673. *The Chemotherapy of Schistosomiasis. Part I. Derivatives and Analogues of αω-Di-(*p*-aminophenoxy)alkanes.*

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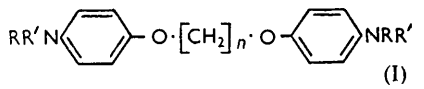
A series of αω-di-(*p*-aminophenoxy)alkanes of the general formula (I; R = R′ = H) has been prepared and tested against *Schistosoma mansoni* infections in mice. Modifications of this fundamental molecular type which have been explored, in an attempt to establish a structure–activity relationship, include substitution in the amino-groups, the rings, and the central chain, and replacement of the central chain by other linkages. Many of the compounds exhibit high schistosomicidal activity.

Schistosomiasis is one of the greatest unsolved problems in tropical medicine, and an inexpensive and safe drug which can be administered orally is an outstanding need. An extensive programme of work has been pursued in these laboratories during the last few years in the search for such a drug and several hundred compounds have been synthesised, and screened by our biological colleagues against *Schistosoma mansoni*.

Schistosomicidal activity was discovered early in 1952 in a series of aromatic diamines

of the general formula (I; R = R′ = H; n = 3—9), many of which had been prepared some ten years earlier for another purpose.



(I)

(II)

A preliminary announcement [1] of this work was made after the disclosure in the patent literature that the same series had been investigated independently by Raison and Standen.[2] Full details of the biological tests and the results obtained are being recorded elsewhere.[3] In this paper, the first of a series dealing mainly with compounds containing the *p*-aminophenoxyalkyl group, we shall describe the preparation of some primary, secondary, and tertiary amines of type (I) together with derivatives and analogues in which, for example, the central chain has been modified or further substituents introduced into the rings. Most of the simpler compounds have already been mentioned in patent specifications.[4,5] Since they were generally obtained by conventional methods, in reasonable yields, and with satisfactory analyses, and their melting points are recorded in these patents, further preparative details, solvents for recrystallisation, analytical figures, etc., have in most cases been omitted from this paper.

The di(nitrophenoxy)alkanes were obtained by condensation of potassium nitrophenoxide with the appropriate dibromide. Compounds not previously reported are listed in Table 1. Reduction of the dinitro-compounds to the diamines (Table 2) was effected either catalytically or by sodium sulphide. An alternative route also employed in some instances was the condensation of the appropriate acetamidophenol with the dibromide, followed by hydrolysis of the acetyl groups. The unsymmetrical dinitro-compounds were prepared by reaction of 1 : 5-dibromopentane with a limited amount of potassium *p*-nitrophenoxide to give 5-*p*-nitrophenoxypentyl bromide, followed by further reaction with potassium *o*- or *m*-nitrophenoxide.

At one time a substantial amount of 1 : 8-dibromo-octane was needed and its preparation from the readily available 1 : 4-dibromobutane was undertaken. Of the methods described in the literature for the preparation of αω-polymethylene dihalides, the Wurtz reaction has the advantage of few stages and is stated to give good overall yields, although the best practical details for the synthesis of 1 : 8-dibromo-octane have not been fully recorded.[6] We investigated this method and obtained 1 : 8-dibromo-octane from 1 : 4-dibromobutane in about 30% overall yield.

In Table 3 are listed compounds in which the simple polymethylene chain of the parent compound has been replaced by branched chains, benzene, or *cyclo*hexane rings, etc. 1 : 5-Dibromo-3-methylpentane has previously been made by treating 1-benzoyl-4-methylpiperidine with phosphorus tribromide.[7] It was more conveniently prepared from 2-ethoxy-3 : 4-dihydro-4-methylpyran by fission with acid to 3-methylglutaraldehyde, catalytic reduction to the glycol, and treatment with hydrobromic acid.[8] The glycol has previously been obtained from diethyl 3-methylglutarate by reduction over copper chromite.[9] When 1 : 1-di-(2-hydroxyethyl)*cyclo*hexane, prepared by reduction of *cyclo*hexylidenediacetic acid, was treated with 50% hydrobromic acid, the dibromide produced was always accompanied by appreciable amounts of the tetrahydropyran (II).

[1] Collins, Davis, and Hill, *Chem. and Ind.*, 1954, 1072.

[2] Raison and Standen, *Trans. Roy. Soc. Trop. Med. Hyg.*, 1954, **48**, 446; *Brit. J. Pharmacol.*, 1955, **10**, 191; Caldwell and Standen, *ibid.*, 1956, **11**, 367; Standen and Walls, *ibid.*, p. 375; Gorvin, Raison, Solomon, Standen, and Walls, *ibid.*, 1957, **12**, 329; Goodwin, Richards, and Udall, *ibid.*, p. 468.

[3] Hill, *Ann. Trop. Med. Parasitol.*, 1956, **50**, 39; Edge, Mason, Wien, and Ashton, *Nature*, 1956, **178**, 806; Collins, Davis, Edge, and Hill, *Brit. J. Pharmacol.*, in the press.

[4] May and Baker Ltd., B.P. 761,888; 768,144.

[5] The Wellcome Foundation Ltd., B.P. 749,907; 749,923; 758,382; 770,410; 770,411; 775,478.

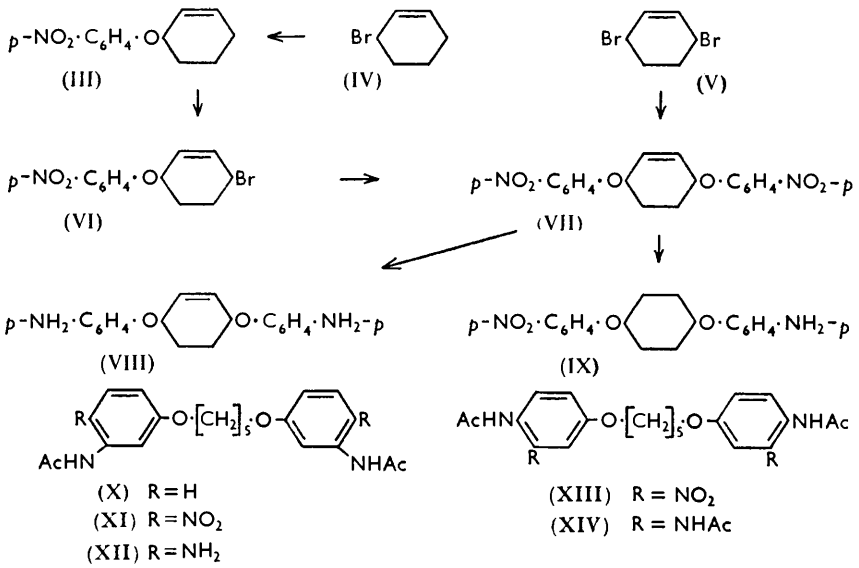
[6] von Braun, *Ber.*, 1909, **42**, 4541; von Braun and Kamp, *Ber.*, 1937, **70**, 973; Ziegler and Weber, *ibid.*, p. 1275; Ziegler, Weber, and Gellert, *Ber.*, 1942, **75**, 1715.

[7] Leonard and Wicks, *J. Amer. Chem. Soc.*, 1946, **68**, 2402.

[8] Longley and Emerson, *ibid.*, 1950, **75**, 3080; cf. Smith, Norton, and Ballard, *ibid.*, 1951, **73**, 5267.

[9] Wojcik and Adkins, *ibid.*, 1933, **55**, 4943.

For the preparation of 1 : 4-di-(*p*-aminophenoxy)but-2-yne condensation of 1 : 4-dibromobut-2-yne [10] with *p*-acetamidophenol, followed by hydrolysis of the product, proved satisfactory. Attempts partially to reduce the triple bond over palladium–calcium carbonate led to a mixture containing both the *cis*- and the *trans*-butene. The pure *cis*-



and *trans*-isomers were obtained by condensation of the appropriate dibromides with potassium *p*-nitrophenoxide in dry acetone to give, respectively, *cis*- and *trans*-1 : 4-di-(*p*-nitrophenoxy)but-2-ene, which were reduced by iron and acetic acid to the corresponding *cis*- and *trans*-1 : 4-di-(*p*-aminophenoxy)but-2-ene. Both amines were reduced catalytically to the known 1 : 4-di-(*p*-aminophenoxy)butane, thus proving that the 1 : 4-dibromobut-2-ene used had not isomerised to 1 : 2-dibromobut-3-ene during the reaction.

The synthesis of the *cyclo*hexene and *cyclo*hexane analogues was then investigated. 3 : 6-Dibromo*cyclo*hexene [11] (V) resembles 1 : 4-dibromobut-2-ene in undergoing allylic rearrangement under certain conditions. Thus, with sodium hydrogen carbonate it is reported [12] to be hydrolysed to a mixture of *cis*- and *trans*-3 : 4-dihydroxy*cyclo*hexene and *cis*-3 : 6-dihydroxy*cyclo*hexene. However, concurrent work described above established that both *cis*- and *trans*-1 : 4-dibromobut-2-ene reacted normally without rearrangement. 3 : 6-Dibromo*cyclo*hexene (V) was therefore treated with potassium *p*-nitrophenoxide in the usual manner; it reacted rapidly and completely to give 3 : 6-di-(*p*-nitrophenoxy)-*cyclo*hexene (VII) in good yield. This compound was also obtained by the following route (explored primarily for the synthesis of other compounds to be described in a later paper). Treatment of *cyclo*hexene with *N*-bromosuccinimide gave the known 3-bromo*cyclo*hexene [13] which with potassium *p*-nitrophenoxide formed 3-*p*-nitrophenoxy*cyclo*hexene (III) in high yield. Further bromination with *N*-bromosuccinimide gave 3-bromo-6-*p*-nitrophenoxy-*cyclo*hexene (VI) which was not isolated but was condensed *in situ* with a further quantity of potassium *p*-nitrophenoxide to yield the diphenoxy-compound (VII). *N*-Bromosuccinimide is normally a specific reagent for a methylene group α to a double bond and it attacks an unsubstituted methylene group [*i.e.*, the 6-position of (III)] more readily than a substituted one (*i.e.*, the 3-position) (cf. Djerassi [14]).

[10] Johnson, *J.*, 1946, 1009.
[11] Farmer and Scott, *J.*, 1929, 172.
[12] Bedos and Ruyer, *Compt. rend.*, 1937, **204**, 1380.
[13] Ziegler, Spaeth, Schaaf, Schumann, and Winkelmann, *Annalen*, 1942, **551**, 80.
[14] Djerassi, *Chem. Rev.*, 1948, **43**, 273.

With iron and acetic acid only the nitro-groups of compound (VII) were reduced, giving 3 : 6-di-(*p*-aminophenoxy)*cyclo*hexene (VIII), which was further reduced over platinum oxide to the saturated base (IX). The nitro-compound could be reduced directly to the saturated base over palladium–calcium carbonate, but not over platinum oxide, the mixture becoming dark and only a trace of the required base being isolated. Probably hydrogenolysis of the ether linkage occurred. 1 : 4-Di-(*p*-aminophenoxy)*cyclo*hexane (IX) was also prepared more directly from *trans*-1 : 4-ditoluene-*p*-sulphonyloxy*cyclo*hexane:[15] condensation with potassium *p*-nitrophenoxide in 2-ethoxyethanol (no reaction occurred in acetone) gave a low yield of 1 : 4-di-(*p*-nitrophenoxy)*cyclo*hexane (together with unidentified unsaturated products), which was reduced over platinum oxide to the diamine (IX). Final confirmation that the unsaturated intermediates employed had not undergone rearrangement was obtained by treatment of this amine (IX) with hydrobromic acid, *trans*-1 : 4-dibromo*cyclo*hexane being obtained.

The nuclear-substituted compounds shown in Tables 4 and 5 were mostly obtained by conventional methods. For the preparation of 1 : 5-di-(3-acetamido-4-aminophenoxy)-pentane (XII), the nitration of 1 : 5-di-(*m*-acetamidophenoxy)pentane (X) was examined, as previous work on the nitration of *m*-acetamido-anisole and -phenetole has shown that the 3-acetamido-4-nitrophenyl ether is the principal product.[16] The orientation of the product, 1 : 5-di-(3-acetamido-4-nitrophenoxy)pentane (XI), was confirmed by catalytic reduction to compound (XII) and acetylation, which gave 1 : 5-di-(3 : 4-bisacetamido-phenoxy)pentane (XIV) identical with a specimen prepared in a like manner from the isomeric 1 : 5-di-(4-acetamido-3-nitrophenoxy)pentane (XIII).

Many different methods were employed to make the *N*-substituted amines, most of which are described in the relevant patents.[4,5] The general procedures are outlined here with particular reference to derivatives of 1 : 5-di-(*p*-aminophenoxy)pentane (I; $n = 5$; R = R′ = H). The *NN*′-dimethyl derivatives (I; R = Me, R′ = H) were formed when *p*-(*N*-methylacetamido)phenol was condensed with the dibromoalkane and the acetyl group then removed by hydrolysis. Alkylation of the primary diamines with methyl iodide gave the bis-quaternary iodides, which on pyrolysis yielded the *NNN*′*N*′-tetramethyl derivatives (I; R = R′ = Me) in high yield. The *NNN*′*N*′-tetraethyl derivatives were similarly prepared, although the quaternary iodides were not obtained crystalline. Treatment of 1 : 5-di-(*p*-methylaminophenoxy)pentane (I; $n = 5$; R = Me, R′ = H) with an excess of ethyl bromide and pyrolysis of the product yielded the *NN*′-diethyl-*NN*′-dimethyl derivative (I; $n = 5$; R = Me, R′ = Et). Loss of ethyl iodide rather than methyl iodide from quaternary salts has been reported by Fahim and Fleifel.[17]

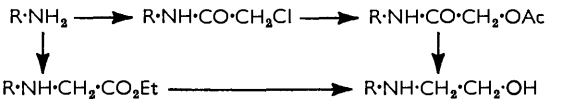
1 : 5-Di-(-*p*-ethylamino- and -*p*-*n*-propylaminophenoxy)pentane (I; $n = 5$; R = Et or Pr^n, R′ = H) were conveniently obtained by reduction of the diacetyl (I; $n = 5$; R = Ac, R′ = H) and dipropionyl derivatives (I; $n = 5$; R = COEt, R′ = H) of the primary diamines with lithium aluminium hydride. The diacetyl derivative was sparingly soluble in ether and tetrahydrofuran, and reduction was incomplete in these solvents, but proceeded satisfactorily in di-*n*-butyl ether. Propionylation and further reduction of the di-*n*-propyl compound afforded the tetra-*n*-propyl derivative. For the unsymmetrical *NN*-diethyl-*N*′*N*′-dimethyl derivative, *p*-(*N*-methylformamido)phenol was condensed with 5-*p*-nitrophenoxypentyl bromide to yield 1-[*p*-(*N*-methylformamido)phenoxy]-5-*p*-nitrophenoxypentane, and the nitro-group of the product was reduced catalytically. Acetylation of the primary amine formed, followed by lithium aluminium hydride reduction, yielded the *N*′-ethyl-*NN*-dimethyl compound. This was again acetylated and reduced to 1-*p*-diethylaminophenoxy-5-*p*-dimethylaminophenoxypentane.

Condensation of *N*-acetyl-*p*-*iso*propylaminophenol with dibromopentane proceeded

[15] Owen and Robins, *J.*, 1949, 320.
[16] Reverdin and Widmer, *Ber.*, 1913, **46**, 4071; Reverdin and Lokietek, *Bull. Soc. chim. France*, 1916, **19**, 253.
[17] Fahim and Fleifel, *J.*, 1951, 2761.

readily giving 1 : 5-di-(*p-iso*propylaminophenoxy)pentane, but removal of the protecting group by hydrolysis proved unexpectedly difficult, and only a small amount of the base could be isolated. Condensation of 1 : 5-di-(*p*-aminophenoxy)pentane with acetone was next examined. Although the unstable *iso*propylidene derivative (I; $n = 5$; $RR' = :CMe_2$) could not be isolated, its reduction *in situ* in the presence of excess of acetone led to a reasonable overall yield of 1 : 5-di-(*p-iso*propylaminophenoxy)pentane (I; $n = 5$; R = Pr^i, R′ = H).

1 : 5-Di-(*p*-hydroxyethylaminophenoxy)pentane (I; $n = 5$; $R = [CH_2]_2{\cdot}OH$, R = H) was prepared by two different routes from 1 : 5-di-(*p*-aminophenoxy)pentane (represented by $R{\cdot}NH_2$ in the annexed scheme). In both instances the final reduction was achieved with lithium aluminium hydride. The *NNN′N′*-tetra(hydroxethyl) derivatives (I; R = R′ = $[CH_2]_2{\cdot}OH$) were made by boiling the primary amines with excess of aqueous ethylene chlorohydrin in the presence of calcium carbonate. The unsymmetrical *NN*-di-



(hydroxyethyl) derivative was obtained by condensation of 5-*p*-nitrophenoxypentyl bromide with *p*-di-(2-hydroxyethylamino)phenol, followed by reduction. After alkylation of 1 : 5-di-(*p*-aminophenoxy)pentane with 2-methoxyethyl chloride only the secondary amine, 1 : 5-di-(*p*-2-methoxyethylaminophenoxy)pentane (I; $n = 5$; $R = [CH_2]_2{\cdot}OMe$, R′ = H), was isolated, albeit in low yield. Similar results attended the use of 2-diethylaminoethyl chloride.

1 : 5-Di-(*p*-pyrrolidinophenoxy)pentane was made both by direct condensation of 1 : 5-di-(*p*-aminophenoxy)pentane with 1 : 4-dibromobutane and by reduction of the corresponding disuccinimide with lithium aluminium hydride. The piperidino- and morpholino-analogues were obtained likewise from the diamine with 1 : 5-dibromopentane and di-(2-chloroethyl) ether respectively.

The *NN′*-dibenzyl derivative (I; $n = 5$; $R = CH_2Ph$, R′ = H) was conveniently made by catalytic reduction of the dibenzylidene derivative of the primary diamine.

The best yields of 1 : 5-di-(*p*-pyrid-2-ylaminophenoxy)pentane were obtained by heating 2-bromopyridine and 1 : 5-di-(*p*-aminophenoxy)pentane with potassium carbonate and copper bronze at 170—180° for a limited period. 1 : 5-Di-(*p*-aminophenoxy)pentane with ammonium thiocyanate formed the thioureide which did not condense with chloroacetaldehyde (as the acetal). With chloroacetone, however, the 4-methylthiazole derivative was readily formed.

The formaldehyde bisulphite derivative (I; $n = 5$; $R = CH_2{\cdot}SO_3Na$, R′ = H) of 1 : 5-di-(*p*-aminophenoxy)pentane was made by heating the base with an aqueous solution of sodium formaldehyde bisulphite.

In Table 6 are listed some diamines in which one or both oxygen linkages of the central dioxyalkane chain have been omitted or replaced by other linkages. The use of *p*-nitrothiophenol in place of *p*-nitrophenol led to the analogue containing two sulphur linkages. For the compound containing two NH linkages the condensation of *p*-aminoacetanilide with 1 : 3-dibromopropane was attempted, but afforded a mixture from which pure 1 : 3-di-(*p*-acetamidoanilino)propane could not be isolated. The alternative method of Veer [18] was therefore used, *p*-chloronitrobenzene being condensed with 1 : 3-diaminopropane, and the 1 : 3-di-(*p*-nitroanilino)propane formed reduced catalytically. The thiolsulphinate linkage —S—S(→O)— was first demonstrated in allicin.[19] Small, Bailey, and Cavallito [20] showed that thiolsulphinates were accessible by oxidation of the corresponding disulphide

[18] Veer, *Rec. Trav. chim.*, 1938, **57**, 989.
[19] Cavallito, Buck, and Suter, *J. Amer. Chem. Soc.*, 1944, **66**, 1952.
[20] Small, Bailey, and Cavallito, *ibid.*, 1947, **69**, 1710.

with perphthalic acid. Addition of the calculated quantity of perphthalic acid to a solution of di-(*p*-aminophenyl) disulphide in ether resulted in the precipitation of a salt (probably the phthalate of the thiolsulphinate). This was decomposed in sodium hydrogen carbonate or sodium acetate solution with liberation of the free thiolsulphinate, which possessed the characteristic properties of this linkage.[19] Thus, it reacted with cysteine in aqueous sodium hydrogen carbonate, its yellow colour being completely discharged in a few seconds. It was fairly stable towards dilute acids, but was decomposed by concentrated acids. For this reason it was not possible to prepare the same compound by acid hydrolysis of di-(*p*-acetamidophenyl) thiolsulphinate, earlier obtained from di-(*p*-acetamidophenyl) disulphide. Crystallisation of the thiolsulphinate required care, as in solvents it was unstable to heat. Acetone or aqueous pyridine gave the best recoveries, which even under favourable conditions did not exceed 40%.

Only the two lowest homologues of the series of αω-di-(*p*-aminophenyl)alkanes are described in the literature. Nitration of the diphenylalkanes is not readily controllable and gives even under mild conditions the 2 : 2′ : 4 : 4′-tetranitro-derivatives.[21] An alternative synthesis was therefore sought. Straus and Grindel [22] were able to reduce cinnamylideneacetophenone to 1 : 5-diphenylpentane over a palladium catalyst in acetone. We first established that this reduction was more rapid over Raney nickel in ethyl acetate and then applied the method to 1 : 5-di-(*p*-nitrophenyl)penta-2 : 4-dien-1-one, readily prepared from *p*-nitrocinnamaldehyde and *p*-nitroacetophenone. Reduction to 1 : 5-di-(*p*-aminophenyl)pentane proceeded smoothly.

Nitration of 5-phenylpentyl chloride at −10° is said to give substantially the *p*-nitro-derivative.[23] Nitration under identical conditions of 5-phenylpentyl bromide gave, however, a mixture of mono- and di-nitro-derivatives in which the latter predominated. It was characterised by condensation with *p*-nitrophenol and reduction of the trinitro-ether to the triamine. By carrying out the nitration of 5-phenylpentyl bromide at −50°, dinitration was minimised and the major product was the required 5-*p*-nitrophenylpentyl bromide. This could not be satisfactorily purified by distillation, but its orientation was confirmed by successive reaction with potassium acetate, hydrolysis, and oxidation with alkaline permanganate, only *p*-nitrobenzoic acid being then isolated. A small amount of *o*-nitrophenylpentyl bromide appeared to be simultaneously formed, since on condensation of the crude nitrated bromide with *p*-nitrophenol and chromatography of the product a small amount of an isomeric ether, probably 1-*p*-nitrophenoxy-5-*o*-nitrophenylpentane, was separated from the *p*-isomer.

Experimental

Light petroleum refers, unless otherwise stated, to the fraction of b. p. 40—60°.

Synthesis of 1 : 8-*Dibromo-octane by the Wurtz Reaction.*—1 : 4-Dibromobutane was prepared on a large scale by passage of dry hydrogen bromide into tetrahydrofuran. Fractionation of the high-boiling residue obtained after distillation of the dibromide gave di-(4-bromobutyl) ether (4%), b. p. 150—151°/13 mm. (Found: C, 33·3; H, 5·6; Br, 55·55. Calc. for $C_8H_{16}OBr_2$: C, 33·1; H, 5·6; Br, 55·5%) (lit.,[24] b. p. 142—147°/10 mm., 97—97·6°/1 mm.).

4-p-*Methoxyphenoxybutyl Bromide.*—Potassium hydroxide (67·5 g.) in methanol (200 ml.) was added to *p*-methoxyphenol (124 g.) in methanol (50 ml.), and the resulting solution was added during 1·5 hr. to 1 : 4-dibromobutane (432 g.) in acetone (400 ml.). The mixture was refluxed for 1 hr., concentrated, and diluted with water. The oil separating was taken up in ether, and the ethereal extract was filtered from 1 : 4-di-(*p*-methoxyphenoxy)butane (29 g.; m. p. 140—142°; Ziegler, Weber, and Gellert [6] give m. p. 142°), washed with dilute sodium hydroxide and water, dried, and distilled, giving recovered 1 : 4-dibromobutane (204 g.) and

[21] von Braun, Deutsch, and Koscielski, *Ber.*, 1913, **46**, 1524.
[22] Straus and Grindel, *Annalen*, 1924, **439**, 276.
[23] von Braun and Deutsch, *Ber.*, 1912, **45**, 2520.
[24] Ziegler and Hall, *Annalen*, 1937, **528**, 143; Müller and Vanc, *Ber.*, 1944, **77**, 669.

4-*p*-methoxyphenoxybutyl bromide (200 g., 73% on dibromide used, 77% on *p*-methoxyphenol used), b. p. 180—193°/13 mm. The distillate had m. p. 42—44° (lit.,[25] m. p. 42—43°, b. p. 125—130°/1·5 mm.).

4-p-*Methoxyphenoxybutyl Iodide*.—A mixture of 4-*p*-methoxyphenoxybutyl bromide (1·545 kg.) and sodium iodide (1·26 kg.) in acetone (15 l.) was stirred and refluxed for 3 hr. The cooled solution was filtered, the filtrate was concentrated, and the residue was poured into water. The solid product was filtered off, ground, and washed with water, then dried over phosphoric oxide and silica gel, to yield 1·771 kg. (98·5%) of product, m. p. 54°. Recrystallisation from ether–light petroleum gave the *iodide* in plates, m. p. 55° (Found: I, 42·1. $C_{11}H_{15}O_2I$ requires I, 41·5%).

1 : 8-*Di*-(p-*methoxyphenoxy*)*octane*.—Sodium (100 g.) was powdered by rapidly stirring the molten metal under toluene. When cool, the toluene was decanted off and the sodium washed with dry ether, then suspended in dry ether (2 l.) and mechanically stirred. 4-*p*-Methoxyphenoxybutyl iodide (444 g.) was added and the stirred mixture was refluxed for 48 hr., then cautiously treated with ethanol and kept overnight. The product was filtered off, cautiously added to water, refiltered, washed, and dried. Recrystallisation of the solid (62—69%), m. p. 129—130°, from acetic acid gave plates, m. p. 131—132°. Ziegler, Weber, and Gellert [6] give m. p. 132°.

1 : 8-*Dibromo-octane*.—A mixture of 1 : 8-di-(*p*-methoxyphenoxy)octane (613 g.), phenol (450 g.), and 50% aqueous hydrobromic acid (1·5 l.) was stirred and refluxed overnight, then steam-distilled. The distillate was extracted with ether, and the extract was washed with dilute aqueous sodium hydroxide and water, dried, and evaporated. Distillation of the residue gave 1 : 8-dibromo-octane (324 g., 70%), b. p. 150—152°/16 mm.

TABLE 1. *Compounds* $NO_2 \cdot C_6H_4 \cdot O \cdot [CH_2]_n \cdot O \cdot C_6H_4 \cdot NO_2$.

Position of NO_2 groups	*n*	Yield (%)	M. p.	Formula	Found (%) N	Reqd. (%) N
2 : 2′	3	54	111—113°	$C_{15}H_{14}O_6N_2$	8·7	8·8
2 : 2′	5	30	84 [a]	$C_{17}H_{18}O_6N_2$	8·5	8·1
2 : 2′	8	47	107	$C_{20}H_{24}O_6N_2$	7·4	7·2
3 : 3′	3	50	122—124	$C_{15}H_{14}O_6N_2$	8·95	8·8
3 : 3′	5	33	90	$C_{17}H_{18}O_6N_2$	8·1	8·1
4 : 2′	5	73	67—68	$C_{17}H_{18}O_6N_2$	8·2	8·1
4 : 3′	5	91	63—65	$C_{17}H_{18}O_6N_2$	8·3	8·1
4 : 4′	8	67	118—120	$C_{20}H_{24}O_6N_2$	7·1	7·2
4 : 4′	9	44	90—92 [a]	$C_{21}H_{26}O_6N_2$	7·1	7·0
4 : 4′	10	25	86	$C_{22}H_{28}O_6N_2$	6·55	6·7
4 : 4′	12	60	81—83	$C_{24}H_{32}O_6N_2$	6·5	6·3

[a] First prepared by Mr. S. S. Berg.

5-p-*Nitrophenoxypentyl Bromide*.—This was prepared by refluxing potassium *p*-nitrophenoxide (3·8 kg.) and 1 : 5-dibromopentane (9·9 kg.) in acetone (9 l.) overnight; 3·41 kg. (55%) of the bromide, containing a small amount of 1 : 5-di-(*p*-nitrophenoxy)pentane, were obtained. Pure 5-*p*-nitrophenoxypentyl bromide, obtained by chromatography or by distillation of the crude product (in small batches), had m. p. 34·5—35·5°, b. p. 160°/0·2 mm. (Found: N, 4·8; Br, 27·35. Calc. for $C_{11}H_{14}O_3NBr$: N, 4·85; Br, 27·8%) (lit.,[5] m. p. 33—34°). Fractionation of the dibromopentane recovered from this experiment gave a small amount of low-boiling material. After re-fractionation it had b. p. 34—38°/18 mm. and appeared to be 5-*bromopentyl pent-4-enyl ether* (Found: C, 51·8; H, 8·0; Br, 33·95. $C_{10}H_{19}OBr$ requires C, 51·1; H, 8·15; Br, 33·95%).

Similarly prepared were 3-p-*nitrophenoxypropyl bromide* (49%), m. p. 51° (Found: Br, 30·7. $C_9H_{10}O_3NBr$ requires Br, 30·7%), and 4-p-*nitrophenoxybutyl bromide* (37%), m. p. 37—40° (Found: N, 4·85; Br, 28·5. $C_{10}H_{12}O_3NBr$ requires N, 5·1; Br, 29·2%).

Di(*nitrophenoxy*)*alkanes* (*Table* 1).—The symmetrical *products* were prepared from potassium *p*-nitrophenoxide and the appropriate dibromide (cf. ref. 4). The unsymmetrical *compounds* were prepared from 5-*p*-nitrophenoxypentyl bromide and the appropriate phenol.

Di(*aminophenoxy*)*alkanes*.—Table 2 lists those *bases* and their *derivatives* which have not already been described elsewhere. All the amines were obtained by catalytic reduction of the nitro-compounds.

[25] Leonard, Felley, and Nicolaides, *J. Amer. Chem. Soc.*, 1952, **74**, 1700.

1 : 4-*Di*-(p-*acetamidophenoxy*)*but*-2-*yne*, prepared from *p*-acetamidophenol and 1 : 4-dibromobut-2-yne,[10] had m. p. 215—217° (lit.,[10] 218—220°). Acid hydrolysis gave 1 : 4-*di*-(p-*aminophenoxy*)*but*-2-*yne* (84%), m. p. 103° (Found: C, 71·5; H, 6·1; N, 10·35. $C_{16}H_{16}O_2N_2$ requires C, 71·6; H, 6·0; N, 10·45%). It formed a *dimethanesulphonate* (Found: N, 5·95; S, 14·0. $C_{16}H_{16}O_2N_2,2CH_4O_3S$ requires N, 6·1; S, 13·9%).

1 : 6-*Di*-(p-*nitrophenoxy*)*hexa*-2 : 4-*diyne*.—A mixture of 1 : 6-dibromohexa-2 : 4-diyne [prepared from hexa-2 : 4-diyne-1 : 6-diol (24·5 g.) with phosphorus tribromide (46 g.)] and potassium *p*-nitrophenoxide (50 g.) in dry acetone (400 ml.) was refluxed for 5 hr. The product was crystallised from acetic acid, giving the *nitro-compound* (30%), m. p. 210—211° (Found: C, 61·2; H, 3·8; N, 8·1. $C_{18}H_{12}O_6N_2$ requires C, 61·4; H, 3·4; N, 8·0%).

1 : 6-*Di*-(p-*aminophenoxy*)*hexa*-2 : 4-*diyne*.—The above dinitro-compound (32·5 g.) was reduced by stannous chloride dihydrate (146 g.) in concentrated hydrochloric acid (160 ml.) and acetic acid (300 ml.). The base was isolated as the dihydrochloride (20 g.). The *diamine* (51%), after recrystallisation from ethanol, had m. p. 51° (Found: C, 73·7; H, 5·9; N, 9·5. $C_{18}H_{16}O_2N_2$ requires C, 73·9; H, 5·5; N, 9·6%).

Further reduction of the diamine (0·5 g.) in ethanol (20 ml.) over platinum oxide (0·1 g.) gave 1 : 6-di-(*p*-aminophenoxy)hexane (0·2 g.), m. p. and mixed m. p. 138—139°.

TABLE 2. *Compounds* $NH_2{\cdot}C_6H_4{\cdot}O{\cdot}[CH_2]_n{\cdot}O{\cdot}C_6H_4{\cdot}NH_2$.

Position of NH_2 groups	n	Deriv.	Yield (%)	M. p.	Solvent for recryst.	Formula	Found (%) N	Found (%) Cl	Required (%) N	Required (%) Cl
2 : 2′	3	Base	85	42—48°	Et_2O	$C_{15}H_{16}O_2N_2$	11·0	—	10·85	—
		2HCl		306—308		$C_{15}H_{18}O_2N_2,2HCl$	8·2	21·4	8·45	21·4
2 : 2′	5	Base	84	62	Aq. EtOH	$C_{17}H_{22}O_2N_2$	9·8	—	9·8	—
		2HCl		266 [a]		$C_{17}H_{22}O_2N_2,2HCl$	7·75	19·6	7·8	19·8
2 : 2′	8	Base	88	97	EtOH	$C_{20}H_{28}O_2N_2$	8·7	—	8·5	—
		2HCl		248	EtOH–Et_2O	$C_{20}H_{28}O_2N_2,2HCl$	7·0	17·6	7·0	17·7
3 : 3′	3	Base	78	148—150	EtOH	$C_{15}H_{18}O_2N_2$	10·6	—	10·85	—
		2HCl		252—254		$C_{15}H_{18}O_2N_2,2HCl,H_2O$	8·3	20·2	8·0	20·35
3 : 3′	5	Base	70	120	C_6H_6 or Aq. EtOH	$C_{17}H_{22}O_2N_2$	9·75	—	9·8	—
		2HCl		272—275		$C_{17}H_{22}O_2N_2,2HCl$	7·85	19·5	7·8	19·9
		Ac_2	60	176—178 [b]	AcOH	$C_{21}H_{26}O_4N_2,0{\cdot}25AcOH$	7·3		7·3	
4 : 2′	5	2HCl	96	238—242	EtOH–Et_2O	$C_{17}H_{22}O_2N_2,2HCl,0{\cdot}5H_2O$	7·8	19·0	7·6	19·3
4 : 3′	5	2HCl	78	225—230	EtOH–Et_2O	$C_{17}H_{22}O_2N_2,2HCl,0{\cdot}5H_2O$	7·8	19·0	7·6	19·3
4 : 4′	1	2HCl	—	240	—	$C_{13}H_{14}O_2N_2,2HCl$	9·2	23·5	9·25	23·4
4 : 4′	2	2HCl	—	270—280	—	$C_{14}H_{16}O_2N_2,2HCl$	8·8	21·9	8·8	22·4
4 : 4′	4	Ac_2	—	227—228	—	$C_{20}H_{24}O_4N_2$	7·9	—	7·85	—
4 : 4′	5	$(EtCO)_2$	100	167—169	EtOH	$C_{23}H_{30}O_4N_2$	7·05	—	7·0	—
		$(Me{\cdot}SO_2)_2$	79	183—185	$COMe_2$	$C_{19}H_{26}O_6N_2S_2$	6·4		6·3	
		Dithio-ureido	66	181—182 [c]	AcOH	$C_{19}H_{24}O_2N_4S_2$	13·45		13·8	
4 : 4′	7	$2Me{\cdot}SO_3H$	—	247—249	EtOH–Et_2O	$C_{19}H_{26}O_2N_2,2CH_4O_3S$	5·4	—	5·5	—
4 : 4′	8	Base	79	130—132 [a]	EtOH or $CHCl_3$	$C_{20}H_{28}O_2N_2$	8·5	—	8·5	—
		$2Me{\cdot}SO_3H$		276—278		$C_{20}H_{28}O_2N_2,2CH_4O_3S$	5·4		5·4	
4 : 4′	9	Base	82	82—83 [a]	Et_2O–Pet. [f]	$C_{21}H_{30}O_2N_2$	8·35	—	8·2	—
4 : 4′	10	Base	87	119 [d]	EtOH	$C_{22}H_{32}O_2N_2$	8·0	—	7·9	—
4 : 4′	12	Base	81	111—113	EtOH	$C_{24}H_{36}O_2N_2$	7·1	—	7·3	—
		$2Me{\cdot}SO_3H$		220—250 [e]		$C_{24}H_{36}O_2N_2,2CH_4O_3S$	4·75		4·9	

[a] First prepared by Mr. S. S. Berg. [b] Found: C, 67·1; H, 7·0; Ac, 24·4. Required: C, 67·0; H, 7·3; Ac, 25·1%. [c] Prepared from the dihydrochloride and ammonium thiocyanate (Found: S, 15·6. Required: S, 15·8%). [d] First prepared by Mr. A. D. H. Self. [e] Found: S, 11·4. Required: S, 11·1%. [f] Pet. = light petroleum.

1 : 6-*Di*-(p-*acetamidophenoxy*)*hexa*-2 : 4-*diyne*.—This *diyne* (7 g.), obtained by refluxing 1 : 6-dibromohexa-2 : 4-diyne [prepared from hexa-2 : 4-diyne-1 : 6-diol (22 g.)], *p*-acetamidophenol (67 g.), and potassium carbonate (60 g.) in dry acetone (300 ml.) for 16 hr., crystallised from acetic acid and had m. p. 234° (decomp.) (Found: C, 69·4; H, 5·4; N, 7·1; Ac, 24·05.

$C_{22}H_{20}O_4N_2$,0·25AcOH requires C, 69·1; H, 5·4; N, 7·15; Ac, 24·7%). Hydrolysis with 10% aqueous hydrochloric acid gave the diamine, identical with the compound described above.

1 : 4-*Di*-(p-*nitrophenoxy*)*benzene*.—Quinol (27·5 g.) was added to a solution of potassium (19·5 g.) in absolute ethanol (250 ml.), *p*-chloronitrobenzene (158 g.) was then added and the mixture was heated in a metal bath to 200°, ethanol being distilled off. The residue was kept at 200° for 2·5 hr., steam-distilled to remove unchanged *p*-chloronitrobenzene, cooled, and filtered. The solid was washed with ethanol, then boiled with dioxan (500 ml.). The cooled suspension was filtered and the solid crystallised from acetic acid, to give 1 : 4-di-(*p*-nitrophenoxy)benzene (20·7 g., 24%), m. p. 232—234° (Found: C, 61·5; H, 4·0; N, 8·1. Calc. for $C_{18}H_{12}O_6N_2$: C, 61·4; H, 3·4; N, 8·0%). Bayer [26] does not give an m. p. for this compound.

3-p-*Nitrophenoxy*cyclo*hexene*.—A mixture of 3-bromo*cyclo*hexene (21 g.) and potassium *p*-nitrophenoxide (26·2 g.) in dry carbon tetrachloride (400 ml.) and dry acetone (400 ml.) was refluxed for 6—8 hr., then filtered, and the filtrate was evaporated *in vacuo*. The residue, in ether, was washed successively with water, dilute aqueous sodium hydroxide, and water, and the ethereal solution was dried and evaporated. Crystallisation of the residue from light petroleum gave 3-p-*nitrophenoxy*cyclo*hexene* (20 g.; 73·5%), m. p. 35—36° (Found: C, 66·0; H, 5·75; N, 6·6. $C_{12}H_{13}O_3N$ requires C, 65·75; H, 5·95; N, 6·4%).

3 : 6-*Di*-(p-*nitrophenoxy*)cyclo*hexene*.—(*a*) A mixture of 3-*p*-nitrophenoxy*cyclo*hexene (22 g.) and *N*-bromosuccinimide (19 g.) in dry carbon tetrachloride (200 ml.) was refluxed for 15—25 min., cooled, and filtered. Dry acetone (200 ml.) and finely ground potassium *p*-nitrophenoxide (20 g.) were added and the whole was stirred and refluxed for 48 hr. The re-filtered solution was evaporated to low bulk, ethanol was added to the residue, and the solid was filtered off, ground with sodium hydroxide solution, washed with water, and crystallised from acetic acid. Recrystallisation of the product (6 g.) from acetic acid gave 3 : 6-di-(*p*-nitrophenoxy)-*cyclo*hexene (5·3 g., 15%), m. p. 160—161°, raised by recrystallisation to 163—164°. (*b*) 3 : 6-Dibromo*cyclo*hexene (7·1 g.) and dry finely powdered potassium *p*-nitrophenoxide (15 g.) in dry acetone (130 ml.) were refluxed for 12 hr., filtered hot, and diluted with water. The solid was filtered off, washed, and crystallised from acetic acid, giving the *nitro-compound* (8·1 g., 77%), m. p. 167—168° (Found: C, 60·4; H, 4·8; N, 7·9. $C_{18}H_{16}O_6N_2$ requires C, 60·6; H, 4·5; N, 7·9%), not depressed by a specimen prepared as in (*a*).

3 : 6-*Di*-(p-*aminophenoxy*)cyclo*hexene*.—3 : 6-Di-(*p*-nitrophenoxy)*cyclo*hexene (3 g.) in 85% acetic acid (40 ml.) was treated with reduced iron (3 g.). The suspension was boiled for 3 min., filtered while still hot, cooled, and slowly treated with concentrated hydrochloric acid (12 ml.) until the brown colour was discharged, then cooled again. After 2 hr., the hydrochloride was filtered off, and the filtrate was evaporated *in vacuo*. The residue, on treatment with a little water, gave more of the hydrochloride. The combined crops were dissolved in the minimum of water, treated with concentrated hydrochloric acid, cooled, and filtered. The hydrochloride (1·5 g., 48%) was washed with acetone and dried. Treatment with aqueous sodium hydroxide and crystallisation from ethanol then gave the *base* (42%), m. p. 123—124° (Found: C, 72·7; H, 6·6; N, 9·3. $C_{18}H_{20}O_2N_2$ requires C, 73·0; H, 6·8; N, 9·5%). It formed a *dihydrochloride* (Found: N, 7·6; Cl, 18·9. $C_{18}H_{20}O_2N_2$,2HCl requires N, 7·6; Cl, 19·25%) and a *dimethanesulphonate* (Found: N, 5·9; S, 13·2. $C_{18}H_{20}O_2N_2$,2CH_4O_3S requires N, 5·75; S, 13·1%).

1 : 4-*Di*-(p-*aminophenoxy*)cyclo*hexane*.—(*a*) 3 : 6-Di-(*p*-aminophenoxy)*cyclo*hexene (0·82 g.) in ethanol (30 ml.) was reduced over platinum oxide (0·1 g.). 1 : 4-*Di*-(p-*aminophenoxy*)cyclo*hexane* after recrystallisation from ethanol had m. p. 157—159° (Found: C, 72·4; H, 7·5; N, 9·4. $C_{18}H_{22}O_2N_2$ requires C, 72·5; H, 7·4; N, 9·4%). It formed a *dimethanesulphonate* (Found: N, 5·9; S, 13·0. $C_{18}H_{22}O_2N_2$,2CH_4O_3S requires N, 5·7; S, 13·1%). (*b*) 3 : 6-Di-(*p*-nitrophenoxy)*cyclo*hexene (7·1 g.) in methanol (300 ml.) was reduced over 1% palladium–calcium carbonate (5 g.), giving the diamine (51%), m. p. 157—159°, not depressed by a sample prepared as in (*a*). (*c*) The same diamine, m. p. 159—161°, was obtained by reduction of 1 : 4-di-(*p*-nitrophenoxy)*cyclo*hexane over Raney nickel in dimethylformamide. 1 : 4-Di-(*p*-aminophenoxy)*cyclo*hexane (1 g.) yielded *trans*-1 : 4-dibromo*cyclo*hexane, m. p. 112° (0·2 g.), identical with an authentic specimen,[27] when refluxed for 1 hr. with 52% aqueous hydrobromic acid.

Condensation of 5-p-*Nitrophenoxypentyl Bromide with Quinol*.—A solution of potassium hydroxide (11·2 g.) in ethanol was slowly added to a stirred, refluxing solution of 5-*p*-nitrophenoxypentyl bromide (57·6 g.) and quinol (22 g.) in ethanol. The mixture was refluxed

[26] Bayer, D.R.-P. 178,803.
[27] Zelmsky and Kozeschkow, *Ber.*, 1927, **60**, 1103.

overnight, then concentrated, and the residue was treated with water. The solid product was extracted with boiling N-sodium hydroxide (2 × 500 ml.). Acidification of the alkaline extract gave 1-p-*hydroxyphenoxy*-5-p-*nitrophenoxypentane* (21 g., 32%) which, after recrystallisation from chloroform, had m. p. 141—143° (Found: N, 4·5. $C_{17}H_{19}O_5N$ requires N, 4·4%).

The alkali-insoluble material was recrystallised from acetic acid (charcoal), yielding p-*di*-(5-p-*nitrophenoxypentyloxy*)*benzene* (22 g., 41%), m. p. 138—139° (after recrystallisation from chloroform) (Found: N, 5·1. $C_{28}H_{32}O_8N_2$ requires N, 5·35%). For maximum conversion into the bis-condensation product, a higher proportion of bromide would have been advantageous but, in this instance, both products were required for further work.

3-*Methylglutaraldehyde*.—2-Ethoxy-3 : 4-dihydro-4-methylpyran (142 g.) (kindly supplied by Dr. B. J. Heywood) was stirred with 4N-sulphuric acid (250 ml.) for 4 hr. at room temperature. The mixture was poured into saturated potassium carbonate solution, then extracted with ether, and the washed and dried extract was distilled, yielding the dialdehyde (83 g.), b. p. 87—92°/18 mm. (lit.,[28] b. p. 140—160°/20 mm.).

3-*Methylpentane*-1 : 5-*diol*.—3-Methylglutaraldehyde (57 g.) in ethanol (200 ml.) was reduced over Raney nickel at 100°/730 lb. The product was distilled, giving the diol (39·55 g., 67%), b. p. 140°/16 mm. (lit.,[9] b. p. 134—137°/6 mm.). Refluxing with 50% hydrobromic acid and concentrated sulphuric acid gave 1 : 5-dibromo-3-methylpentane (60·4 g., 74%), b. p. 106°/16 mm. (Found: Br, 65·6. Calc. for $C_6H_{12}Br_2$: Br, 65·6%) (lit.,[7] 97—98·5°/10 mm.).

1 : 1-*Di*-(2-*hydroxyethyl*)cyclo*hexane*.—*cyclo*Hexylidenediacetic acid [29a] (39·5 g.) in dry tetrahydrofuran (300 ml.) was reduced by lithium aluminium hydride (27·35 g.) in dry ether (1 l.). The product was distilled, giving the *diol* (29·6 g., 87%), b. p. 176—186°/14 mm. (Found: C, 68·9; H, 11·2. $C_{10}H_{20}O_2$ requires C, 69·7; H, 11·7%). The *ditoluene*-p-*sulphonate* had m. p. 69—70° (Found: S, 13·05. $C_{24}H_{32}O_6S_2$ requires S, 13·35%).

1 : 1-*Di*-(2-*bromoethyl*)cyclo*hexane*.—A mixture of the preceding diol (19·6 g.) and 50% hydrobromic acid (75 ml.) was treated slowly with concentrated sulphuric acid (37 ml.), and heated on the steam-bath for 20 hr. Distillation of the product, isolated in the usual way, gave the *dibromide* (64%), b. p. 166—173°/13 mm. A redistilled specimen had b. p. 179—182°/20 mm. (Found: C, 40·7; H, 6·0; Br, 52·1. $C_{10}H_{18}Br_2$ requires C, 40·3; H, 6·1; Br, 53·6%). In a similar experiment under reflux (6 hr.), the yield of dibromide fell to 31%, and a low-boiling

TABLE 3. *Compounds* p-$NH_2{\cdot}C_6H_4{\cdot}X{\cdot}C_6H_4{\cdot}NH_2$-*p*.

–X–	Deriv.	Yield (%)	M. p.	Solvent for recryst.	Formula	Found (%) N	Reqd. (%) N
p-O·CH_2·C_6H_4·CH_2O	Base	70	143—144°	EtOH	$C_{20}H_{20}O_2N_2$	8·75	8·75
p-O·$[CH_2]_5$·O·C_6H_4·O·$[CH_2]_5$·O	Base	61	133	EtOAc–Pet [a]	$C_{28}H_{36}O_4N_2$	5·8 [c]	6·0
O·$[CH_2]_2$·O·$[CH_2]_2$·O	Base	—	80	—	$C_{16}H_{20}O_3N_2$	9·7	9·7
	2Me·SO_3H	—	237—239 *		$C_{16}H_{20}O_3N_2,2CH_4O_3S$	5·9	5·8
O·CH_2·CH(OH)·CH_2·O	Base	63	114	EtOH	$C_{15}H_{18}O_3N_2$	10·05	10·2
	2Me·SO_3H		230		$C_{15}H_{18}O_3N_2,2CH_4O_3S$	5·9	6·0
O·$[CH_2]_2$·CHPh·$[CH_2]_2$·O	2Me·SO_3H	86	194—200	EtOH–Et_2O	$C_{23}H_{26}O_2N_2,2CH_4O_3S$	5·0	5·05
O·$[CH_2]_2$·CMe_2·$[CH_2]_2$·O	Base	97	55—56	$CHCl_3$–Pet	$C_{19}H_{26}O_2N_2$	8·8	8·9
	2Me·SO_3H		188—192	EtOH–Et_2O	$C_{19}H_{26}O_2N_2,2CH_4O_3S$	5·5 [d]	5·5
$[CH_2]_5$>C(CH_2·CH_2·O)$_2$	2Me·SO_3H	87 [b]	214—216	EtOH	$C_{22}H_{30}O_2N_2,2CH_4O_3S$	5·2	5·1

* With decomp. [a] Pet = light petroleum. [b] Over Raney nickel in dimethylformamide (Found: S, 12·1. Required: S, 11·75%). [c] Found: C, 72·2; H, 8·3. Required: C, 72·5; H, 7·8%. [d] Found: C, 49·4; H, 6·9. Required: C, 49·8; H, 6·7%.

by-product (51%) was formed. After fractionation from solid potassium hydroxide the latter had b. p. 87°/12 mm. (Found: C, 77·2; H, 11·8. $C_{10}H_{18}O$ requires C, 77·8; H, 11·8%) and was presumably cyclo*hexane*spiro-4-*tetrahydropyran* (II).

[28] Riban, *Bull. Soc. chim. France*, 1872, **18**, 63.
[29] Majer, U.S.P. 1,978,433/1934.
[29a] Vogel, *J.*, 1934, 1761.

The following nitro-compounds were prepared by condensation of potassium *p*-nitrophenoxide with, except where stated, the appropriate dibromide in ethylene glycol or 2-ethoxyethanol: trans-1 : 4-*di*-(p-*nitrophenoxy*)cyclo*hexane* (from the *trans*-ditoluene-*p*-sulphonate [15]) (7·5%), m. p. 208—210° (from acetic acid) (Found: C, 60·2; H, 5·0; N, 7·8. $C_{18}H_{18}O_6N_2$ requires C, 60·3; H, 5·0; N, 7·8%); p-*di*-(p-*nitrophenoxymethyl*)*benzene* (52%), m. p. 222—225° (from acetic acid) (Found: N, 7·3. $C_{20}H_{16}O_6N_2$ requires N, 7·4%); 1 : 5-*di*-(p-*nitrophenoxy*)-3-*phenylpentane* (25%), m. p. 132° (from ethanol) (Found: N, 6·8. $C_{23}H_{22}O_6N_2$ requires N, 6·7%); 3 : 3-*dimethyl*-1 : 5-*di*-(p-*nitrophenoxy*)*pentane* (51%), m. p. 81° (from ethanol) (Found: N, 7·8. $C_{19}H_{22}O_6N_2$ requires N, 7·5%); and 1 : 1-*di*-(2-p-*nitrophenoxyethyl*)cyclo*hexane* (46% overall from glycol), m. p. 115—117° (from acetic acid) (Found: N, 6·9. $C_{22}H_{26}O_6N_2$ requires N, 6·8%). The corresponding *amines* (Table 3) were prepared by catalytic reduction of the nitro-compounds.

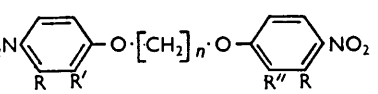
1 : 3-*Di*-(4-*acetamido*-3-*nitrophenoxy*)*propane* (*Experiment by* Mr. S. S. Berg).—4-Hydroxy-2-nitroacetanilide [34] (372 g.), 1 : 3-dibromopropane (202 g.), anhydrous potassium carbonate (151·8 g.), potassium iodide (1 g.), and anhydrous acetone (10 l.) were stirred and refluxed for 24 hr., cooled, and filtered. The solid was washed with N-sodium hydroxide, water, and ethanol, and recrystallised from acetic acid (charcoal), giving yellow needles (300 g., 70%), m. p. 203—204° (Found: C, 52·4; H, 4·75; N, 12·8. $C_{19}H_{20}O_8N_4$ requires C, 52·8; H, 4·6; N, 12·95%). Evaporation of the acetone mother-liquors and extraction of the residue with light petroleum (b. p. 60—80°) gave 3-(4-*acetamido*-3-*nitrophenoxy*)*propyl bromide* (6·1 g.). After repeated recrystallisation from light petroleum (b. p. 60—80°), it formed yellow needles, m. p. 81—82° (Found: N, 8·8; Br, 25·0. $C_{11}H_{13}O_4N_2Br$ requires N, 8·8; Br, 25·2%). 1 : 5-*Di*-(4-*acetamido*-3-*nitrophenoxy*)*pentane*, similarly prepared, had m. p. 194—195° (Found: C, 54·6; H, 5·05; N, 12·4. $C_{21}H_{24}O_8N_4$ requires C, 54·8; H, 5·2; N, 12·2%).

1 : 3-*Di*-(4-*amino*-3-*nitrophenoxy*)*propane* (*Experiment by* Mr. S. S. Berg).—Hydrogen chloride was bubbled for 1·25 hr. through a suspension of the foregoing compound in boiling ethanol. The hydrochloride, which separated, was treated with alkali, and the *base* was crystallised from 2-ethoxyethanol, yielding red prisms (91%), m. p. 188—189° (Found: C, 51·6; H, 4·55; N, 16·5. $C_{15}H_{16}O_6N_4$ requires C, 51·7; H, 4·6; N, 16·1%). 1 : 5-*Di*-(4-*amino*-3-*nitrophenoxy*)*pentane*, similarly prepared, had m. p. 134—135° (Found: C, 54·1; H, 5·45; N, 14·7. $C_{17}H_{20}O_6N_4$ requires C, 54·25; H, 5·3; N, 14·9%).

1 : 5-*Di*-(4-*acetamido*-3-*aminophenoxy*)*pentane*.—The nitro-compound was reduced catalytically to the *amine*, m. p. 180—181° (Found: N, 14·1. $C_{21}H_{28}O_4N_4$ requires N, 14·0%).

1 : 5-*Di*-(3-*acetamido*-4-*nitrophenoxy*)*pentane*.—Nitric acid (*d* 1·5; 6·3 ml.) was added during 45 min. to a stirred suspension of 1 : 5-di-(*m*-acetamidophenoxy)pentane (13 g.) in acetic anhydride (100 ml.) at 5—10°. After a further 15 min., the mixture was filtered through a sintered-glass funnel to remove unchanged material, and the filtrate was poured into ice-water and kept for 2 hr. The aqueous layer was decanted and the residual gum was dissolved in acetone. The solid which separated was filtered off, washed with acetone and ether, and

TABLE 4. *Compounds*



								Found (%)		Reqd. (%)	
n	R	R′	R″	Yield (%)	M. p.	Solvent for recryst.	Formula	N	Hal	N	Hal
3	H	Br	H	50 [a]	154°	EtOH	$C_{15}H_{13}O_6N_2Br$	7·2	20·0	7·1	20·15
5	H	Cl	Cl	34	118—120	AcOH	$C_{17}H_{16}O_6N_2Cl_2$	6·7	17·1	6·75	17·1
5	Cl	H	H	47	92—93	AcOH	$C_{17}H_{16}O_6N_2Cl_2$	7·1	16·85	6·75	17·1
5	Me	H	H	39	100—102	EtOH	$C_{19}H_{22}O_6N_2$	7·75	—	7·5	—
5	H	OMe	OMe	85	126—128	AcOH	$C_{19}H_{22}O_8N_2$	6·8	—	6·9	—

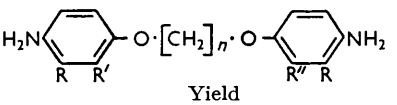
[a] From 3-*p*-nitrophenoxypropyl bromide and 2-bromo-4-nitrophenol in ethanol.

crystallised from acetic acid, giving 1 : 5-*di*-(3-*acetamido*-4-*nitrophenoxy*)*pentane* (1·5 g., 9%), m. p. 154—155° (Found: C, 54·6; H, 5·0; N, 12·5. $C_{21}H_{24}O_8N_4$ requires C, 54·8; H, 5·2; N, 12·2%). Its orientation was established by reduction and acetylation to 1 : 5-*di*-(3 : 4-*diacetamidophenoxy*)*pentane*, m. p. 186—188° (Found: N, 11·4; Ac, 32·9. $C_{25}H_{32}O_6N_4$ requires N, 11·6; Ac, 35·5%), identical with specimens prepared from authentic 1 : 5-di-(3 : 4-diaminophenoxy)pentane and from 1 : 5-di-(4-acetamido-3-aminophenoxy)pentane. Other *nitro-compounds* are listed in Table 4, and the corresponding *amines* in Table 5.

ON-*Diacetyl*-p-iso*propylaminophenol*.—*p-iso*Propylaminophenol [29] (30·2 g.) was boiled with acetic anhydride (100 ml.) for 1 hr., excess of reagent then being removed under reduced pressure. The residue, after trituration with light petroleum, gave an almost quantitative yield of crude product, pure enough for hydrolysis (see below). Crystallisation from light petroleum gave ON-*diacetyl*-p-iso*propylaminophenol* in prisms, m. p. 78—80° (Found: N, 6·0. $C_{13}H_{17}O_3N$ requires N, 5·95%).

N-*Acetyl*-p-iso*propylaminophenol*.—The above *ON*-diacetyl compound (1·9 g.) was shaken with 2N-sodium hydroxide (10 ml.), and the solution obtained was filtered and acidified with acetic acid. The washed and dried product (1·2 g., 77%, m. p. 150°) crystallised from acetone–light petroleum, giving *N-acetyl*-p-iso*propylaminophenol* in needles, m. p. 154° (Found: N, 7·0. $C_{11}H_{15}O_2N$ requires N, 7·25%).

1 : 5-*Di*-(p-iso*propylaminophenoxy*)*pentane*.—A solution of 1 : 5-di-(*p*-aminophenoxy)pentane (2 g.) in acetone (50 ml.) was boiled under reflux for 20 hr., then reduced catalytically over platinum oxide. When the initial rapid uptake of hydrogen had ceased and there was only a slow uptake due to reduction of the solvent, the mixture was filtered and evaporated. Chromatography of the residue in light petroleum (b. p. 60—80°) over alumina gave 1 : 5-*di*-(p-iso*propylaminophenoxy*)*pentane* (41%), m. p. 49—50° (after recrystallisation from ether–light

TABLE 5. *Compounds* 

No.	*n*	R	R′	R″	Deriv.	Yield (%)	M. p.	Solvent for recryst.
1	3	H	Br	H	Base	—	103—105°	$CHCl_3$–Pet [d]
2	—	—	—	—	2HCl	73	282—284 [a]	Dil. HCl
3	3	H	NH_2	NH_2	Base	78	118—120	EtOH
4	3	NO_2	H	H	Base	—	185	$COMe_2$
5	5	H	Cl	Cl	Base	85	95—96	EtOH
6	—	—	—	—	2HCl	—	270—280 *	—
7	5	Cl	H	H	2Me·SO_3H	70	202—206	EtOH–Et_2O
8	5	Me	H	H	Base	79	69—71	C_6H_6–Pet [d]
9	—	—	—	—	2HCl	—	246—248	—
10	5	NH_2	H	H	Base	95	105—106 [ab]	Pr^{i}OH
11	5	NHAc	H	H	Base	64	179	MeOH
12	5	H	OMe	OMe	Base	88	106—107	EtOH
13	—	—	—	—	2Me·SO_3H	—	228—230 [c]	—

		Found (%)				Required (%)			
No.	Formula	C	H	N	Hal	C	H	N	Hal
1	$C_{15}H_{17}O_2N_2Br$	—	—	—	23·5	—	—	—	23·7
2	$C_{15}H_{17}O_2N_2Br,2HCl$	—	—	6·6	17·9	—	—	6·8	17·3
3	$C_{15}H_{20}O_2N_4$	—	—	19·6	—	—	—	19·4	—
4	$C_{15}H_{16}O_6N_4$	52·05	4·8	16·3	—	51·8	4·6	16·1	—
5	$C_{17}H_{20}O_2N_2Cl_2$	—	—	8·0	—	—	—	7·9	—
6	$C_{17}H_{20}O_2N_2Cl_2,2HCl$	—	—	6·5	32·7	—	—	6·5	33·1
7	$C_{17}H_{20}O_2N_2Cl_2,2CH_4O_3S,2H_2O$	—	—	5·2	12·0	—	—	4·8	12·15
8	$C_{19}H_{26}O_2N_2$	—	—	8·8	—	—	—	8·9	—
9	$C_{19}H_{26}O_2N_2,2HCl$	58·5	6·85	7·2	18·3	58·9	7·2	7·2	18·35
10	$C_{17}H_{24}O_3N_4$	—	—	17·6	—	—	—	17·7	—
11	$C_{21}H_{28}O_4N_4$	62·7	7·2	14·35	—	63·0	7·0	14·0	—
12	$C_{19}H_{26}O_4N_2$	—	—	8·0	—	—	—	8·1	—
13	$C_{19}H_{26}O_4N_2,2CH_4O_3S$	—	—	5·2	—	—	—	5·2	—

* With decomp. [a] First prepared by Mr. S. S. Berg. [b] From 1 : 5-di-(4-amino-3-nitrophenoxy)-pentane over PtO_2 in dioxan. [c] Found: S, 11·9. Required: S, 11·9%. [d] Pet = light petroleum.

petroleum) (Found: C, 74·8; H, 9·2; N, 7·5. $C_{23}H_{34}O_2N_2$ requires C, 74·6; H, 9·3; N, 7·6%). The *diacetyl derivative* had m. p. 98—100° [from light petroleum (b. p. 60—80°)] (Found: N, 6·1. $C_{27}H_{38}O_3N_2$ requires N, 6·2%).

1-p-*Di*(iso*propylamino*)*phenoxy*-5-p-iso*propylaminophenoxypentane*.—A mixture of the foregoing bis*iso*propyl compound (2·3 g.), anhydrous sodium carbonate (1 g.), *iso*propyl bromide (10 ml.), and ethanol (15 ml.) was refluxed for 20 hr., then evaporated. The residue was basified

and extracted with ether. The washed and dried extract was evaporated and the residue was chromatographed in light petroleum, yielding the *triisopropyl derivative* (0·7 g.), m. p. 56—57° (Found: C, 75·8; H, 9·8; N, 6·9. $C_{26}H_{40}O_2N_2$ requires C, 75·7; H, 9·8; N, 6·8%).

1 : 5-*Di*-(p-2-*methoxyethylaminophenoxy*)*pentane*.—A mixture of 1 : 5-di-(*p*-aminophenoxy)-pentane (31·4 g.), 2-methoxyethyl chloride [30] (41·5 g., 4 mol.), and calcium carbonate (30 g.) in water (250 ml.) was refluxed for 24 hr., cooled, shaken with chloroform, and filtered. The chloroform solution was separated, dried, concentrated, and treated with ether. The product, which separated, was recrystallised from ether and aqueous methanol and chromatographed in chloroform–benzene over alumina. The purified *base* (23%) had m. p. 68—69° (Found: C, 68·6; H, 8·4; N, 6·9. $C_{23}H_{34}O_4N_2$ requires C, 68·6; H, 8·5; N, 7·0%). It failed to give a diazo-test for aromatic amino-groups.

1 : 5-*Di*-[p-(*diethylaminoethyl*)*aminophenoxy*]*pentane*.—An intimate mixture of 1 : 5-di-(*p*-aminophenoxy)pentane (56·4 g.) and 2-diethylaminoethyl chloride hydrochloride (80 g.) was heated at 135° for 20 hr. A solution of the product in warm water was basified with 50% sodium hydroxide solution and extracted with ether (3 × 600 ml.), and the combined extracts were washed with water, dried, and evaporated. The residue was distilled in small batches and the fractions of b. p. 260—280°/0·05 mm. (20 g.) were combined and redistilled, to give the *amine* (13·6 g.), b. p. 270—280°/0·05 mm. (Found: C, 71·9; H, 9·9; N, 11·5. $C_{29}H_{48}O_2N_4$ requires C, 72·0; H, 9 9; N, 11·6%).

1 : 5-*Di*-(p-*succinimidophenoxy*)*pentane*.—A mixture of 1 : 5-di-(*p*-aminophenoxy)pentane (5 g.) and succinic anhydride (25 g.) was boiled under reflux for 15 min. The cooled product was extracted with boiling water and with boiling ethanol, and the insoluble residue was crystallised from acetic acid, giving 1 : 5-*di*-(p-*succinimidophenoxy*)*pentane* (7·2 g., 91·5%), m. p. 204·5—205·5° (Found: C, 66·5; H, 5·85; N, 6·0. $C_{25}H_{26}O_6N_2$ requires C, 66·7; H, 5·8; N, 6·2%).

1 : 5-*Di*-(p-*pyrrolidinophenoxy*)*pentane*.—(*a*) 1 : 5-Di-(*p*-aminophenoxy)pentane (28·6 g.) 1 : 4-dibromobutane (43·2 g., 2 mol.), and sodium carbonate (21·2 g., 4 equivs.) in ethanol (400 ml.) were refluxed overnight, then treated with a little dilute sodium hydroxide, cooled, and filtered. The product was extracted with chloroform, which was washed, concentrated, diluted with ethanol, cooled, and filtered. 1 : 5-*Di*-(p-*pyrrolidinophenoxy*)*pentane* (76%), after recrystallisation from benzene–light petroleum, had m. p. 126° (partially melts at 120—121°) (Found: C, 76·3; H, 8·6; N, 7·2. $C_{25}H_{34}O_2N_2$ requires C, 76·1; H, 8·7; N, 7·1%). The compound is probably dimorphic. (*b*) 1 : 5-Di-(*p*-succinimidophenoxy)pentane (7·1 g.) in tetrahydrofuran (200 ml.) was reduced with lithium aluminium hydride (8 g.) in tetrahydrofuran (200 ml.). The base (49%) had m. p. 126—127° (partially melts at 120—121°).

1 : 5-*Di*-(p-*piperidinophenoxy*)*pentane*, prepared (47%) from 1 : 5-di-(*p*-aminophenoxy)-pentane and 1 : 5-dibromopentane by method (*a*) above, and crystallised from ether, had m. p. 73—74° (Found: C, 76·4; H, 8·7; N, 6·6. $C_{27}H_{38}O_2N_2$ requires C, 76·7; H, 9·1; N, 6·6%).

1 : 5-*Di*-(p-*morpholinophenoxy*)*pentane*.—Di-(2-chloroethyl) ether (28·6 g.), 1 : 5-di-(*p*-aminophenoxy)pentane (28·6 g.), and sodium carbonate (29·2 g.) in 2-ethoxyethanol (100 ml.) were refluxed for 20 hr., then poured into water. The product was taken up in chloroform, which was washed, dried, and evaporated, and the residue was heated for 1 hr. on the steam-bath with acetic anhydride (50 ml.) and pyridine (50 ml.). The resulting solution was poured into dilute hydrochloric acid, which was extracted with chloroform, then filtered and basified. The product was filtered off, washed, and crystallised from ethanol, giving 1 : 5-*di*-(p-*morpholinophenoxy*)*pentane* (44%), m. p. 115—117° (Found: C, 70·4; H, 7·9; N, 6·6. $C_{25}H_{34}O_4N_2$ requires C, 70·4; H, 8·0; N, 6·6%). When a similar experiment was conducted in ethanol a mixture of unchanged base and the monomorpholino-compound was obtained. Acetylation removed the insoluble 1 : 5-di-(*p*-acetamidophenoxy)pentane (6·9 g., 19%) from the acid-soluble 1-p-*acetamidophenoxy*-5-*morpholinophenoxypentane* (8·45 g., 21%), which after recrystallisation from ethanol had m. p. 136—137° (Found: C, 69·5; H, 7·7; N, 6·9. $C_{23}H_{30}O_4N_2$ requires C, 69·3; H, 7·6; N, 7·0%). A similar experiment, carried out without any solvent but with heating for 8 hr. at 135—140°, gave the dimorpholino-compound (29%).

1 : 5-*Di*-(p-*pyrid*-2′-*ylaminophenoxy*)*pentane*.—1 : 5-Di-(*p*-aminophenoxy)pentane (4·5 g.), 2-bromopyridine (6·5 g.), anhydrous potassium carbonate (1·7 g.), and copper bronze (0·9 g.) were heated for 180° for 20 min., after which evolution of gas ceased. The cooled mixture was treated with aqueous sodium hydroxide and extracted with chloroform. The washed extract was evaporated and the residue was crystallised from ethyl acetate–light petroleum, giving

[30] Bennett and Heathcoat, *J.*, 1929, 270.

1 : 5-*di*-(p-*pyrid*-2'-*ylaminophenoxy*)*pentane* (72%), m. p. 150—152° (Found: N, 12·6. $C_{27}H_{28}O_2N_4$ requires N, 12·7%).

1 : 5-*Di*-(p-4'-*methylthiazol*-2'-*ylaminophenoxy*)*pentane*.—1 : 5-Di-(*p*-thioureidophenoxy)-pentane (8·1 g.) and twice redistilled chloroacetone (6·1 g.) were heated in ethanol (20 ml.) under reflux for 4 hr., then slowly treated with 2N-sodium hydroxide (approx. 100 ml.). The product was filtered off, washed with water, and dried. Recrystallisation from chloroform–light petroleum gave 1 : 5-*di*-(p-4'-*methylthiazol*-2'-*ylaminophenoxy*)*pentane* (78%), m. p. 188—190° (Found: N, 11·8; S, 13·4. $C_{25}H_{28}O_2N_4S_2$ requires N, 11·7; S, 13·3%).

Sodium Formaldehyde Bisulphite Derivative of 1 : 5-*Di*-(p-*aminophenoxy*)*pentane*.—1 : 5-Di-(*p*-aminophenoxy)pentane (10 g.) and sodium formaldehyde bisulphite (13 g.) were heated in water (100 ml.) on the steam-bath for 1 hr., then treated with charcoal, filtered, and cooled. The *sodium formaldehyde bisulphite derivative* (61%) was filtered off, washed with a little water and acetone, and dried. It decomposed at 270—290° (Found: N, 5·3. $C_{19}H_{24}O_8N_2S_2Na_2$ requires N, 5·4%).

The following amines and derivatives are not fully described elsewhere: 1 : 3-*di*-(p-*methylaminophenoxy*)*propane*, m. p. 90—91° (from ethanol) (Found: C, 71·4; H, 7·7; N, 10·0. $C_{17}H_{22}O_2N_2$ requires C, 71·3; H, 7·7; N, 9·8%) {*diacetyl derivative*, m. p. 109—111° [from light petroleum (b. p. 100—120°)] (Found: C, 67·9; H, 7·35; N, 7·5. $C_{21}H_{26}O_4N_2$ requires C, 68·1; H, 7·1; N, 7·6%)}; 1 : 3-*di*-(p-*dimethylaminophenoxy*)*propane*, m. p. 67—69° (from ethanol) (Found: N, 8·9. $C_{19}H_{26}O_2N_2$ requires N, 8·9%); 1 : 8-*di*-(p-*methylaminophenoxy*)*octane*, m. p. 87—87·5° [from light petroleum (b. p. 80—100°)] (Found: C, 74·3; H, 9·1; N, 7·6. $C_{22}H_{32}O_2N_2$ requires C, 74·1; H, 9·1; N, 7·85%) {*diacetyl derivative*, m. p. 86—88° (from light petroleum) (Found: N, 6·2. $C_{26}H_{36}O_4N_2$ requires N, 6·4%)}; 1 : 8-*di*-(p-*dimethylaminophenoxy*)*octane*, m. p. 126—127° (from chloroform–ethanol) (Found: C, 75·3; H, 9·4; N, 7·3. $C_{24}H_{36}O_2N_2$ requires C, 75·0; H, 9·5; N, 7·3%) {*bismethiodide*, m. p. 195—197° (from water) (Found: N, 4·0; I, 36·4. $C_{26}H_{42}O_2N_2I_2,2H_2O$ requires N, 4·0; I, 36·1%)}; 1 : 5-*di*-(p-*ethylmethylaminophenoxy*)*pentane dipicrate*, m. p. 165—167° (Found: N, 13·6. $C_{23}H_{34}O_2N_2,2C_6H_3O_7N_3$ requires N, 13·5%); 1 : 3-*di*-(p-*diethylaminophenoxy*)*propane*, b. p. 244—248°/0·1 mm. (Found: C, 74·5; H, 9·1; N, 7·75. $C_{23}H_{34}O_2N_2$ require C, 74·6; H, 9·3; N, 7·55%); and 1 : 5-*di*-(p-*di*-n-*propylaminophenoxy*)*pentane disulphate*, m. p. 125—127° (Found: N, 4·3; S, 10·3. $C_{29}H_{46}O_2N_2,2H_2SO_4$ requires N, 4·3; S, 9·9%).

Di-(p-*nitrophenyl*) *Glutarate*.—Glutaryl chloride (16·9 g.), dissolved in dry acetone, was slowly added to a suspension of dry potassium *p*-nitrophenoxide (36·3 g.) in dry acetone, the resulting mixture then being heated under reflux for 4 hr., concentrated, and poured into sodium hydrogen carbonate solution. The product was filtered off, washed, and dried *in vacuo*. Crystallisation from ethyl acetate gave *di*-(p-*nitrophenyl*) *glutarate* (38%), m. p. 138—140° (Found: N, 7·65. $C_{17}H_{14}O_8N_2$ requires N, 7·5%). A further 2·1 g. (6%), m. p. 130—132°, were obtained from the mother-liquors.

Di-(2-p-*nitrophenoxyethyl*) *ether* (86%) had m. p. 153° (Found: N, 8·1. $C_{16}H_{16}O_7N_2$ requires N, 8·05%).

1 : 5-*Di*-(p-*nitrophenyl*)*penta*-2 : 4-*dien*-1-*one*.—A solution of *p*-nitrocinnamaldehyde (7·08 g.) in hot ethanol (100 ml.) was slowly added to a stirred solution of *p*-nitroacetophenone (6·6 g.) in hot ethanol (100 ml.), containing a few drops of aqueous potassium hydroxide. The cooled suspension was filtered and the product was crystallised from ethyl methyl ketone and from acetone, giving 1 : 5-*di*-(p-*nitrophenyl*)*penta*-2 : 4-*dien*-1-*one* (48%), m. p. 210—212° (Found: N, 8·8. $C_{17}H_{12}O_5N_2$ requires N, 8·6%).

1 : 5-*Di*-(p-*acetamidophenyl*)-3-*acetoxypentane*.—When 1 : 5-di-(*p*-nitrophenyl)penta-1 : 4-dien-3-one [31] (2·5 g.) was reduced over Raney nickel in ethyl acetate at 100°/420 lb. per sq. in., the product did not crystallise. It was heated with acetic anhydride in pyridine at 100°, yielding 1 : 5-*di*-(p-*acetamidophenyl*)-3-*acetoxypentane* (1·75 g.), m. p. 126—128°. Recrystallisation from ethanol–ether gave needles, m. p. 128—130° (Found: C, 69·6; H, 7·1; N, 7·1; Ac, 31·8. $C_{23}H_{28}O_4N_2$ requires C, 69·7; H, 7·1; N, 7·1; Ac, 32·5%).

1-(2 : 4-*Dinitrophenyl*)-5-p-*nitrophenoxypentane*.—5-Phenylpentyl bromide (1·85 g.) was slowly added to nitric acid (*d* 1·5; 10 ml.) kept at between 0° and −10° by addition of solid carbon dioxide. The solution was set aside for 1 hr. at room temperature, then diluted with water. The oil separating was extracted into ether, which was washed with warm water and sodium hydrogen carbonate solution, dried and evaporated.

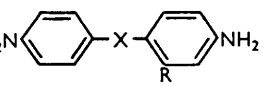
[31] Petrenko-Kritschenko, *Ber.*, 1898, **31**, 1508.

The oily bromide thus obtained and potassium *p*-nitrophenoxide (2 g.) in ethanol (10 ml.) were refluxed for 20 hr., then poured into 2N-sodium hydroxide and extracted with chloroform. The washed and dried extract was evaporated and the residue chromatographed in benzene. Recrystallisation of the product from acetone–ethanol gave the *trinitro-compound* (1·2 g., 39% overall), m. p. 78° (Found: N, 11·3. $C_{17}H_{17}O_7N_3$ requires N, 11·2%).

5-p-*Nitrophenylpentyl Bromide*.—5-Phenylpentyl bromide (22·7 g.) was added during 40 min. to stirred nitric acid (*d* 1·5; 45 ml.) at −50° to −55°. The mixture was immediately poured into 50% sodium hydroxide solution (60 ml.) and ice, and the product was extracted with ether. The washed and dried extract was evaporated and the residue was distilled in three portions. The combined distillates (17·3 g.) of b. p. 141—180°/0·07 mm. were redistilled, giving as principal fractions: (i) 5·8 g., b. p. 155—165°/0·1 mm. (Found: N, 5·3; Br, 28·2. $C_{11}H_{14}O_2NBr$ requires N, 5·15; Br, 29·4%), and (ii) 7·75 g., b. p. 165—190°/0·1 mm. (Found: N, 5·9· Br, 27·65%). The structure of the crude 5-*p*-nitrophenylpentyl bromide was proved by successive condensation with fused potassium acetate in acetic acid, hydrolysis with ethanolic sodium hydroxide, and oxidation with alkaline potassium permanganate. *p*-Nitrobenzoic acid was thus obtained (m. p. and mixed m. p. 235—238°).

1-p-*Nitrophenoxy*-5-p-*nitrophenylpentane*.—A mixture of potassium *p*-nitrophenoxide (8 g.), crude 5-*p*-nitrophenylpentyl bromide (prepared by nitration of 6·6 g. of 5-phenylpentyl bromide at −25° to −40°), and 2-ethoxyethanol (20 ml.) was refluxed for 20 hr. The product, obtained as earlier described for the trinitro-compound, was chromatographed in benzene–light petroleum. Recrystallisation of the *product* (3·7 g., 39% overall; m. p. 55—58°) from methanol gave prisms, m. p. 69—71° (Found: N, 8·7. $C_{17}H_{18}O_5N_2$ requires N, 8·5%).

Chromatography of the crude nitro-compound revealed the presence of a small amount of

TABLE 6. *Compounds* 

No.	X	R	Deriv.	Yield (%)		Solvent for recryst.
1	S·[CH$_2$]$_3$·S	H	Base	74·5 [a]	53—54°	EtOH
2			2HCl	59	255 *	Conc. HCl
3	O·[CH$_2$]$_3$·NH	H	Base	72	71	Aq. EtOH
4	NH·[CH$_2$]$_3$·NH	H	Base	62	110	EtOH–Pet [b]
5	NAc·[CH$_2$]$_3$·NAc	H	Base	96 [c]	193	Aq. EtOH
6	O·CO·[CH$_2$]$_3$·CO·O	H	Base	86	104—106	EtOAc–Et$_2$O
7	—	—	2Me·SO$_3$H	—	—	—
8	[CH$_2$]$_5$	H	Base	81 [d]	96—98	Pet [b]
9	—	—	2Me·SO$_3$H	—	212—215	EtOH–Et$_2$O
10	O·[CH$_2$]$_5$	NH$_2$	Base	62	107—110	CHCl$_3$–Et$_2$O

		Found (%)				Required (%)			
No.	Formula	C	H	N	S	C	H	N	S
1	$C_{15}H_{18}N_2S_2$	—	—	9·3	21·7	—	—	9·6	22·1
2	$C_{15}H_{18}N_2S_2$,2HCl	—	—	7·7	17·9	—	—	7·7	17·6
3	$C_{15}H_{19}ON_3$	70·0	7·7	16·2	—	70·0	7·4	16·3	—
4	$C_{15}H_{20}N_4$	70·4	8·0	21·6	—	70·3	7·8	21·9	—
5	$C_{19}H_{24}O_2N_4$	67·2	7·4	16·4	—	67·0	7·1	16·5	—
6	$C_{17}H_{18}O_4N_2$	65·2	6·0	8·8	—	65·0	5·8	8·9	—
7	$C_{17}H_{18}O_4N_2$,2CH_4O_3S	—	—	5·5	12·8	—	—	5·5	12·7
8	$C_{17}H_{22}N_2$	80·0	8·8	10·8	—	80·3	8·7	11·0	—
9	$C_{17}H_{22}N_2$,2CH_4O_3S	—	—	6·4	—	—	—	6·3	—
10	$C_{17}H_{23}ON_3$	—	—	15·0	—	—	—	14·7	—

* With decomp. [a] The dinitro-compound was reduced by the method of Waldron and Reid,[35] who describe the base as an oil. [b] Pet = light petroleum. [c] From the dinitro-compound.[18] [d] From 1 : 5-di-(*p*-nitrophenyl)penta-1 : 3-dien-5-one over Raney Ni in EtOAc.

an isomeric nitro-compound, presumably 1-p-*nitrophenoxy*-5-o-*nitrophenylpentane*. It crystallised from acetone–methanol in prisms, m. p. 81—82° (Found: N, 8·7%), depressed to 58—60° by the *p*-isomer.

Di-(p-*acetamidophenyl*) *Thiolsulphinate*.—A solution of monoperphthalic acid (3·12 g.) in ether (93 ml.) was added to a stirred solution of di-(*p*-acetamidophenyl) disulphide (4·9 g.) in acetone (300 ml.) at 0°. The solution was allowed to come to room temperature, kept for 1 hr.,

then filtered. The solid recrystallised from acetic acid, giving the *thiolsulphinate* (3·2 g.), m. p. 201° (decomp.) (Found: C, 55·15; H, 4·8; N, 8·1. $C_{16}H_{16}O_3N_2S_2$ requires C, 55·2; H, 4·6; N, 8·05%). A sample prepared by acetylation of di-(*p*-aminophenyl) thiolsulphinate had m. p. 207°.

Di-(p-*aminophenyl*) *Thiolsulphinate*.—Monoperphthalic acid (56 g.) in ether was added during 30 min. to a stirred solution of di-(*p*-aminophenyl) disulphide (76 g.) in ether (1·5 l.), the temperature being maintained below 0°. After a further 40 min., the solid was filtered off, dried in air, and stirred into saturated sodium acetate solution (1·5 l.). The solid was filtered off again and washed with water, ethanol and ether. Recrystallisation of the product (51 g.; m. p. 143—144°) was carried out by extracting it with four 300 ml. portions of pyridine at 60°; the extracts were diluted with two volumes of water at 60° and cooled, to give the *thiolsulphinate* (18·7 g., 23·5%), m. p. 153° (Found: C, 54·15; H, 4·85; N, 10·4; S, 23·6. $C_{12}H_{12}ON_2S_2$ requires C, 54·5; H, 4·55; N, 10·6; S, 24·2%).

3-p-*Aminoanilino*-1-p-*nitrophenoxypropane*.—3-*p*-Nitrophenoxypropyl bromide (10·4 g.), *p*-aminoacetanilide (5·44 g.), and potassium carbonate (5·4 g.) in acetone (100 ml.) were boiled under reflux for 24 hr. The hot mixture was filtered, then evaporated and the residue was boiled with 10% hydrochloric acid (100 ml.) for 30 min. The hot solution was treated with charcoal, filtered through Hyflo in a sintered-glass funnel, treated with an equal volume of concentrated hydrochloric acid, and cooled. The hydrochloride (5·5 g.) was filtered off and converted into the base. Crystallisation from ethanol gave 3-p-*aminoanilino*-1-p-*nitrophenoxypropane* (3·6 g., 31%), m. p. 148° (Found: C, 62·6; H, 6·05; N, 14·5. $C_{15}H_{17}O_3N_3$ requires C, 62·7; H, 5·9; N, 14·6%).

1 : 5-*Di-*(4-*nitro*-1-*naphthyloxy*)*pentane*.—1 : 5-Dibromopentane (11·5 g.) was added to a solution of 4-nitro-1-naphthol [32] (18·9 g.) and potassium hydroxide (5·6 g.) in 2-ethoxyethanol (150 ml.) and the mixture was refluxed for 4·5 hr., cooled, and filtered. Recrystallisation of the product (12·9 g., 58%; m. p. 148—152°) from aqueous dimethylformamide and from acetic acid gave yellow prisms, m. p. 155—157° (Found: N, 6·4. $C_{25}H_{22}O_6N_2$ requires N, 6·3%). Catalytic reduction yielded 1 : 5-di-(4-amino-1-naphthyloxy)pentane, isolated as the *dimethanesulphonate* (99%), m. p. 256—260° (Found: N, 4·9; S, 11·2. $C_{25}H_{26}O_2N_2,2CH_4O_3S$ requires N, 4·8; S, 11·05%).

1 : 5-*Di-*(4-*nitro*-4′-*diphenylyloxy*)*pentane*.—The potassium salt of 4-hydroxy-4′-nitrodiphenyl [33] (20·5 g.) was heated under reflux for 48 hr. with 1 : 5-dibromopentane (10 g.) in ethanol (400 ml.). The solution was poured into dilute aqueous sodium hydroxide, and the product was crystallised from acetic acid, giving 1 : 5-*di-*(4-*nitro*-4′-*diphenylyloxy*)*pentane* (13·35 g., 70%), m. p. 130—131° (Found: N, 5·6. $C_{29}H_{26}O_6N_2$ requires N, 5·6%). Catalytic reduction in ethyl acetate gave 1 : 5-*di-*(4-*amino*-4′-*diphenylyloxy*)*pentane* (85%), m. p. 169—171° (from aqueous pyridine) (Found: N, 6·35. $C_{29}H_{30}O_2N_2$ requires N, 6·3%).

Tetra-(p-*nitrophenoxymethyl*)*methane*.—A mixture of pentaerythritol bromide (7·76 g.), potassium *p*-nitrophenoxide (17·7 g.) and ethanol (40 ml.) was heated in a sealed tube at 170° for 20 hr. The combined products from four such experiments were recrystallised from dimethylformamide, giving the *product* (30·3 g., 61%), m. p. 274° (Found: N, 9·1. $C_{29}H_{24}O_{12}N_4$ requires N, 9·0%). Catalytic reduction over Raney nickel in dimethylformamide yielded *tetra-*(p-*aminophenoxymethyl*)*methane* (71%), m. p. 205—207° (from aqueous pyridine) (Found: C, 70·0; H, 6·4; N, 11·25. $C_{29}H_{32}O_4N_4$ requires C, 69·6; H, 6·4; N, 11·2%). The *tetramethanesulphonate*, recrystallised from ethanol, had m. p. 234—236° (Found: N, 6·3. $C_{29}H_{32}O_4N_4,4CH_4O_3S$ requires N, 6·3%).

The *amines* listed in Table 6 were obtained by catalytic reduction of the nitro-compounds.

The authors thank Dr. H. J. Barber, F.R.I.C., for his continued interest and helpful discussions, numerous colleagues for suggestions, Mr. S. Bance, B.Sc., A.R.I.C., for the semi-microanalyses, and the Directors of May and Baker Ltd. for permission to publish this work.

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[*Received, January* 31*st*, 1958.]

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