183. *The Chemotherapy of Schistosomiasis. Part II.* Some Ethers of* p-*Aminophenol.*

By J. N. Ashley, R. F. Collins, M. Davis, and N. E. Sirett.

Some alkyl, *cyclo*alkyl, aralkyl, alkoxyalkyl, and aryloxyalkyl ethers of *p*-aminophenol have been prepared. Many of the compounds are schistosomicides.

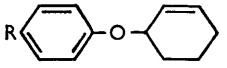
In Part I of this series * we described a series of schistosomicidal aromatic diamines of the general formula p-$NH_2 \cdot C_6H_4 \cdot O \cdot [CH_2]_{3-9} \cdot O \cdot C_6H_4 \cdot NH_2$-$p$, together with some derivatives and analogues. Subsequently it was found that activity was retained by analogues of the foregoing series which contained only one amino-group, and that many simpler ethers of *p*-aminophenol were curative against *S. mansoni* infections in mice.

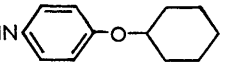
In the present paper we record the preparation of some alkyl, *cyclo*alkyl, aralkyl, alkoxyalkyl, and aryloxyalkyl ethers, together with a few other substituted alkyl ethers required in connection with work on the metabolism of these compounds. The biological results have been published elsewhere.[1] A few compounds of this type have been independently synthesised by The Wellcome Foundation Ltd.,[2] and some others have been adequately described in patent specifications [3] and have therefore been omitted from, or only mentioned briefly in, this paper.

Compounds of the general formula p-$NH_2 \cdot C_6H_4 \cdot OR$ were first studied. *n*-Alkyl and ω-phenylalkyl ethers of *p*-aminophenol were obtained from *p*-nitrophenol and the appropriate bromide according to the general method used in Part I, and the amines were obtained from these by catalytic reduction. Only those derivatives which are new or are inadequately described in the literature are reported here.

Hydrogenation of 3-*p*-nitrophenoxy*cyclo*hexene (I) over palladium–calcium carbonate gave some *p*-aminophenol together with the expected *p*-aminophenoxy*cyclo*hexane (IV). The latter amine was subsequently prepared by Bowden and Green [4] by condensation of *p*-fluoronitrobenzene with potassium *cyclo*hexyl oxide followed by reduction with iron and hydrochloric acid. When, however, the nitro-ether (I) was reduced with iron and acetic acid and the amine was dissolved in hydrochloric acid, the only product isolated was *cyclo*hex-2-enol (as the known phenylurethane). Further investigation showed that the amino-ether (II) initially formed had been hydrolysed by the hydrochloric acid. Acid-

(I): R = NO_2
(II): R = NH_2
(III): R = NHAc





(IV): R = H
(V): R = Ac

hydrolysis of allyl and *cyclo*hexyl ethers is known to be much more rapid at room temperature than that of simple alkyl ethers.[5] Combination of both structural types in the same molecule has obviously led to a compound unstable to acid, in contrast to the acid-stable, saturated ether (IV). Reduction of the nitro-compound (I) using substantially neutral conditions—iron in ethanol containing ferric chloride—yielded (II) in moderate yield. The free base appeared to be stable, but its crystalline hydrochloride decomposed on storage. Its acetyl derivative (III) on reduction over a platinum catalyst gave the saturated acetyl derivative (V), no hydrogenolysis apparently occurring.

The effect on schistosomicidal activity of varying the group R in the series p-$NH_2 \cdot C_6H_4 \cdot O \cdot [CH_2]_5 \cdot OR$ was then studied, and a few lower homologues were also prepared.

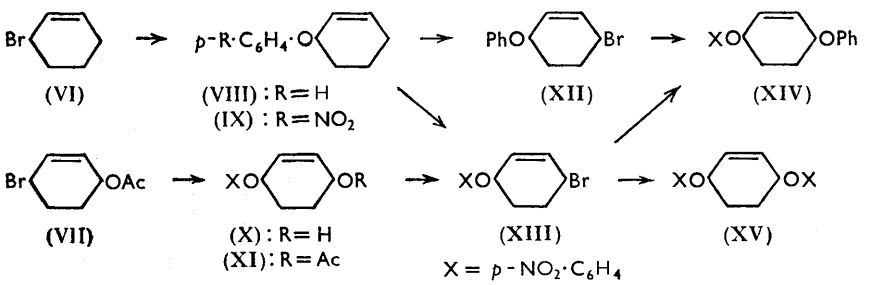
* Part I, Ashley, Collins, Davis, and Sirett, *J.*, 1958, 3298.

[1] Collins, Davis, Edge, and Hill, *Brit. J. Pharmacol.*, 1958, **13**, 238.
[2] The Wellcome Foundation Ltd., B.P. 770,411.
[3] May and Baker Ltd., B.P. 768,144, 770,870.
[4] Bowden and Green, *J.*, 1954, 1797.
[5] Tronow and Ladigina, *Ber.*, 1929, **62**, 2844.

The common intermediates for most of these amines were 3-*p*-nitrophenoxypropyl bromide and 5-*p*-nitrophenoxypentyl bromide. Reaction of these with the appropriate sodium alkoxide gave the methoxy-, ethoxy-, 2-hydroxyethoxy-, 2-methoxyethoxy-, and propoxy-derivatives, respectively. These ethers of *p*-nitrophenol were very susceptible to nucleophilic attack by methoxide ion. Thus, when 3-*p*-nitrophenoxypropyl bromide was treated with excess of sodium methoxide, the principal product was *p*-nitroanisole and some was formed, together with required ether, 1-methoxy-3-*p*-nitrophenoxypropane, even when the theoretical amount of methoxide was used. This procedure failed when applied to benzyl alcohol and it was shown that the benzyl alcohol was partially oxidised by the nitro-group to benzaldehyde, which was isolated as its 2 : 4-dinitrophenylhydrazone. The sodium salt of benzyl alcohol was therefore treated with excess of 1 : 5-dibromopentane to form 5-benzyloxypentyl bromide which was subsequently converted by *p*-nitrophenol into the required ether. The *cyclo*hexyl ether was similarly obtained. Catalytic reduction of all these nitro-compounds proceeded smoothly.

Most of the aryl and heterocyclic ethers were similarly prepared. 1-*p*-Ethoxyphenoxy-5-*p*-nitrophenoxypentane was obtained by alkylation of the available *p*-hydroxyphenoxy-derivative. Some of the *p*-acylaminophenyl ethers were conveniently obtained from 1-*p*-acetamidophenoxy-5-*p*-nitrophenoxypentane by hydrolysis to the amine and subsequent treatment with the acid chloride. The *p*-chloroacetamidophenyl ether with potassium acetate in acetic acid gave the *p*-acetoxyacetamidophenyl derivative, which was partially hydrolysed by dilute sodium hydroxide in cold acetone to the *p*-hydroxyacetamidophenyl ether. The silver salt of 2-hydroxypyridine was employed to make the 2-pyridyl ether since it is known that *N*-alkylation occurs when the sodium salt is used.

Replacement of the central alkane chain of the active diamines by a 1 : 4-linked *cyclo*hexane ring was described in Part I. Since this compound retained schistosomicidal activity, the preparation of a corresponding monoamine was undertaken and was eventually achieved by two different routes. Condensation of crude 3-bromo-6-*p*-nitrophenoxy*cyclo*hexene (XIII), prepared from 3-bromo*cyclo*hexene (VI) *via* 3-*p*-nitrophenoxy*cyclo*hexene (IX) as described in Part I, with potassium phenoxide was unsatisfactory. Since it was not possible to purify this nitro-bromide by distillation, 3-bromo-6-phenoxy*cyclo*hexene (XII) was prepared from 3-phenoxy*cyclo*hexene [6] (VIII) and *N*-bromosuccinimide. This bromide was distilled with only slight decomposition, but on condensation with potassium *p*-nitrophenoxide gave only a low yield of the required product (XIV). An alternative route was therefore examined. 3-Acetoxy-6-bromo*cyclo*hexene [7] (VII) on condensation with



potassium *p*-nitrophenoxide yielded two products, both giving analyses correct for the expected 3-acetoxy-6-*p*-nitrophenoxy*cyclo*hexene (XI), but showing depression of melting points on admixture. The hydroxy-compound (X) corresponding to each isomer was separately treated with phosphorus tribromide and then with potassium *p*-nitrophenoxide to give the same 3 : 6-di-(*p*-nitrophenoxy)*cyclo*hexene (XV) (see Part I). Epimerisation

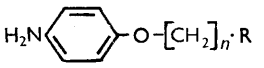
[6] Crossley, *J.*, 1904, 1403; Cornforth, Hughes, and Lions, *J. Proc. Roy. Soc. N.S. Wales*, 1938, **71**, 323.

[7] Ziegler, Spaeth, Schaaf, Schumann, and Winkelmann, *Annalen*, 1942, **551**, 80.

of one isomer probably occurred at the final stage. Condensing the 1-bromo-6-*p*-nitrophenoxy*cyclo*hexene (XIII) obtained from one of the isomeric hydroxy-compounds (X) with potassium phenoxide then gave the mononitro-diether (XIV). Reduction over palladium–calcium carbonate to the saturated amine proceeded normally.

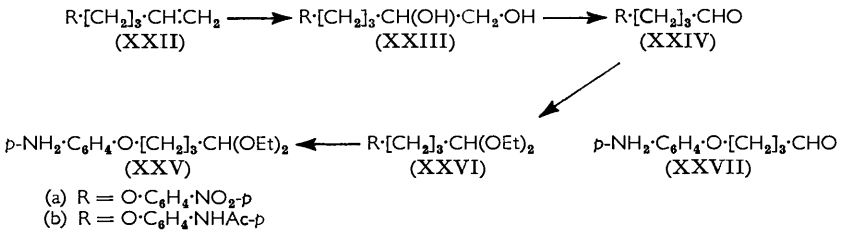
It seemed likely from the biological results [1] that the similar activity found for many different mono- and di-amines derived from *p*-aminophenol might be due to a common active metabolite. A few of the simpler compounds which could be formed by metabolic fission of the polymethylene chain were synthesised but none showed activity *in vivo*.

The primary alcohols (XVI) and (XVII) were obtained by hydrolysis of the corresponding acetates (XVIII) and (XIX), prepared by condensation of the appropriate *p*-nitrophenoxyalkyl bromide with potassium acetate and subsequent catalytic reduction. For



(XVI): $n = 3$, R = OH. (XIX): $n = 5$, R = OAc.
(XVII): $n = 5$, R = OH. (XX): $n = 4$, R = CO_2H.
(XVIII): $n = 3$, R = OAc. (XXI): $n = 5$, R = CO_2H.

the acids (XX) and (XXI), the *p*-nitrophenoxyalkyl bromides were condensed with potassium cyanide and the resulting cyano-compounds were hydrolysed with alkali and then reduced catalytically. When the period of hydrolysis was reduced from 20 to 3 hours, a mixture of the corresponding amide and acid was formed. 6-*p*-Nitrophenoxyhexanoic acid was obtained from the nitrile in higher yield by direct conversion into the methyl ester followed by hydrolysis with potassium hydrogen carbonate; formation of *p*-nitrophenol was thereby minimised. The amides were best obtained by keeping the cyanides in concentrated sulphuric acid and then pouring the solution into water. The nitro-compounds were reduced catalytically.



(a) R = O·C_6H_4·NO_2-*p*
(b) R = O·C_6H_4·NHAc-*p*

The analogous aldehyde diethyl acetal (XXV) was prepared from 5-*p*-nitrophenoxypent-1-ene (XXIIa), which was obtained from potassium *p*-nitrophenoxide and 5-toluene-*p*-sulphonyloxypent-1-ene. An attempt to make compound (XXIIa) by condensation of 5-*p*-nitrophenoxypentyl iodide with trimethylamine and pyrolysis of the corresponding quaternary hydroxide led instead to 1-dimethylamino-5-*p*-nitrophenoxypentane and *p*-nitroanisole. The latter was probably formed by nucleophilic attack of methoxide ion (from the methanol released) at the ether linkage. Refluxing 5-*p*-nitrophenoxypentyl toluene-*p*-sulphonate with pyridine yielded only the quaternary salt. The pentene (XXIIa) was oxidised to the glycol diacetate by iodine and silver acetate [8] and then hydrolysed to the glycol (XXIIIa), which was cleaved quantitatively by periodate to the aldehyde (XXIVa). The corresponding diethyl acetal (XXVIa) was reduced catalytically to the aminoacetal (XXV). Attempts to hydrolyse this acetal to free 4-*p*-aminophenoxybutyraldehyde (XXVII) gave only gums. In the hope that the amino-aldehyde (XXVII) would be more stable under acid conditions, the nitro-glycol (XXIIIa) was reduced and acetylated to give the acetamido-glycol (XXIIIb), which was cleaved with periodate to 5-*p*-acetamidophenoxybutyraldehyde (XXIVb). Acid-hydrolysis gave only an impure salt of the base (XXVII), which could not be purified.

[8] Barkley, Farrar, Knowles, Raffelson, and Thompson, *J. Amer. Chem. Soc.*, 1954, **76**, 5014.

p-*Aminophenyl ethers*, p-$NH_2 \cdot C_6H_4 \cdot O \cdot [CH_2]_n \cdot R$.

			Yield		Solvent for		Found (%)			Required (%)		
n	R	Derivative	(%)	M. p.	crystn.[g]	Formula	C	H	N	C	H	N
5	Me	Me·SO_3H	80	196—198°[a]	EtOH–Et_2O	$C_{12}H_{19}ON,CH_4O_3S$	—	—	4·8	—	—	4·8
9	Me	Acetyl	88	90—92[b]	EtOH	$C_{18}H_{29}O_2N$	—	—	4·6	—	—	4·8
3	CH:CH_2	Base	85	[c]		$C_{11}H_{15}ON$	74·0	8·4	8·35	74·5	8·5	7·9
		Me·SO_3H		202—203[d]	MeOH–Et_2O	$C_{11}H_{15}ON,CH_4O_3S$	—	—	5·15	—	—	5·1
3	CH(OH)·CH_2·OH	Base	96	114—116	EtOH	$C_{11}H_{17}O_3N$	62·35	7·4	6·6	62·6	8·1	6·6
3	$CH(OEt)_2$	Base	94	[e]		$C_{14}H_{23}O_3N$	66·4	9·2	5·5	66·4	9·1	5·5
5	CO·NH_2	Base	80	141—142	EtOH	$C_{13}H_{18}O_2N_2$	—	—	12·4	—	—	12·6
4	CO_2H	Base	67	173—174[f]	H_2O	$C_{11}H_{15}O_3N$	—	—	6·6	—	—	6·7
5	CO_2H	Base	81	138	H_2O or EtOH–Pet	$C_{12}H_{17}O_3N$	—	—	6·2	—	—	6·3
2	Ph	Base	74	59	Pet[r]	$C_{14}H_{15}ON$	—	—	6·4	—	—	6·55
		Me·SO_3H		151—152[h]	EtOH–Et_2O	$C_{14}H_{15}ON,CH_4O_3S$	—	—	4·6	—	—	4·5
3	Ph	Base	85	58—59	Et_2O–Pet	$C_{15}H_{17}ON$	—	—	6·3	—	—	6·15
5	Ph	Acetyl		106	EtOH–H_2O	$C_{19}H_{23}O_3N$	—	—	4·7	—	—	4·7
3	OAc	Base	77	52—54	Et_2O–Pet	$C_{11}H_{15}O_3N$	—	—	6·9	—	—	6·7
5	OAc	Base	95	39	Et_2O–Pet	$C_{13}H_{19}O_3N$	65·6	8·1	5·8	65·8	8·0	5·9
5	OEt	Base	91	[i]		$C_{13}H_{21}O_2N$	70·0	9·4	6·4	69·9	9·5	6·3
		Me·SO_3H		175—177[j]	EtOH–Et_2O	$C_{13}H_{21}O_2N,CH_4O_3S$	—	—	4·4	—	—	4·4
5	O·$[CH_2]$·OMe	Base	91	—	—	$C_{14}H_{23}O_3N$	66·4	9·05	5·6	66·4	9·1	5·5
		Me·SO_3H		154—156		$C_{14}H_{23}O_3N,CH_4O_3S$	—	—	4·1	—	—	4·0
5	*cyclo*Hexyloxy	Base	87	[l]		$C_{17}H_{27}O_2N$	73·4	9·65	5·05	73·7	9·75	5·05
		Me·SO_3H		145—150	EtOH–Et_2O	$C_{17}H_{27}O_2N,CH_4O_3S$	—	—	3·7	—	—	3·75
5	O·C_6H_4Me-*p*	Base	65	61	EtOH	$C_{18}H_{23}O_2N$	75·9	8·0	5·0	75·7	8·1	4·9
5	O·$C_6H_3Me_2$-1 : 3 : 5	Base	63	88—89	Et_2O	$C_{19}H_{25}O_2N$	76·0	8·3	4·7	76·2	8·4	4·7
		Me·SO_3H		[m]		$C_{19}H_{25}O_2N,CH_4O_3S$	—	—	3·8	—	—	3·9
5	O·C_6H_4Ph-*p*	Base	90	88—90	Et_2O–Pet	$C_{23}H_{25}O_2N$	—	—	4·1	—	—	3·9
		Me·SO_3H		197—199	EtOH	$C_{23}H_{25}O_2N,CH_4O_3S$	65·3	6·7	3·2	65·0	6·5	3·2
5	O·C_6H_4·OH-*p*	Base	67	108—110[n]	EtOH–H_2O	$C_{17}H_{21}O_3N$	—	—	4·9	—	—	4·9
		Me·SO_3H	90	155—157		$C_{17}H_{21}O_3N,CH_4O_3S$	—	—	3·65	—	—	3·65
5	O·C_6H_4·OMe-*o*	Base	75	55—56	Et_2O–Pet	$C_{18}H_{23}O_3N$	—	—	4·65	—	—	4·65
5	O·C_6H_4·OMe-*p*	Base	67	64—65	EtOH	$C_{18}H_{23}O_3N$	—	—	4·7	—	—	4·65
5	O·C_6H_4·OPh-*p*	Base	68	64—65	Et_2O–Pet	$C_{23}H_{25}O_3N$	—	—	3·7	—	—	3·8
		Me·SO_3H		195—198[o]	EtOH	$C_{23}H_{25}O_3N,CH_4O_3S$	63·2	6·5	3·1	63·0	6·3	3·1
5	O·C_6H_4Cl-*p*	Base	58	50[p]	Et_2O–Pet	$C_{17}H_{20}O_2NCl$	—	—	4·5	—	—	4·6
5	O·C_6H_4·CO_2Et-*p*	Base	85	74—76	EtOH	$C_{20}H_{25}O_4N$	69·8	7·6	—	70·0	7·3	—
5	O·C_6H_4·NH·CO·CH_2·OH-*p*	Base	92	137—138	EtOH	$C_{19}H_{24}O_4N_2$	66·7	7·4	8·0	66·3	7·0	8·1
5	1-$C_{10}H_7$·O	Me·SO_3H	88	167—170	EtOH	$C_{21}H_{23}O_2N,CH_4O_3S$	—	—	3·4	—	—	3·4
5	2-$C_{10}H_7$·O	Base	75	54—56	Et_2O	$C_{21}H_{23}O_2N$	—	—	4·2	—	—	4·4
5	6-Quinolyloxy	HCl	75	161—163[q]	EtOH–Et_2O	$C_{20}H_{22}O_2N_2,2HCl$	—	—	6·85	—	—	7·1
5	2-Pyridyloxy	Base	77	95—96	EtOH	$C_{16}H_{20}O_2N_2$	70·5	7·4	10·15	70·6	7·4	10·3

[a] Found: S, 11·4. Reqd.: S, 11·1%. Base described by Allen and Gates (*Org. Synth.*, Coll. Vol. III, p. 140). [b] Base described by General Aniline and Film Corp. (U.S.P. 2,629,658). [c] B. p. 94°/0·01 mm. Nitro-compound reduced with sodium sulphide. [d] Found: S, 11·9. Reqd.: S, 11·7%. [e] B. p. 130—132°/0·04 mm. [f] Hydrochloride described by Davis, Roberts, and Ross (*J.*, 1955, 893). [g] Pet = light petroleum, b. p. 40—60° (but see footnote *r*). [h] Found: S, 10·2. Reqd.: S, 10·4%. [i] B. p. 140—154°/0·04 mm. [j] Found: S, 10·4. Reqd.: S, 10·0%. [k] B. p. 150—155°/0·06 mm. [l] B. p. 170°/0·3 mm. [m] Found: S, 8·55. Reqd.: S, 8·1%. [n] Nitro-compound described in Part I. [o] Found: S, 6·9. Reqd.: S, 7·0%. [p] Found: Cl, 11·4. Reqd.: Cl, 11·6%. [q] Found: Cl, 18·5. Reqd.: Cl, 18·0%. [r] B. p. 60—80°.

Some earlier attempts to prepare an aldehyde from available intermediates were unsuccessful. Conversion of 6-*p*-nitrophenoxyhexanoyl chloride into the Reissert complex, by using liquid hydrogen cyanide and quinoline,[9] proceeded normally, but hydrolysis then resulted in recovery of the acid. α-Bromination of 6-*p*-nitrophenoxyhexanoic acid was also tried since the corresponding α-hydroxy-acid could probably be cleaved with lead tetra-acetate to an aldehyde.[10] However, treating the acid with bromine containing some phosphorus tribromide led to nuclear bromination. Oxidation of 5-*p*-nitrophenoxypentanol with the theoretical amount of chromic acid yielded the ester, 5-*p*-nitrophenoxypentyl 5-*p*-nitrophenoxypentanoate, formed by oxidation of some of the alcohol to the carboxylic acid and subsequent esterification with the starting material.[11]

Experimental

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

The following compounds were prepared by condensation of potassium *p*-nitrophenoxide with the appropriate bromide: 1-p-*nitrophenoxydecane* (67%), m. p. 57—58° (from aqueous acid) (Found: N, 4·9. $C_{16}H_{25}O_3N$ requires N, 5·0%); 1-p-*nitrophenoxy*-3-*phenylpropane* (78%), m. p. 80·5—81·5° (from ethanol) (Found: N, 5·6. $C_{15}H_{15}O_3N$ requires N, 5·5%).

The following 5-substituted 1-p-*nitrophenoxypentanes* were prepared (except where otherwise stated) by condensation of 5-*p*-nitrophenoxypentyl bromide with the appropriate phenol (using 1 equiv. of alkali) or alcohol (using 1 equiv. of sodium): *ethoxy*- (70%), b. p. 165—176°/0·2 mm. (Found: N, 5·75. $C_{13}H_{19}O_4N$ requires N, 5·55%); 2′-*methoxyethoxy*- (67%), b. p. 165—170°/0·05 mm. (Found: C, 59·65; H, 7·3; N, 5·0. $C_{14}H_{21}O_5N$ requires C, 59·4; H, 7·4; N, 4·95%); (3 : 5-*dimethylphenoxy*)- (77%), m. p. 74° (from ethanol) (Found: C, 69·2; H, 6·9; N, 4·5. $C_{19}H_{23}O_4N$ requires C, 69·3; H, 7·0; N, 4·3%); p-*phenylphenoxypentane* (66%), m. p. 97—98° (from ethanol) (Found: C, 73·3; H, 6·25; N, 3·9. $C_{23}H_{23}O_4N$ requires C, 73·2; H, 6·1; N, 3·7%); o-*methoxyphenoxy*- (35%; from 5-guaiacyloxypentyl bromide), m. p. 54—56° (from ethanol) (Found: N, 4·35. $C_{18}H_{21}O_5N$ requires N, 4·2%); p-*phenoxyphenoxy*- (48%), m. p. 86—87° (from ether) (Found: C, 70·3; H, 5·8; N, 3·7. $C_{23}H_{23}O_5N$ requires C, 70·2; H, 5·9; N, 3·6%); 1′-*naphthyloxy*- (59%), m. p. 99—100° (from benzene–light petroleum) (Found: N, 3·8. $C_{21}H_{21}O_4N$ requires N, 4·0%); 2′-*naphthyloxy*- (70%), m. p. 93—94° (from ethanol) (Found: N, 4·25. $C_{21}H_{21}O_4N$ requires N, 4·0%); and 6′-*quinolyloxy*- (45%), m. p. 115—117° (from benzene–light petroleum) (Found: N, 7·5. $C_{20}H_{20}O_4N_2$ requires N, 7·95%).

5-*Toluene*-p-*sulphonyloxypentene*.—Toluene-*p*-sulphonyl chloride (55 g.) was added during 30 min. to a stirred mixture of 1-hydroxypent-4-ene [12] (22 g.) and dry pyridine (120 ml.) below 20°. After a further 1 hr. the mixture was poured on ice and extracted with chloroform, and the washed and dried extract was distilled, yielding the *ester* (56 g., 91%), b. p. 122—126°/0·03 mm. (Found C, 59·8; H, 6·8; S, 13·8. $C_{12}H_{16}O_3S$ requires C, 60·0; H, 6·7; S, 13·3%). Condensation with potassium *p*-nitrophenoxide gave 5-p-*nitrophenoxypentene* (80%), b. p. 126°/0·04 mm. (Found: N, 7·0. $C_{11}H_{13}O_3N$ requires N, 6·8%).

5-p-*Nitrophenoxypentane*-1 : 2-*diol*.—Iodine (9·9 g.) was added during 15 min. to a stirred suspension of silver acetate (15 g.) in acetic acid (250 ml.) and water (0·7 ml.) containing 5-*p*-nitrophenoxypentene (8·1 g.). After 1 hr. at 20—25°, the mixture was heated at 90—95° for 3 hr., filtered, and concentrated to low bulk. Methanol (200 ml.) was added and the filtered solution was treated with potassium hydroxide (until just alkaline), and a solution of potassium hydrogen carbonate (8 g.) in water (40 ml.) was added. The whole was then refluxed for 3 hr., solvent was distilled off, water was added, and the mixture was extracted with chloroform. The dried extract was evaporated and the residue crystallised from ethyl acetate–light petroleum, yielding the *diol* (7·9 g., 85%), m. p. 68—69° (Found: C, 54·9; H, 6·4; N, 6·15. $C_{11}H_{15}O_5N$ requires C, 54·7; H, 6·2; N, 5·8%).

5-p-*Acetamidophenoxypentane*-1 : 2-*diol*.—A mixture of 5-*p*-aminophenoxypentane-1 : 2-diol (2·8 g.), acetic anhydride (10 g.), and pyridine (30 ml.) was heated on the steam-bath, then

[9] Grosheintz and Fischer, *J. Amer. Chem. Soc.*, 1941, **63**, 2021.
[10] Jackson, *Organic Reactions*, 1944, **2**, 345.
[11] Rodd, "Chemistry of Carbon Compounds," Elsevier, London, 1951, Vol. IA, p. 462.
[12] Gaubert, Linstead, and Rydon, *J.*, 1937, 1972.

immediately poured into water. The solid product was refluxed for 2 hr. with potassium hydrogen carbonate (3 g.) in water (15 ml.) and sufficient methanol to give a clear solution. The solvent was then distilled off, water was added, and the mixture was extracted with chloroform and with ethyl acetate. The combined extracts were dried and evaporated, and the residue was crystallised from ethyl acetate, giving the *diol* (1·9 g.), m. p. 96—98° (softens at 92°) (Found: C, 61·85; H, 7·8; N, 5·5. $C_{13}H_{19}O_4N$ requires C, 61·6; H, 7·5; N, 5·5%).

4-p-*Acetamidophenoxybutyraldehyde*.—0·05N-Sodium metaperiodate (13·2 ml.) was added rapidly to a solution of 5-*p*-acetamidophenoxypentane-1 : 2-diol (1·6 g.) in methanol (20 ml.) cooled to 0°. The solution was kept overnight at room temperature, then filtered, and the filtrate was evaporated *in vacuo*. Water was added and the product was extracted into chloroform. Evaporation of the extract and crystallisation of the residue from ethyl acetate–light petroleum (b. p. 60—80°) gave the *aldehyde* (1 g.), m. p. 87—88° (Found: C, 65·5; H, 7·2; N, 6·4. $C_{12}H_{15}O_3N$ requires C, 65·2; H, 6·8; N, 6·3%).

4-p-*Nitrophenoxybutyraldehyde* was similarly prepared (96%) and had m. p. 76—77° (Found: C, 57·6; H, 5·6; N, 6·7. $C_{10}H_{11}O_4N$ requires C, 57·5; H, 5·3; N, 6·7%). A mixture of the aldehyde (9·7 g.), redistilled ethyl orthoformate (6·9 g., 7·8 ml.), concentrated hydrochloric acid (0·04 ml.), and dry ethanol (50 ml.) was kept at room temperature for 24 hr., refluxed for 10 min., made just alkaline with ethanolic potassium hydroxide, and concentrated. The residue was extracted with ether, and the washed and dried extract was distilled, yielding the *diethyl acetal* (12·8 g.), b. p. 142—145°/0·03 mm. (Found: C, 59·3; H, 7·4; N, 4·9. $C_{14}H_{21}O_5N$ requires C, 59·4; H, 7·4; N, 4·95%).

3·p-*Nitrophenoxypropyl Cyanide*.—3-*p*-Nitrophenoxypropyl bromide (5·2 g.) was added to a solution of potassium cyanide (1·43 g., 1·1 mol.) in water (5 ml.) and ethanol (50 ml.), and the mixture was boiled for 4 hr., then evaporated. The residue was treated with water and extracted with ether. The extract was washed, dried, and evaporated, the residue was triturated with light petroleum and filtered, and the product was crystallised from ether, yielding the *cyanide* (46%), m. p. 50—52° (Found: N, 13·2. $C_{10}H_{10}O_3N_2$ requires N, 13·6%).

4-p-*Nitrophenoxybutyl cyanide*, similarly obtained, and purified by chromatography in benzene–light petroleum over alumina and recrystallisation from ether, had m. p. 35—36° (Found: N, 12·7. $C_{11}H_{12}O_3N_2$ requires N, 12·7%).

5-p-*Nitrophenoxypentyl cyanide* was similarly prepared, but was distilled, and the fraction, b. p. 200—210°/0·02 mm. (34·6 g., 74%), was recrystallised from ether, giving the cyanide, m. p. 38—39° (Found: N, 12·1. $C_{12}H_{14}O_3N_2$ requires N, 12·0%).

5-p-*Nitrophenoxypentanoic Acid*.—Crude 4-*p*-nitrophenoxybutyl cyanide (prepared from 54·8 g. of bromide) was hydrolysed by refluxing 2N-sodium hydroxide (150 ml.) and ethanol (150 ml.) overnight. The product recrystallised from aqueous methanol and from benzene, giving 5-p-*nitrophenoxypentanoic acid* (25·7 g., 54%) in needles, m. p. 98—100° (Found: N, 6·2. $C_{11}H_{13}O_5N$ requires N, 5·9%).

4-p-*Nitrophenoxybutane*-1-*carboxyamide*.—From an experiment similar to the above, but with refluxing for only 3 hr., there were obtained 19·65 g. (41%) of the foregoing acid together with 7·8 g. (16%) of the intermediate *amide*, m. p. 108—112°. Recrystallisation of the latter from benzene gave sparingly soluble prisms, m. p. 117—118° (Found: N, 11·6. $C_{11}H_{14}O_4N_2$ requires N, 11·8%).

6-p-*Nitrophenoxyhexanoic Acid*.—(*a*) Crude 5-*p*-nitrophenoxypentyl cyanide (from 28·8 g. of bromide) was hydrolysed as described for the lower homologue. Crystallisation of the product from benzene gave 6-*p-nitrophenoxyhexanoic acid* (9·65 g. 38%) in prisms, m. p. 101—103° (Found: N, 5·8. $C_{12}H_{15}O_5N$ requires N, 5·5%). (*b*) Dry hydrogen chloride was passed for 2 hr. into a refluxing mixture of 5-*p*-nitrophenoxypentyl cyanide (40 g.), methanol (200 ml.). and water (3·1 g.). Solvent was removed, water was added to the residue, and the solid was filtered off and recrystallised from ethanol, yielding the *methyl ester* (30 g., 66%), m. p. 85—86° (Found: C, 58·0; H, 6·4; N, 5·3. $C_{13}H_{17}O_5N$ requires C, 58·4; H, 6·4; N, 5·2%). Hydrolysis with potassium hydrogen carbonate in boiling aqueous methanol yielded the acid (65%), m. p. 104—105°, together with some unhydrolysed ester (28%). The acid chloride, prepared by using thionyl chloride, was converted directly into the N-*methylanilide*, m. p. 89—90° (from light petroleum, b. p. 100—120°) (Found: C, 66·5; H, 6·25; N, 8·4. $C_{19}H_{22}O_4N_2$ requires C, 66·6; H, 6·4; N, 8·2%).

5-p-*Nitrophenoxypentane*-1-*carboxyamide*.—A mixture of 5-*p*-nitrophenoxypentyl cyanide (29·3 g.) and concentrated sulphuric acid (10 ml.) was kept at room temperature for 24 hr.,

then treated with ice and 2N-sodium hydroxide. The product was filtered off, washed, dried and crystallised from benzene and from chloroform–light petroleum, giving 5-p-*nitrophenoxypentane*-1-*carboxyamide* (17·0 g., 54%), in needles, m. p. 127—129° (Found: N, 11·2. $C_{12}H_{16}O_4N_2$ requires N, 11·1%).

3-p-*Nitrophenoxypropyl Acetate*.—3-*p*-Nitrophenoxypropyl bromide (52 g.) and potassium acetate (52 g.) in acetic acid (100 ml.) were heated under reflux for 1·5 hr., and the mixture then poured into water. The solid was crystallised from ethanol, giving the *acetate* (42·1 g., 88%), m. p. 63—65° (Found: N, 6·0. $C_{11}H_{13}O_5N$ requires N, 5·9%).

5-p-*Nitrophenoxypentyl acetate* was similarly prepared (92%) and had m. p. 72° (Found: C, 58·5; H, 5·9; N, 5·4. $C_{13}H_{17}O_5N$ requires C, 58·5; H, 6·4; N, 5·2%).

5-p-*Nitrophenoxypentan*-1-*ol*.—5-*p*-Nitrophenoxypentyl acetate (20 g.) was stirred and heated with 2N-hydrochloric acid (150 ml.) at 100° for 24 hr. The product was extracted into ether, the extract was dried and evaporated, and the residue was triturated with methanol; the insoluble portion was unchanged ester (3 g.; m. p. 65—68°). The solution was evaporated and the residue repeatedly extracted with light petroleum (b. p. 60—80°). Evaporation of the extract gave 5-p-*nitrophenoxypentan*-1-*ol* (11 g., 77%), m. p. 33—35° (Found: C, 58·9; H, 6·9; N, 6·1. $C_{11}H_{15}O_4N$ requires C, 58·7; H, 6·7; N, 6·2%).

5-p-*Nitrophenoxypentyl* 5-p-*Nitrophenoxypentanoate*.—A solution of chromium trioxide (3·1 g.) in 80% acetic acid (24 ml.) was added during 1 hr. to a solution of 5-*p*-nitrophenoxypentan-1-ol (10·3 g.) in acetic acid (50 ml.). After a further 2 hr. the acetic acid was distilled off and the residue was treated with water and extracted with chloroform. The washed and dried extract was evaporated and the residue was crystallised from ethanol, giving the *ester* (2·3 g.), m. p. 84—86°, raised by recrystallisation from acetic acid to 92—93° (Found: C, 59·2; H, 5·6; N, 6·4%; *M*, 480. $C_{22}H_{26}O_8N_2$ requires C, 59·2; H, 5·8; N, 6·3%; *M*, 446).

1-*Dimethylamino*-5-p-*nitrophenoxypentane*.—A mixture of 5-*p*-nitrophenoxypentyl bromide (14·4 g.) and 25% w/w ethanolic dimethylamine (48 ml., 4 mol.) was heated for 24 hr. at 100° in a sealed tube. The solution was concentrated, basified, and extracted with chloroform. The extract was washed, dried, and distilled, giving 1-*dimethylamino*-5-p-*nitrophenoxypentane* (6·1 g., 49%), b. p. 150—155°/0·01 mm. (with partial decomp.), m. p. 34—35° (Found: N, 10·95. $C_{13}H_{20}O_3N_2$ requires N, 11·1%). The *picrate* had m. p. 125—127° (Found: N, 14·6. $C_{13}H_{20}O_3N_2,C_6H_3O_7N_3$ requires N, 14·6%).

5-p-*Nitrophenoxypentyl iodide* was prepared from the corresponding bromide with sodium iodide in acetone in 89% yield (Found: I, 37·9. $C_{11}H_{14}O_3NI$ requires I, 37·9%).

Trimethyl-5-p-*nitrophenoxypentylammonium Iodide*.—A mixture of the foregoing iodide (52·5 g.) and 33% ethanolic trimethylamine (200 ml.) was refluxed for 1 hr., cooled, and diluted with ether, giving the quaternary *salt* (54 g.), m. p. 134—135° (Found: N, 6·7; I, 32·2. $C_{14}H_{23}O_3N_2I$ requires N, 7·1; I, 32·2%).

Pyrolysis of Trimethyl-5-p-*nitrophenoxypentylammonium Hydroxide*.—The foregoing salt (52 g.) in water (250 ml.) was shaken with freshly precipitated silver oxide (from 32 g. of silver nitrate) for 2 hr. The mixture was filtered and the filtrate was evaporated. The residue was pyrolysed and distilled at 110—140°/0·1 mm. The distillate was dissolved in ether, extracted with 2N-hydrochloric acid, washed, dried, and evaporated. The residue (13·5 g., 49·5%) was *p*-nitroanisole (Found: C, 55·25; H, 5·1; N, 9·2. Calc. for $C_7H_7O_3N$: C, 55·0; H, 4·6; N, 9·15%), identified by comparison with an authentic specimen. The acid extract was basified and extracted with ether. Distillation of the extract gave 1-dimethylamino-5-*p*-nitrophenoxypentane (5 g.), b. p. 155°/0·01 mm. The picrate had m. p. 123—126°, not depressed by an authentic specimen.

1-p-*Nitrophenoxy*-5-*toluene*-p-*sulphonyloxypentane*.—5-*p*-Nitrophenoxypentanol (prepared from 10 g. of the acetate) was treated with toluene-*p*-sulphonyl chloride (10 g.) in pyridine (30 ml.) at 0°, yielding the *ester* (7·2 g., 51%), m. p. 62—63° (Found: C, 57·15; H, 5·7; N, 3·7. $C_{18}H_{21}O_6NS$ requires C, 57·0; H, 5·55; N, 3·7%). When refluxed for 6 hr. with pyridine, this ester gave the quaternary *pyridinium toluene*-p-*sulphonate* m. p. 137—138° (Found: N, 6·0. $C_{23}H_{26}O_6N_2S$ requires N, 6·1%).

3-p-*Aminophenoxypropan*-1-*ol*.—1-Acetoxy-3-*p*-aminophenoxypropane (14·6 g.) was dissolved in 2N-hydrochloric acid (100 ml.), and the solution was kept for 2 days, then basified with 50% aqueous sodium hydroxide. 3-p-*Aminophenoxypropan*-1-*ol* (10·5 g., 90%), after recrystallisation from chloroform, had m. p. 90—92° (Found: N, 8·3. $C_9H_{13}O_2N$ requires N, 8·4%). The *methanesulphonate* had m. p. 169—171° (Found: N, 5·4. $C_9H_{13}O_2N,CH_4O_3S$ requires N, 5·3%).

5-p-*Aminophenoxypentan*-1-*ol* was similarly prepared (92%) and had m. p. 93° (Found: C, 67·7; H, 8·9; N, 7·2. $C_{11}H_{17}O_2N$ requires C, 67·7; H, 8·7; N, 7·2%).

5-p-*Acetamidophenoxypentan*-1-*ol*.—(*a*) A mixture of 1-*p*-acetamidophenoxy-5-acetoxypentane (6·7 g.), potassium hydrogen carbonate (6·7 g.), methanol (150 ml.), and water (20 ml.) was refluxed for 2 hr., concentrated, and diluted with water. The product was extracted into chloroform, the extract was dried and concentrated, and the residue was recrystallised from toluene, giving the *alcohol* (4·5 g.), m. p. 113—115° (Found: C, 66·0; H, 8·2; N, 5·9. $C_{13}H_{19}O_3N$ requires C, 65·8; H, 8·0; N, 5·9%). (*b*) The same compound, m. p. 113—115°, was obtained from 5-*p*-aminophenoxypentan-1-ol by treatment with an excess of acetic anhydride in aqueous sodium hydrogen carbonate.

3-p-*Aminophenoxy*cyclo*hexene*.—A mixture of 3-*p*-nitrophenoxy*cyclo*hexene (see Part I) (8 g.), reduced iron powder (8 g.), and anhydrous ferric chloride (2 g.) in ethanol (200 ml.) and water (2 ml.) was stirred and refluxed overnight, then cooled and filtered through "Celite." The filtrate was evaporated *in vacuo*, the residue was dissolved in ether, and the solution was rapidly washed with N-sodium hydroxide and extracted 7 times with 2N-acetic acid. The acid extracts were basified with sodium carbonate, the product was extracted into ether, and the extract was washed, dried, and evaporated. Distillation of the residue afforded 3-p-*amino*-*phenoxy*cyclo*hexene* (3·4 g., 49%), b. p. 120—122°/0·3 mm. (Found: C, 76·0; H, 8·2; N, 7·4. $C_{12}H_{15}ON$ requires C, 76·2; H, 7·9; N, 7·4%). The *acetyl derivative* had m. p. 127° (Found: C, 72·7; H, 7·2; N, 6·1. $C_{14}H_{17}O_2N$ requires C, 72·7; H, 7·35; N, 6·1%).

p-*Aminophenoxy*cyclo*hexane*.—3-*p*-Nitrophenoxy*cyclo*hexene (30 g.) in methanol (500 ml.) was reduced over 1% palladium–calcium carbonate (10 g.). The filtered solution was evaporated *in vacuo* and the residue was dissolved in ether and filtered from *p*-aminophenol (3·4 g.). The ethereal solution was washed with 2N-sodium hydroxide and water and extracted with 2N-hydrochloric acid. The acid extract was made alkaline, the base was taken up in ether, and the ether solution was dried and evaporated. Distillation of the residue gave p-*aminophenoxy*cyclo-*hexane* (16 g., 62%), b. p. 101—102°/0·05 mm. (Found: C, 75·1; H, 9·1; N, 7·15. $C_{12}H_{17}ON$ requires C, 75·4; H, 8·9; N, 7·3%). The base formed a *methanesulphonate* (Found: N, 5·05; S, 11·5. $C_{12}H_{17}ON,CH_4O_3S$ requires N, 4·9; S, 11·15%).

The acetyl derivative, m. p. 154—155° (lit.,[3] 155°), was identical with a specimen, m. p. 154°, obtained by catalytic reduction of 3-*p*-acetamidophenoxy*cyclo*hexene over platinum oxide in ethanol.

3-*Acetoxy*-6-p-*nitrophenoxy*cyclo*hexene*.—A mixture of 3-acetoxy-6-bromo*cyclo*hexene [7] (12·2 g.) and potassium *p*-nitrophenoxide (15 g.) in dry acetone (100 ml.) was refluxed for 18 hr. and filtered hot, and the filtrate was concentrated and treated with ether. The ethereal solution was washed with dilute alkali and water, dried, and evaporated, and the residue was triturated thrice with warm light petroleum. The insoluble residue was combined with some solid which separated gradually from the light petroleum washings, and crystallised twice from methanol, giving the *isomer* A (2·15 g.) in prismatic needles, m. p. 117—118° (Found: C, 60·9; H, 5·7; N, 5·4. $C_{14}H_{15}O_5N$ requires C, 60·7; H, 5·4; N, 5·1%). Evaporation of the light petroleum and methanol solutions gave a low-melting solid (2·2 g.) which was dissolved in benzene–light petroleum (b. p. 80—100°) and chromatographed over alumina. Recrystallisation of the product from methanol gave the pure *isomer* B, m. p. 65° (Found: C, 60·8; H, 5·4; N, 5·4%).

4-p-*Nitrophenoxy*cyclo*hex*-2-*enol*.—(*a*) The preceding acetoxy-compound A (0·5 g.) was refluxed with potassium hydrogen carbonate (0·6 g.) in water (5 ml.) and methanol (30 ml.) for 1·5 hr. After distillation of the methanol, the residue was treated with water, and the product filtered off and recrystallised from ethanol, giving 4-p-*nitrophenoxy*cyclo*hex*-2-*enol*, *isomer* A (0·4 g.), m. p. 89—90° (Found: C, 61·0; H, 5·4; N, 6·1. $C_{12}H_{13}O_4N$ requires C, 61·3; H, 5·5; N, 6·0%). (*b*) Similar hydrolysis of the acetate isomer B (6·65 g.) yielded 4-p-*nitrophenoxy*-cyclo*hex*-2-*enol*, *isomer* B (5·35 g.; m. p. 65—70°) which on recrystallisation from methanol gave first some 3 : 6-di-(*p*-nitrophenoxy)*cyclo*hexene (0·15 g.; m. p. 165—166°; present as impurity in the B-acetate). Dilution of the mother-liquors with water gave the *hydroxy-compound*, *isomer* B (4·8 g.) which after recrystallisation from ether–light petroleum had m. p. 87—88° (Found: C, 61·2; H, 5·5; N, 6·0%), depressed to 70—76° on admixture with isomer A.

3-*Bromo*-6-p-*nitrophenoxy*cyclo*hexene*.—(*a*) Phosphorus tribromide (1 g.) in dry benzene (5 ml.) was slowly added to a stirred suspension of the hydroxy-compound A (2 g.) in dry benzene (20 ml.) at 10—20°. The mixture was stirred overnight, then poured on ice. The product was extracted into ether, and the extract was washed, dried, and evaporated. The oily product

was condensed with potassium *p*-nitrophenoxide and yielded 3 : 6-di-(*p*-nitrophenoxy)*cyclo*hexene, m. p. 171°, identical with a specimen previously prepared (see Part I). (*b*) The bromo-compound B was similarly prepared from the hydroxy-compound B. On reaction with potassium *p*-nitrophenoxide it afforded the same product, m. p. 164—166°, mixed m. p. 169—170°.

3-*Bromo*-6-*phenoxy*cyclo*hexene*.—A mixture of 3-phenoxy*cyclo*hexene [6] (42 g.), *N*-bromosuccinimide (43 g.), and dry benzoyl peroxide (0·1 g.) in dry carbon tetrachloride (300 ml.) was refluxed for 1 hr., cooled, filtered, concentrated, and distilled. The fraction (20 g.) of b. p. 90—110°/0·3 mm. was redistilled, giving 3-*bromo*-6-*phenoxy*cyclo*hexene* (6·2 g.), b. p. 100°/0·3 mm. (Found: C, 56·1; H, 5·2; Br, 32·4. $C_{12}H_{13}OBr$ requires C, 56·95; H, 5·1; Br, 31·6%).

3-p-*Nitrophenoxy*-6-*phenoxy*cyclo*hexene*.—(*a*) A mixture of 3-bromo-6-*p*-nitrophenoxy*cyclo*hexene (prepared from 33·2 g. of hydroxy-compound, isomer A) and potassium phenoxide (33·1 g.) in dry acetone (500 ml.) was refluxed for 6 hr., then concentrated, and the residue was treated with water. The product was filtered off and recrystallised from acetic acid, giving 3-p-*nitrophenoxy*-6-*phenoxy*cyclo*hexene* (25·2 g., 57% from hydroxy-compound), m. p. 125—126°. (*b*) A similar condensation between 3-*bromo*-6-*phenoxy*cyclo*hexene* (6·2 g.) and potassium *p*-nitrophenoxide (6·2 g.) gave the same product (0·25 g.), m. p. 126° (Found: C, 69·6; H, 5·7; N, 5·0. $C_{18}H_{17}O_4N$ requires C, 69·45; H, 5·5; N, 4·5%).

Catalytic reduction over 1% palladium–calcium carbonate in methanol yielded 1-p-*amino*-*phenoxy*-4-*phenoxy*cyclo*hexane* (72%), m. p. 118—119° (from methanol) (Found: C, 76·6; H, 7·4; N, 5·1. $C_{18}H_{21}O_2N$ requires C, 76·4; H, 7·4; N, 5·0%).

1-*Methoxy*-3-p-*nitrophenoxypropane*.—3-*p*-Nitrophenoxypropyl bromide (26 g.) was added to a solution of sodium (2·3 g.) in methanol (100 ml.), and the solution was refluxed overnight, concentrated, diluted with water, and extracted with ether. The washed and dried ether solution was distilled. Some *p*-nitroanisole distilled first, followed by crude 1-methoxy-3-*p*-nitrophenoxypropane (14·75 g., 70%), b. p. 120—140°/0·3 mm. Redistillation gave the pure *nitro-compound*, b. p. 127—130°/0·1 mm., m. p. 35—36° (Found: N, 6·7. $C_{10}H_{13}O_4N$ requires N, 6·6%). When a similar experiment was carried out using 4·6 g. (2 equiv.) of sodium, the principal product, which separated crystalline on pouring of the solution into water, was *p*-nitroanisole (8·3 g., 54%), m. p. and mixed m. p. 52—53° (Found: C, 55·3; H, 4·7; N, 9·0. Calc. for $C_7H_7O_3N$: C, 55·0; H, 4·6; N, 9·15%).

1-p-*Aminomethylphenoxy*-5-p-*aminophenoxypentane*.—1-*p*-Cyanophenoxy-5-*p*-nitrophenoxypentane (35·7 g.) was reduced catalytically in two stages, (*a*) over 2% of platinum oxide in ethanol and (*b*) over 10% of Raney nickel in ethanolic ammonia at 100°/500 lb. per sq. in. The filtered solution was evaporated, and the residue in ethanol (400 ml.) treated with methanesulphonic acid (20 g.), cooled, and filtered. The *dimethanesulphonate* (52%) crystallised from ethanol in plates, m. p. 208—210° (Found: N, 5·6; S, 13·1. $C_{19}H_{24}O_2N_2,2CH_4O_3S$ requires N, 5·7; S, 13·0%). The base partially decomposed on attempted distillation.

The second stage of the reduction was also effected less satisfactorily with lithium aluminium hydride.

5-cyclo*Hexyloxypentyl Bromide*.—*cyclo*Hexanol (64 g.) was added slowly (40 min.) to a stirred, refluxing suspension of powdered sodamide (25 g.) in dry toluene (500 ml.). After a further 1·5 hr. when evolution of ammonia had ceased, the mixture was cooled, 1 : 5-dibromopentane (300 g.) was added, and the suspension was slowly reheated until a vigorous exothermic reaction occurred. When this had moderated (15 min.), heating and stirring were continued for 20 hr. The filtered solution was then washed with water, dried, and distilled. The fraction (90 g.) of b. p. 130—145°/12 mm. was redistilled, giving the *bromide* (58·4 g., 37%), b. p. 135—140°/12 mm. (Found: Br, 30·95. $C_{11}H_{21}OBr$ requires Br, 32·1%).

1-p-*Aminophenoxy*-5-p-*carboxyphenoxypentane*.—A solution of 1-*p*-aminophenoxy-5-*p*-ethoxycarbonylphenoxypentane (2 g.) in water (20 ml.) and concentrated hydrochloric acid (20 ml.) was boiled for 2·25 hr., then cooled and filtered. The *hydrochloride* (2·0 g., 98%) was recrystallised from very dilute hydrochloric acid, and had m. p. 215—220° (decomp.) (Found: C, 61·5; H, 6·65; N, 4·0; Cl, 10·0. $C_{18}H_{21}O_4N$,HCl requires C, 61·4; H, 6·25; H, 4·0; Cl, 10·1%).

1-p-*Chloroacetamidophenoxy*-5-p-*nitrophenoxypentane*.—Chloroacetyl chloride (58 ml.) was added in one portion to a rapidly stirred solution of 1-*p*-aminophenoxy-5-*p*-nitrophenoxypentane (58 g.) in water (700 ml.) and methanesulphonic acid (18·5 ml.), cooled in ice. After

orbitals at B are then denoted by $B_{p+1/2}$. The proper combinations are as follows, defined with the aid of a ring quantum number l:

$$\left.\begin{aligned}\phi_A{}^l &= n^{-1/2}\sum_p \exp(2\pi i l p/n)\,.\,A_p \\ \phi_B{}^l &= n^{-1/2}\sum_p \exp\{(2\pi i l)(p+1/2)/n\}\,.\,B_{p+1/2}\end{aligned}\right\} \quad . \quad . \quad . \quad . \quad . \quad (1)$$

These combinations have the symmetry properties listed in Table 1.

As usual, molecular orbitals are found by combining functions (1) of the same l to give stationary values of the energy. If the orbitals at A and B are identical $p\pi$-orbitals our problem is that of the monocyclic aromatic hydrocarbons, and the energies and molecular orbitals may be found from the roots of the secular equation:

$$\begin{vmatrix}\alpha-\varepsilon & 2\beta\cos(\pi l/n) \\ 2\beta\cos(\pi l/n) & \alpha-\varepsilon\end{vmatrix} = 0 \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where α and β have the meanings usual in simple molecular-orbital calculations, namely, coulomb and resonance integrals, respectively. The roots $\varepsilon_l = \alpha \pm 2\beta\cos(\pi l/n)$ are the well-known hydrocarbon molecular-orbital energies which can of course be found directly by using the higher symmetry appropriate to a molecule in which A and B are identical. If the orbitals are both of $p\pi$-type, but one is more electronegative than the other by an amount which may be expressed as ρ times the resonance integral β (as in 1 : 3 : 5-triazine, where A is carbon and B nitrogen), the secular equation is derived from (2) by putting $\alpha + \rho\beta - \varepsilon$ for the diagonal entry referring to the more electronegative atom. We find that, for all values of ρ, equation (2) leads to orbital energies which are least for $l = 0$, β being a negative quantity. The situation is no different if one of the orbit types is d_{yz} because according to the Table a d_{yz} orbital in the site group has the same symmetry behaviour as $p\pi$, and the secular equation is of the form of (2) with appropriate allowance for the different electronegativities.

Where A and B provide π-orbitals of different site symmetries, one d_{xz} and the other $p\pi$, we may take B to be the $p\pi$ centre and again write for the coulomb integral $\alpha_B = \alpha_A + \rho\beta$, allowing the parameter ρ to vary according to the different electronegativities of the orbitals. The Table shows that the orbitals $l = 0$ belong to different species and cannot interact. Accordingly the energies ε_0 must be α_A and $\alpha_A + \rho\beta$. For other values of l the secular equation must be solved:

$$\begin{vmatrix}\alpha_A-\varepsilon & 2i\beta\sin(\pi l/n) \\ -2i\beta\sin(\pi l/n) & \alpha_A+\rho\beta-\varepsilon\end{vmatrix} = 0 \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

The appearance of the sine in the off-diagonal element of (3) leads to important differences from the normal aromatic secular equation (2). First, the most stable orbital is that for $l = n/2$ or $(n-1)/2$ for n even or odd instead of $l = 0$; and, secondly, the energies of the molecular orbitals are either different from the normal aromatic case (odd n) or the same in magnitude but inverted with respect to their associated l values (even n). Typical energy level schemes are illustrated in Fig. 2.

Proceeding conventionally we may exhibit the features of the systems in a convenient way by assigning electrons to the orbitals and calculating the total energy and from it the delocalization energy per electron. We consider six- and eight-membered rings for $p\pi$–$p\pi$ and $p\pi$–d_{xz} systems and allow the electronegativity difference between atoms A and B to vary between zero and 2β. The results are shown in Fig. 3.

There are three types of behaviour. The centre curve applies to eight-membered ring systems of both aromatic types. The top curve, recording larger values of delocalization energy per electron, applies to $p\pi$–$p\pi$ six-membered rings and the lower curve, with smaller delocalization energy values, to $p\pi$–$d\pi$ six-membered rings. When A and B are equally