydroxy-groups; although ethylation increases the activity to five times that of the parent compound and butylation restores part of the activity in the absence of serum, these two compounds are partly inactivated by serum. Analogues of 1 : 5-*di*-(p-*N*-*phenylamidinophenoxy*)*pentane* (I; R = Ph, n = 5) containing *p*-alkoxy-groups in the *N*-phenyl substituents of the amidine groups, are consistently less active than the parent compound. The cyclic diamidine (II; X = NH) and its oxygen isostere (II; X = O) are of about the same low order of activity as the corresponding unsubstituted diamidine, propamidine. Notwithstanding the appreciable activities *in vitro* which were observed in several of these diamidines, no demonstration of activity against experimental tuberculosis in guinea-pigs was possible; this may have been due to the high toxicity of these compounds.

Experimental.

p-*Chloroanilinium Benzenesulphonate.*—*p*-Chloroaniline (12·8 g.) in hot methanol (75 c.c.), neutralised to Congo-red with hydrated benzenesulphonic acid (17 g., 1 mol.) in hot methanol (75 c.c.) and decolourised with charcoal, afforded p-*chloroanilinium benzenesulphonate* (17·5 g., 61%), m. p. 234—235° (Found: N, 4·9. $C_{12}H_{12}O_3NClS$ requires N, 4·9%). The following were similarly prepared.

p-*Hydroxyanilinium benzenesulphonate*, prisms (from *iso*propanol), m. p. 230—231° (decomp.) (Found: N, 5·2. $C_{12}H_{13}O_4NS$ requires N, 5·2%).

	Yield, %.	Salt.	M. p.	Formula.	Found, N, %.	Req., N, %.	Activity.‡ In absence of serum.	Activity.‡ In presence of serum.
(1) 4-Aminosalicylic acid	—	—	—	—	—	—	10	—
(2) 1 : 3-Di-(*p*-amidinophenoxy)propane	—	—	—	—	—	—	1 (10)	—
(3) 1 : 2-Di-(*p*-*N*-phenylamidinophenoxy)ethane	38	*dihydrochloride*	287—288° *	$C_{28}H_{26}O_2N_4,2HCl,3H_2O$	9·7, 9·7	9·7	<1	—
(4) 1 : 3-Di-(*p*-*N*-phenylamidinophenoxy)propane	—	—	—	—	—	—	100	50—100
(5) 1 : 4-Di-(*p*-*N*-phenylamidinophenoxy)butane	55	*dihydrochloride*	283—284 *	$C_{30}H_{30}O_2N_4,2HCl,2H_2O$	9·9	9·6	<1	—
(6) 1 : 5-*Di*-(p-N-*phenylamidinophenoxy*)*pentane*	91	—	176—177	$C_{31}H_{32}O_2N_4$	11·5	11·4	500	500
(7) 1 : 6-Di-(p-N-*phenylamidinophenoxy*)*hexane*	69	—	219—221	$C_{32}H_{34}O_2N_4$	10·8	11·1	<1	<1
(8) 1 : 3-*Di*-(p-N-p′-*tolylamidinophenoxy*)*propane*	21	—	204—206	$C_{31}H_{32}O_2N_4$	11·3	11·4	100	—
(9) 1 : 3-*Di*-(p-N-p′-*chlorophenylamidinophenoxy*)*propane*	61	—	234—235	$C_{29}H_{26}O_2N_4Cl_2$	10·8	10·5	<1	—
(10) 1 : 3-Di-(*p*-*N*-*p*′-hydroxyphenylamidinophenoxy)propane	33	*dibenzenesulphonate*	197—199	$C_{41}H_{40}O_{10}N_4S_2$	7·0	6·9	10 (100)	—
(11) 1 : 3-*Di*-(p-N-p′-*methoxyphenylamidinophenoxy*)*propane*	32	—	182—183	$C_{31}H_{32}O_4N_4$	10·6	10·7	100	100
(12) 1 : 3-*Di*-(p-N-p′-*ethoxyphenylamidinophenoxy*)*propane*	38	—	188—189	$C_{33}H_{36}O_4N_4$	10·3	10·2	500	100
(13) 1 : 3-*Di*-(p-N-p′-*butoxyphenylamidinophenoxy*)*propane*	48	—	185—186	$C_{37}H_{44}O_4N_4$	9·3	9·2	50	10
(14) 1 : 5-*Di*-(p-N-p′-*methoxyphenylamidinophenoxy*)*pentane*	70	—	182—183	$C_{33}H_{36}O_4N_4$	10·2	10·2	—	10—50
(15) 1 : 5-*Di*-(p-N-p′-*ethoxyphenylamidinophenoxy*)*pentane*...	40	—	203—205	$C_{35}H_{40}O_4N_4$	9·5	9·65	—	10—50
(16) 1 : 5-*Di*-(p-N-p′-*propoxyphenylamidinophenoxy*)*pentane*	85	—	200—201	$C_{37}H_{44}O_4N_4$	9·1	9·2	10 (500)	10
(17) 1 : 5-*Di*-(p-N-p′-*butoxyphenylamidinophenoxy*)*pentane*	81	—	178—179	$C_{39}H_{48}O_4N_4$	8·8	8·7	100	50—100
(18) 1 : 3-*Di*-(p-4 : 5-*dihydro*-2-*glyoxalinylphenoxy*)*propane*	—	—	—	—	—	—	5 (10)	—
(19) 1 : 3-*Di*-(p-2-*oxazolinylphenoxy*)*propane*	—	—	—	—	—	—	1	—

* With decomposition.

‡ Dilution (in thousands) at which complete inhibition of the growth of *M. tuberculosis* (human virulent strain) was maintained for 4 weeks in modified Long's medium (by the floating pellicle method). Figures in parentheses represent dilutions (in thousands) at which partial inhibition occurred.

(3) Needles (from water) (Found : loss at 100°/vac., 9·5. $C_{28}H_{26}O_2N_4,2HCl,3H_2O$ requires H_2O, 9·4%). (5) Needles (from water) (Found : loss at 100°/vac., 6·4. $C_{30}H_{30}O_2N_4,2HCl,2H_2O$ requires H_2O, 6·1%). (6) Leaflets from methanol. (7) Leaflets from ethoxyethanol. (8) *p*-Toluidinium chloride was used in preparing this compound; the diamidine crystallised in needles from *n*-butanol. (9) Prisms from *n*-butanol. The *dihydrochloride* crystallised in needles (from ethanol), m.p. 283—284° (decomp.) (Found : N, 8·9; loss at 100°/vac., 5·1. $C_{29}H_{26}O_2N_4,2HCl,2H_2O$ requires N, 8·8; H_2O, 5·6%); the *di-isethionate* formed needles (from water), m. p. 218—225° (decomp.) (Found : N, 7·4. $C_{33}H_{38}O_{10}N_4Cl_2S_2$ requires N, 7·2%). (10) The reaction was strongly exothermic and a considerable quantity of tar was produced; the dibenzenesulphonate crystallised in prisms from water. (11) Prisms from acetone. (12) Prisms from ethanol. (13) Prisms from methanol. The hydrated *p*-*n*-butoxyanilinium benzenesulphonate was dried at 100°/vac. for the preparation of this compound. (14), (15), (16) Leaflets from ethanol. (17) Leaflets from ethanol. Anhydrous *p*-*n*-butoxyanilinium benzenesulphonate was used in the preparation of this compound.

p-*Methoxyanilinium benzenesulphonate*, prisms (from *iso*propanol), m. p. 179—180° (Found: N, 5·1. $C_{13}H_{15}O_4NS$ requires N, 5·0%).

p-*Ethoxyanilinium benzenesulphonate*, prisms (from *iso*propanol), m. p. 167—168° (Found: N, 4·9. $C_{14}H_{17}O_4NS$ requires N, 4·8%).

p-n-*Propoxyanilinium benzenesulphonate*, obtained by interaction of its constituents in water and purified by crystallisation from ethyl acetate containing a trace of ethanol, leaflets, m. p. 214—215° (Found: N, 4·8. $C_{15}H_{19}O_4NS$ requires N, 4·5%).

p-n-*Butoxyanilinium benzenesulphonate*, hydrated needles (from water), m. p. 191—192° (decomp.) (Found, in material dried at 100°/vac.: N, 4·4. $C_{16}H_{21}O_4NS$ requires N, 4·3%).

p-n-*Amyloxyanilinium Benzenesulphonate.*—*p*-Nitrophenyl *n*-amyl ether, on reduction with aqueous sodium sulphide and treatment with benzenesulphonic acid, gave a 62% yield of p-n-*amyloxyanilinium benzenesulphonate*, leaflets (from water), m. p. 172—173° (Found: loss at 100°/vac., 2·3. Found, on dried material, N, 4·3. $C_{17}H_{23}O_4NS,\frac{1}{2}H_2O$ requires H_2O, 2·6%. $C_{17}H_{23}O_4NS$ requires N, 4·2%).

N-n-*Butyl*-p-*bromoanilinium Benzenesulphonate.*—*p*-Bromoformanilide (20 g.) was alkylated with *n*-butyl bromide (21 g., 1·5 mols.) as described by King and Tonkin (*J.*, 1946, 1063). After removal of the solvent, the residue was heated under reflux for 3 hours with 2·28N-aqueous benzenesulphonic acid (44 c.c., 1 mol.) and afforded N-n-*butyl*-p-*bromoanilinium benzenesulphonate* (27·5 g., 78%) as prisms, m. p. 118—119°, on crystallisation from *iso*propanol (Found: N, 3·75. $C_{16}H_{20}O_3NBrS$ requires N, 3·6%).

Di-(p-N-*arylamidinophenoxy*)*alkanes.*—The di-(*p*-*N*-arylamidinophenoxy)alkanes described in the table were prepared by heating the appropriate di-(*p*-cyanophenoxy)alkane (Ashley *et al.*, *loc. cit.*) with 2 equivalents of an arylammonium benzenesulphonate at 210° for 1—2 hours (Oxley and Short, *J.*, 1946, 147). The experiments were conducted on a 0·015—0·1-g.-mol. scale. The diamidine was liberated by aqueous ammonia from a solution of the product in ethanol and purified as the free base, as a salt, or as the free base after separation from non-basic material as the lactate. The yields given are those of purified material.

1 : 3-*Di*-(p-4 : 5-*dihydro*-2-*glyoxalinylphenoxy*)*propane.*—1 : 3-Di-(*p*-cyanophenoxy)propane (8·2 g.) and 2-aminoethylammonium toluene-*p*-sulphonate (14 g.; 2 mols.) were heated in a refluxing nitrobenzene bath (210°) for 90 minutes; the reaction was exothermic, the temperature of the reaction mixture reaching 20° above that of the vapour-bath. A solution of the cooled melt in ethanol (50 c.c.), poured into aqueous ammonia (*d* 0·880; 30 c.c.) and crushed ice (100 g.), afforded 1 : 3-*di*-(p-4 : 5-*dihydro*-2-*glyoxalinylphenoxy*)*propane* (5·1 g., 47%), m. p. 237—238° (decomp.), as leaflets on crystallisation from ethanol (Found: N, 15·2. $C_{21}H_{24}O_2N_4$ requires N, 15·4%).

1 : 3-*Di*-(p-2-*oxazolinylphenoxy*)*propane.*—1 : 3-Di-(*p*-*N*-phenylamidinophenoxy)propane dibenzenesulphonate (Oxley, Partridge, and Short, *loc. cit.*) (15·6 g.) and ethanolamine (6·1 g., 5 mols.) were heated together at 100° for 2 hours. The solid which separated on adding water (50 c.c.) afforded 1 : 3-*di*-(p-2-*oxazolinylphenoxy*)*propane* (1·9 g., 26%), m. p. 196—197°, as prisms on crystallisation from aqueous methanol (Found: N, 7·8. $C_{21}H_{24}O_4N_2$ requires N, 7·6%).

The author gratefully acknowledges his indebtedness to Mr. C. E. Coulthard, Dr. L. Dickinson, and Miss B. Croshaw for the biological tests, and to Drs. W. F. Short and D. A. Peak for their interest in the work. Thanks are due to Miss M. Birchmore and Miss F. Skidmore for carrying out the analyses.

RESEARCH LABORATORIES, BOOTS PURE DRUG CO. LTD., NOTTINGHAM.
UNIVERSITY OF NOTTINGHAM.
[*Received, June 18th*, 1949.]