783. *The Chemotherapy of Schistosomiasis. Part III.** N-p-*Aminophenoxyalkyl-amides, -imides, and -sulphonamides.*

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Many acyl- and diacyl-aminoalkyl ethers of *p*-aminophenol have been prepared by a number of routes. Some of these compounds are effective schistosomicides.

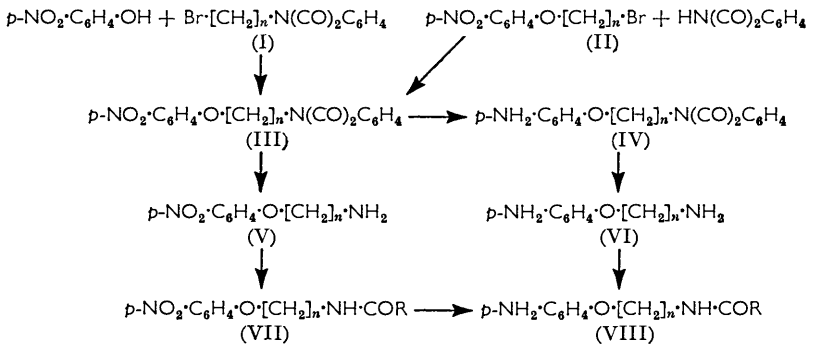
After the discovery (see Part II *) that many simple ethers of *p*-aminophenol were curative against *S. mansoni* infections in mice, some basic alkyl ethers were examined. These were ineffective, but an intermediate in their preparation, 1-*p*-aminophenoxy-5-phthalimidopentane (IV; $n = 5$), showed high activity. This unexpected result led us to prepare a large number of related amides, imides, and sulphonamides, some of which are now reported. Many others have been briefly described in patent specifications [1] and are therefore omitted from this paper. The biological results will be published elsewhere.[2]

* Part II, Ashley, Collins, Davis, and Sirett, *J.*, 1959, 897.

[1] May and Baker Ltd., B.P. 769,706; 778,919; 808,952.

[2] Collins, Davis, Edge, and Turnbull, *J. Pharm. Pharmacol.*, 1959, in the press.

The homologous series of 1-*p*-nitrophenoxy-ω-phthalimidoalkanes (III) was prepared (as far as the decane) by condensing the appropriate ω-phthalimidoalkyl bromide (I) with potassium *p*-nitrophenoxide. Catalytic reduction over Raney nickel afforded the amines (IV) in high yield. All the amines in this series formed bright yellow crystals giving almost colourless, dilute solutions in organic solvents, from which they were precipitated initially in a colourless amorphous form which became yellow as crystallisation set in. Reduction of the nitro-group of the ether (III) over platinum oxide under pressure invariably resulted in some reduction of the phthalimide ring. In one case, when the reduction was allowed to proceed to completion, the hexahydro-derivative (IXc) was isolated in good yield. The phthalimide base (IV; $n = 5$) with tin and hydrochloric acid gave the phthalimidine (Xc).



An alternative method used for the preparation of the phthalimide (III; $n = 5$) and for the analogous camphorimide, phthalylhydrazide, 2-pyridone, thiazolidine-2,4-dione, 2,3-dihydro-3-oxobenzisothiazole, butane-1,4-sultam, and naphthalene-1,8-sultam derivatives was the reaction of 5-*p*-nitrophenoxypentyl bromide (II) or iodide with the appropriate cyclic amide or imide. In the case of 2,3-dihydro-3-oxobenzisothiazole (XI; R = H), condensation of the sodium salt with 5-*p*-nitrophenoxypentyl bromide in 2-ethoxyethanol gave the *N*-alkylated derivative (XIa), the structure of which was confirmed by oxidation with hydrogen peroxide to the known saccharin compound (XIIa).[1] However, when the condensation was effected by using potassium carbonate in acetone, the product was an isomer of (XIIa), probably the *O*-ether (XIIIa). Both *N*- and *O*-alkyl-2,3-dihydro-3-oxobenzisothiazoles are known.[3] Since chemical reduction of the nitro-group also appeared to rupture the heterocyclic ring,[4] the acetamido-derivative (XIb) was made from 5-*p*-acetamidophenoxypentyl bromide and was hydrolysed with acid to the required amine (XIc).

In a third route employed for the 3-nitrophthalimide, tetrachlorophthalimide, and homophthalimide analogues of (III; $n = 5$), the phthalimide was hydrolysed with hydrazine to 1-amino-5-*p*-nitrophenoxypentane (V; $n = 5$) which was fused with the appropriate cyclic anhydride. 5-Amino-1-*p*-nitrophenoxypentane served also as an intermediate for the preparation of a large number of aliphatic, aromatic, and heterocyclic amides (VII; $n = 5$) and sulphonamides, most of which were made by standard acylation procedures.[1] The maleamic acid (VII; $n = 5$; R = CH:CH·CO_2H) obtained from nitro-amine (V; $n = 5$) and maleic anhydride was cyclised to the maleimide by acetic anhydride and sodium acetate,[5] and the nitro-group was reduced with stannous chloride. The maleimide ring of the base obtained was very sensitive to alkali, readily opening to give the maleamic acid (VIII: $n = 5$; R = CH:CH·CO_2H). The analogous glutaramic acid (XVa; R′ = H), similarly prepared, was best cyclised to the imide (XVIa) by acetyl chloride.[6] When

[3] Reissert and Manns, *Ber.*, 1928, **61**, 1308.
[4] McClelland and Gait, *J.*, 1926, 923; McKibben and McClelland, *J.*, 1923, 172.
[5] Du Pont, U.S.P. 2,444,536.
[6] Henbest and Owen, *J.*, 1955, 2968.

TABLE 1. *Nitro-amides*, p-R·C_6H_4·O·$[CH_2]_n$·NHR'.

			Yield				Found (%)				Required (%)			
n	R	R'	(%)	M. p.	Recryst. from	Formula	C	H	N		C	H	N	
4	NO_2	Bz	82	102—103°	Aq.AcOH	$C_{17}H_{16}O_4N_2$	65·5	6·0	9·2		64·9	5·7	8·9	
5	NO_2	p-Br·C_6H_4·CO	81	153—154	EtOH	$C_{18}H_{19}O_4N_2Br$			6·7	19·1 [a]			6·9	19·6 [a]
5	NO_2	p-Me·C_6H_4·CO	73 [b]	132—133	AcOH	$C_{19}H_{22}O_4N_2$	66·65	6·5	8·0		66·7	6·5	8·2	
5	NO_2	p-NO_2·C_6H_4·CO	49 [b]	148—150	$COMe_2$	$C_{18}H_{19}O_6N_3$			11·4				11·25	
5	NO_2	p-AcO·C_6H_4·CO	54	131—133	$COMe_2$	$C_{20}H_{22}O_6N_2$	62·0	5·9	7·1		62·1	5·7	7·25	
5	NO_2	p-HO·C_6H_4·CO	91 [c]	147—150	PhMe	$C_{18}H_{20}O_5N_2$	62·5	5·7	8·4		62·8	5·8	8·15	
5	NO_2	o-CO_2Me·C_6H_4·CO	61	140—141	C_6H_6	$C_{20}H_{22}O_6N_2$	62·2	5·3	7·2		62·1	5·7	7·25	
5	NO_2	p-CO_2Me·C_6H_4·CO	56	164—166	EtOH	$C_{20}H_{22}O_6N_2$	62·0	5·95	7·45		62·1	5·7	7·25	
5	NO_2	p-Me·SO_2·C_6H_4·CO	22 [d]	169—171	AcOH	$C_{19}H_{22}O_6N_2S$	56·3	5·8	6·6		56·2	5·4	6·9	
5	NO_2	Hexahydrobenzoyl	87	123	AcOH	$C_{18}H_{26}O_4N_2$	64·4	7·9	8·3		64·6	7·8	8·6	
5	NO_2	Et·CO	69	79—80	Aq. EtOH	$C_{14}H_{20}O_4N_2$			10·05				10·0	
5	NO_2	n-C_5H_{11}·CO	60	59—60	Et_2O	$C_{17}H_{26}O_4N_2$	63·4	8·3	8·8		63·4	8·1	8·7	
5	NO_2	Ph_2CH·CO	53	104—106	Aq. $COMe_2$	$C_{25}H_{26}O_4N_2$	71·4	6·1	6·9		71·7	6·3	6·7	
5	NO_2	Ph·$[CH_2]_4$·CO	82	87—89	Aq. EtOH	$C_{22}H_{26}O_4N_2$			7·3				7·3	
5	NO_2	2,4-$Cl_2C_6H_3$·O·CH_2·CO	37	112—114	EtOH	$C_{19}H_{20}O_5N_2Cl_2$			6·5	16·3 [e]			6·55	16·6 [e]
5	NO_2	$C_6H_4(CO)_2N$·CH_2·CO	68	183·5—185	EtO·$[CH_2]_2$·OH	$C_{21}H_{21}O_6N_3$			9·95				10·2	
5	AcNH	p-NO_2·C_6H_4·CO		214—217·5	EtOH or EtO·$[CH_2]_2$·OH	$C_{20}H_{23}O_5N_3$	62·3	5·6	10·9		62·3	6·0	10·9	
8	NO_2	Ph·SO_2	71	73—75	EtOH	$C_{20}H_{26}O_5N_2S$			6·8	8·25 [f]			6·9	7·9 [f]
5	NO_2	p-Me·C_6H_4·SO_2	93	154—156	Aq. EtOH	$C_{18}H_{22}O_5N_2S$			7·8				7·4	
5	NO_2	p-NHAc·C_6H_4·SO_2	77	129—131	Aq. EtOH	$C_{19}H_{23}O_6N_3S$			9·7	7·9 [f]			10·0	7·6 [f]

[a] Br. [b] Overall from the phthalimide. [c] Prepared by alkaline hydrolysis of the acetoxy-derivative. [d] Overall from carboxylic acid. [e] Cl. [f] S.

TABLE 2. *Compounds*, p-NH_2·C_6H_4·O·$[CH_2]_n$·R.

			Yield				Found (%)				Required (%)			
n	R	Derivative	(%)	M. p.	Recryst. from	Formula	C	H	N	S	C	H	N	S
2	Phthalimido	Base	59	159—160°	EtOH	$C_{16}H_{14}O_3N_2$			9·6				9·9	
		Me·SO_3H		198—199		$C_{16}H_{14}O_3N_2,CH_4O_3S$			7·2				7·4	
3	Phthalimido	Base	94	67—68 or 92—93 [a]	$CHCl_3$–Et_2O	$C_{17}H_{16}O_3N_2$	69·1	5·75	9·4		68·9	5·4	9·4	
		Me·SO_3H		163—165	EtOH–Et_2O	$C_{17}H_{16}O_3N_2,CH_4O_3S$			7·1				7·1	
4	Phthalimido	Base	59	124—125	EtOH	$C_{18}C_{18}O_3N_2$	69·2	5·7	8·9		69·6	5·8	9·0	
10	Phthalimido	Base	70	98	EtOH	$C_{24}H_{30}O_3N_2$	73·1	7·8	7·1		73·1	7·6	7·1	
5	Tetrachlorophthalimido	Base	55	180—182	2-Ethoxyethanol	$C_{19}H_{16}O_3N_2Cl_4$			6·1 [d]				6·05	
5	3-Nitrophthalimido	Base	30 [b]	117—118	EtOH	$C_{19}H_{19}O_5N_3$			10·95				11·35	
		Me·SO_3H		183—185	EtOH–Et_2O	$C_{19}H_{19}O_5N_3,CH_4O_3S$			8·8	7·05			9·0	6·9
5	3-Aminophthalimido	Base	87	105—107	EtOH	$C_{19}H_{21}O_3N_3$	66·85	6·6	12·2		67·25	6·2	12·4	
5	Homophthalimido	Me·SO_3H	85	187—189	MeOH	$C_{20}H_{22}O_3N_2,CH_4O_3S$	58·4	6·2	6·55		58·0	6·0	6·45	
5	3,4-Dihydro-2,4-dioxo-5,6-benz-1,3-oxazin-3-yl	Base	95	136—138	EtOH	$C_{19}H_{20}O_4N_2$	67·25	6·25	8·1		67·0	5·9	8·2	
5	Camphorimido	0·5H_2SO_4	54	183—185	EtOH–Et_2O	$C_{21}H_{30}O_3N_2,0{\cdot}5H_2SO_4$			7·1	4·0			6·9	3·9
5	1,2,3,4-Tetrahydro-1,4-dioxo-phthalazin-2-yl	Base	43	169—171	EtOH	$C_{19}H_{21}O_3N_3$	67·15	6·4	12·25		67·25	6·2	12·4	

TABLE 2. (*Continued.*)

			Yield				Found (%)				Required (%)			
n	R	Derivative	(%)	M. p.	Recryst. from	Formula	C	H	N	S	C	H	N	S
5	Glutarimido	Base	93	109	EtOH	$C_{16}H_{22}O_3N_2$	65·85	7·75	9·8		66·2	7·6	9·2	
5	β-Ethyl-β-methylglutarimido	Base	57 [c]	99—100	C_6H_6	$C_{19}H_{28}O_3N_2$	68·7	8·25	8·4		68·6	8·4	8·4	
5	Hexahydro-2,4,6-trioxopyrimidin-1-yl	Base	78	211—214 (efferv.)	NMe_2·CHO–EtOH	$C_{15}H_{19}O_4N_3$	59·05	6·3	13·7		59·0	6·2	13·8	
4	α-Phthalimidobenzyl	Base	73	112—113	EtOH	$C_{25}H_{24}O_3N_2$	75·0	6·1	7·0		75·0	6·0	7·0	
4	α-Benzamidobenzyl	Me·SO_3H	63	177—179	EtOH–Et_2O	$C_{24}H_{26}O_2N_2,CH_4O_3S$			5·8	7·2			6·0	6·8
5	NH·CHO	Base	89	74—76	C_6H_6	$C_{12}H_{18}O_2N_2$	65·1	8·3	12·4		64·9	8·1	12·6	
5	NH·COEt	Base	70	77·5—79	C_6H_6	$C_{14}H_{32}O_2N_2$	67·1	11·1	8·8		67·2	11·2	8·8	
		CHPh:		122·5—123·5		$C_{21}H_{26}O_2N_2$			8·3				8·3	
5	NH·CO·C_5H_{11}-n	Base	74	86—87	EtOH–Et_2O	$C_{17}H_{25}O_2N_2$	69·8	10·0	9·8		69·8	9·6	9·6	
5	NH·CO·$[CH_2]_4$·Ph	Base	87	92	$CHCl_3$–Pet [e]	$C_{22}H_{30}O_2N_2$			7·95				7·9	
5	NH·CO·CO_2Et	Base	85	78—80	$CHCl_3$–Pet	$C_{15}H_{22}O_4N_2$	61·25	7·25	9·7		61·2	7·5	9·5	
		Me·SO_3H		142—143	EtOH–Et_2O	$C_{15}H_{22}O_4N_2,CH_4O_3S$			7·2	8·3			7·2	8·2
5	NH·CO·$CHPh_2$	Base	80	101—102·5	EtOH–Pet	$C_{25}H_{28}O_2N_2$	76·8	7·1	7·3		77·25	7·3	7·2	
5	NH·CO·CH_2·$C_6H_3Cl_2$-1,2,4	Base	84	104·5—106·5	EtOH	$C_{19}H_{22}O_3N_2Cl_2$			7·1				7·05	
5	NH·CO·CH_2·$N(CO)_2$·C_6H_4-*o*	Base	98	156·5—158·5	EtOH	$C_{21}H_{23}O_4N_3$			11·1				11·1	
5	NH·CO·CH_2·NH·COPh	Base	81	119—121	EtOH	$C_{20}H_{25}O_3N_3$	67·6	7·4	11·7		67·6	7·1	11·8	
5	Pantothenamido	Base	86	[g]		$C_{20}H_{33}O_5N_3,0{\cdot}5C_2H_5$·OH	60·6	9·0	10·1		60·2	8·7	10·0	
5	Hexahydrobenzamido	Base	85	103—104	C_6H_6	$C_{18}H_{28}O_2N_2$	71·4	9·3	9·2		71·0	9·2	9·2	
5	$N(COPh)_2$	Base	87	92—93	EtOH	$C_{25}H_{26}O_3N_2$	74·6	6·4	6·75		74·6	6·6	6·95	
4	NH·COPh	Base	80	108	EtOH	$C_{17}H_{20}O_2N_2$	72·0	7·25	9·6		71·9	7·05	9·85	
5	NH·CO·C_6H_4Me-*p*	Base	84	123—124	$CHCl_3$–Pet	$C_{19}H_{24}O_2N_2$	73·35	7·7	8·85		73·1	7·75	8·95	
5	NH·CO·C_6H_4Br-*p*	Base	47	118—120	EtOH	$C_{18}H_{21}O_2N_2Br$	57·4	5·6	7·6		57·3	5·6	7·4	
		CHPh:		154—155	EtOH	$C_{25}H_{25}O_2N_2Br$			5·95				5·9	
5	NH·CO·C_6H_4·OH-*p*	Base	67	192·5—194	EtOH	$C_{18}H_{22}O_3N_2$	68·4	7·1	8·6		68·8	7·0	8·9	
5	NH·CO·C_6H_4·OH-*o*	Base	80	122—123	Aq. MeOH	$C_{18}H_{22}O_3N_2$	68·7	7·2	8·7		68·8	7·0	8·9	
5	NH·CO·C_6H_4·CO_2Me-*p*	Base	77	141—143	PhMe	$C_{20}H_{24}O_4N_2$	67·8	6·7	8·0		67·5	6·75	7·9	
5	NH·CO·C_6H_4·CO_2H-*p*	Base	93 [h]	242—244 [i]	Aq. H·CO·NMe_2	$C_{19}H_{22}O_4N_2$	67·1	6·95	8·6		66·7	6·4	8·2	
5	NH·CO·C_6H_4·SO_2Me-*p*	Base	77	144—145	EtOH	$C_{19}H_{24}O_4N_2S$	60·35	6·45	7·2		60·6	6·4	7·4	
5	NH·CO·C_6H_4·NO_2-*p*	Base	75 [b]	139—141	EtOAc	$C_{18}H_{21}O_4N_3$	63·1	6·1	12·2		63·0	6·1	12·25	
5	NH·CO·C_6H_4·NHAc-*p*	Base	89	173·5—174·5	EtOH	$C_{20}H_{25}O_3N_3$	67·5	6·9	11·9		67·6	7·1	11·8	
5	NH·CO·C_6H_4·NH_2-*p*	Base	80	121—123	EtOH	$C_{18}H_{23}O_2N_3$			13·4				13·2	
		2Me·SO_3H		272—274 [f]	EtOH–Et_2O	$C_{18}H_{23}O_2N_3,2CH_4O_3S$			8·3				8·3	
5	NPh·COMe	Base	62 [j]	66—68	Et_2O–Pet	$C_{19}H_{24}O_2N_2$	72·9	7·4	8·9		73·1	7·7	9·0	
5	*N*-Cyclohexylbenzamido	Base	80	72—75	Et_2O–Pet	$C_{24}H_{32}O_2N_2$			7·2				7·4	
5	N(O·CH_2Ph)·COPh	Base	96	77—78	Aq. EtOH	$C_{25}H_{28}O_3N_2$	74·05	6·8	6·9		74·3	6·9	6·9	
5	N(OH)·COPh	Base	78 [k]	105—107	EtOH	$C_{18}H_{22}O_3N_2$	69·0	6·9	8·7		68·8	7·0	8·9	
5	N(COPh)·$[CH_2]_5$·O·C_6H_4·NH_2-*p*	2Me·SO_3H	82	137—139	EtOH–Et_2O	$C_{29}H_{37}O_3N_3,2CH_4O_3S$			6·3	10·35			6·3	9·6
5	1,2-Dihydro-2-oxopyridyl	Base	96 [l]	114—115	EtOH	$C_{16}H_{20}O_2N_2$	70·3	7·5	10·2		70·6	7·35	10·3	
5	2-Oxopiperidino	Base	56 [m]	97—98	H_2O	$C_{16}H_{24}O_2N_2$	69·7	9·0	10·0		69·5	8·7	10·0	
5	2,3-Dihydro-3-oxobenzisothiazol-2-yl	Base	78 [n]	117—119	C_6H_6	$C_{18}H_{20}O_2N_2S$			8·5	10·1			8·5	9·8
5	2-Phthalimidoethoxy	Base	94	104—106	EtOH	$C_{21}H_{24}O_4N_2$	68·4	6·7	7·6		68·5	6·5	7·6	

TABLE 2. (*Continued.*)

n	R	Derivative	Yield (%)	M. p.	Recryst. from	Formula	Found (%) C	H	N	S	Required (%) C	H	N	S
2	4-Phthalimidobut-1-enyl	Base [o]		101—103	Aq. EtOH	$C_{20}H_{20}O_3N_2$	71·55	6·1	8·5		71·45	5·95	8·3	
5	NH·CO·NH [r]	Base	72	160—162	EtOH	$C_{23}H_{34}O_3N_4$	66·25	8·15	13·4		66·6	8·3	13·5	
5	NH·CO·CO·NH [r]	Base	79	150—152	2-Ethoxyethanol	$C_{24}H_{34}O_4N_2$	65·2	7·8	12·6		65·1	7·7	12·7	
5	*p*-NH·CO·C_6H_4·CO·NH [r]	Base	53	176—178	Xylene	$C_{30}H_{38}O_4N_4$	69·7	7·4	10·4		69·5	7·3	10·8	
5	NH·CO·[CH_2]$_3$·CO·NH [r]	Base	94	133—135 and 140—141	EtOH	$C_{27}H_{40}O_4N_4$	66·75	8·0	11·4		66·9	8·3	11·6	
		Me·SO_3H		227—230	EtOH	$C_{27}H_{40}O_4N_4$,2CH_4O_3S			8·2	9·6			8·3	9·45
8	NH·SO_2Ph	Base	79	121—122	EtOH	$C_{20}H_{28}O_3N_2S$			7·4	8·9			7·45	8·5
5	NH·SO_2·C_6H_4Me-*p*	Base	67	168—169	EtOH	$C_{18}H_{24}O_3N_2S$,H_2O [p]			7·5	9·0			7·6	8·75
5	NH·SO_2·C_6H_4·NHAc-*p*	Base	79	117—119	Aq. MeOH	$C_{19}H_{25}O_4N_3S$			10·3				10·7	
		H_2SO_4		198—201		2$C_{19}H_{25}O_4N_3S$,H_2SO_4			9·25	11·3			9·5	10·95
5	NH·SO_2·C_6H_4·NH_2-*p*	Base	64 [q]	125—128	Aq. EtOH	$C_{17}H_{23}O_3N_3S$			11·6	9·1			12·0	9·2
		2Me·SO_3H		235—237		$C_{17}H_{23}O_3N_3S$,2CH_4O_3S			7·7	18·15			7·75	17·8
5	NPh·SO_2Me	Base	81	67—68	MeOH	$C_{18}H_{24}O_3N_2S$			7·9	9·1			8·0	9·2
5	NMe·SO_2Me	Base	81	76—77	EtOH–Et_2O	$C_{13}H_{22}O_3N_2S$			9·6	11·3			9·8	11·1
5	Tetrahydro-1,1-dioxo-1,2-thiazin-2-yl	Base	60	73	Et_2O	$C_{15}H_{24}O_3N_2S$	57·5	7·5	8·8		57·7	7·9	9·0	
5	1,1-Dioxonaphtho[1,8a,8-*cd*]-isothiazol-2-yl	Base	92	106—107	EtOH	$C_{21}H_{22}O_3N_2S$			7·3	8·35			7·3	8·4

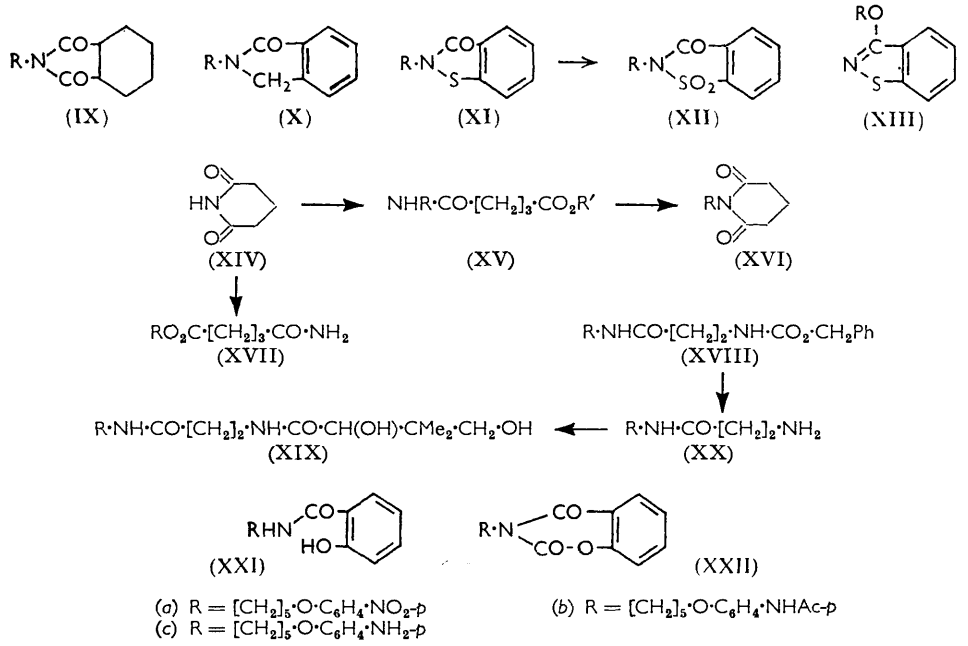
[a] Lit.,[19] m. p. 92—94°. [b] By acid hydrolysis of the *N*-acetyl derivative. [c] Overall from 1-amino-5-*p*-nitrophenoxypentane. [d] Found: Cl, 30·2. Required, Cl, 30·7%. [e] Pet = light petroleum. [f] Found: Cl, 17·7. Required, Cl, 17·9%. [g] Not obtained crystalline. Found: OEt, 5·8. Required OEt, 5·4%. [h] By alkaline hydrolysis of the corresponding methyl ester. [i] With decomp. [j] Overall from 1-anilino-5-*p*-nitrophenoxypentane. B. p. 215—220°/0·01 mm. [k] From 1-(*N*-benzyloxybenzamido)-5-*p*-nitrophenoxypentane. [l] By use of sodium sulphide. [m] From the preceding amine, or directly from 1-*p*-nitrophenoxy-5-(1,2-dihydro-2-oxopyridyl)pentane. [n] From the *N*-acetyl derivative, by refluxing for 48 hr. with N-hydrochloric acid (1 equiv.) in ethanol. [o] Methanesulphonate described in ref. 1. [p] Found: H_2O, 4·2. Required H_2O, 4·9%. [q] From the preceding acetyl derivative by hydrolysis with 2N-aqueous sodium hydroxide at 100°. [r] Bis-compound.

TABLE 3. *Miscellaneous compounds*, R·C_6H_4·O·[CH_2]$_5$·R'.

R	R'	M. p.	Recryst. from	Formula	Found (%) C	H	N	Required (%) C	H	N
p-NH·CHO	NHBz	163—164°	EtOH	$C_{19}H_{22}O_3N_2$			8·4			8·6
p-NHAc	NHBz	165—167	EtOH	$C_{20}H_{24}O_3N_2$			8·2			8·2
p-NHAc	NHAc	155—157	H_2O	$C_{15}H_{22}O_3N_2$	64·8	8·0	10·0	64·7	7·9	10·0
p-CO_2H·[CH_2]$_2$·CO·NH	$C_6H_4(CO)_2N$	185—187	AcOH	$C_{23}H_{24}O_6N_2$	65·3	6·0	6·6	65·1	5·7	6·6
p-NH_4O_2C·[CH_2]$_2$·CO·NH	$C_6H_4(CO)_2N$	174—176		$C_{23}H_{24}O_6N_2$,NH_3,+1·5H_2O	59·0	6·3	8·9	59·0	6·45	9·0
p-(5-Nitrofurfurylidene)amino	$C_6H_4(CO)_2N$	138—139	$CHCl_3$–EtOH	$C_{24}H_{21}O_6N_3$	64·6	5·0	9·4	64·6	4·7	9·4
p-Ph·CH=N	NHBz	133—134	EtOH	$C_{25}H_{26}O_2N_2$			7·3			7·25
p-MeN(NO)	$C_6H_4(CO)_2N$	104—105	EtOH	$C_{20}H_{21}O_4N_3$	65·65	5·9	11·2	65·4	5·8	11·4
o-NO_2	$C_6H_4(CO)_2N$	99·5	EtOH	$C_{19}H_{18}O_5N_2$			7·5			7·9
o-NH_2	$C_6H_4(CO)_2N$	94—95	EtOH	$C_{19}H_{20}O_3N_2$	70·4	6·2	8·6	70·4	6·2	8·6
m-NHAc	$C_6H_4(CO)_2N$	127·5—129	EtOH	$C_{21}H_{22}O_4N_2$			7·7			7·65
m-NH_2	$C_6H_4(CO)_2N$	102—103	EtOH	$C_{19}H_{20}O_3N_2$	70·35	6·2	8·7	70·4	6·2	8·6

preparation of this imide (XVIa) was attempted directly from 5-*p*-nitrophenoxypentyl bromide and glutarimide (XIV), the product was either the ethyl ester (XVa; R′ = Et) (when sodium ethoxide in ethanol was used for the condensation) or the 5-*p*-nitrophenoxypentyl ester (XVIIa) (when sodium hydroxide in aqueous ethanol was used).

Direct reaction of the amine (V; $n = 5$) with *p*-acetamidobenzoic acid to give the amide (VII; $n = 5$, R = *p*-C_6H_4·NHAc) was effected by using toluene-*p*-sulphonyl chloride in pyridine [7] or tetraethyl pyrophosphite in diethyl phosphite.[8] The latter method proved useful also in the synthesis of the pantothenamide (XIXc), providing the amide



(XVIIIa) from the starting nitro-amine (V; $n = 5$) and benzyloxycarbonyl-β-alanine in high yield. Removal of the protecting group with hydrogen bromide–acetic acid [9] and treatment of the β-alanylamide (XXa) with DL-pantolactone gave the nitro-pantothenamide (XIXa), which was reduced catalytically to the non-crystalline base (XIXc).

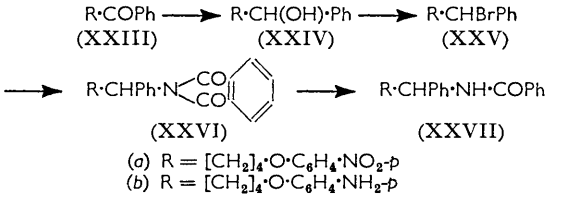
Attempts to reduce only the nitro-group of the cyanoacetamide (VII; $n = 5$; R = CH_2·CN) failed, but the amine (VIII; $n = 5$; R = CH_2·CN) was formed in high yield by preferential reaction of ethyl cyanoacetate with the aliphatic amino-group of 1-amino-5-*p*-aminophenoxypentane (VI; $n = 5$). Other reactive esters such as methyl dichloroacetate and trichloroacetate behaved similarly. Special methods employed for individual compounds included the reaction of the nitro-amine (V; $n = 5$) with 2-phenyloxazolone to form the hippuramide (VII; $n = 5$; R = CH_2·NH·COPh), and successively with methyl salicylate and with ethyl chloroformate to give first the salicylylamide (XXIa) and then the 3,4-dihydro-2,4-dioxo-5,6-benz-1,3-oxazine (XXIIa). Catalytic reduction then gave the required amines (XXIc) and (XXIIc).

Since both the 5-phenylpentyl ether [1] and the 5-phthalimidopentyl ether of *p*-aminophenol were active schistosomicides, the preparation of the 5-phenyl-5-phthalimidopentyl ether (XXVIb) was undertaken. 4-Benzoylbutyl bromide [10] was converted into the *p*-nitrophenyl ether (XXIIIa) which was reduced by the Meerwein–Ponndorf method to

[7] Brewster and Ciotti, *J. Amer. Chem. Soc.*, 1955, **77**, 6214.
[8] Anderson, Blodinger, and Welcher, *ibid.*, 1952, **74**, 5309.
[9] Ben-Ishai, *J. Org. Chem.*, 1954, **19**, 62.
[10] Perkin, *J.*, 1887, 731.

the alcohol (XXIVa). The bromide (XXVa), formed by means of phosphorus tribromide, was treated with potassium phthalimide, yielding the nitro-imide (XXVIa) which was reduced catalytically to the base (XXVIb). Treating the phthalimide (XXVIa) with hydrazine gave the free nitro-amine which was successively benzoylated and reduced to the analogous 5-benzamido-5-phenyl ether (XXVIIb).

Condensation of *p*-*N*-methylacetamidophenol with 5-phthalimidopentyl bromide and subsequent hydrolysis of the acetyl group led to the *N*-methyl derivative of the amino-imide (IV; $n = 5$). This compound was remarkable for its scarlet colour in the solid



(*a*) R = $[CH_2]_4$·O·C_6H_4·NO_2-*p*
(*b*) R = $[CH_2]_4$·O·C_6H_4·NH_2-*p*

state, although its dilute solutions were colourless. The corresponding *NN*-dimethyl derivative was only pale yellow. The colour of the primary amines of this series had already been noted by Belotsvetov,[11] who recorded the orange-yellow colour of both 1-*p*-aminophenoxy- and 1-*p*-dimethylaminophenoxy-3-phthalimidopropane. *N*-Acetyl-1-*p*-methylaminophenoxy-5-phthalimidopentane with hydrazine gave the 5-amino-derivative which was benzoylated and hydrolysed to 5-benzamido-1-*p*-methylaminophenoxypentane: use of the *N*-formyl compound was less satisfactory. An attempt to prepare this amine by partial benzoylation of 5-amino-1-*p*-methylaminophenoxypentane was unsuccessful, giving a mixture of dibenzoyl derivative and unchanged amine.

Several miscellaneous secondary and tertiary amines of a similar type are described in the Experimental section.

Experimental

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

Nitro- and acylamido-compounds.

1-p-*Nitrophenoxy*-2-*phthalimidoethane* was prepared (22%) from potassium *p*-nitrophenoxide and 2-phthalimidoethyl bromide by the method already described.[1] After crystallisation from acetic acid, it had m. p. 152—154° (Found: N, 9·2. $C_{16}H_{12}O_5N_2$ requires N, 9·0%). Similarly prepared in either ethanol or 2-ethoxyethanol were: 1-p-*nitrophenoxy*-3-*phthalimidopropane* (44%), m. p. 189—191·5° (from dioxan) (Found: N, 8·75. $C_{17}H_{14}O_5N_2$ requires N, 8·6%); 1-p-*nitrophenoxy*-4-*phthalimidobutane* (64%), m. p. 119° (from acetic acid) (Found: C, 63·8; H, 4·7; N, 8·5. $C_{18}H_{16}O_5N_2$ requires C, 63·5; H, 4·7; N, 8·2%); 1-p-*nitrophenoxy*-10-*phthalimidodecane* (60%), m. p. 102—103° (from acetic acid) (Found: C, 67·8; H, 7·0; N, 6·6. $C_{24}H_{28}O_5N_2$ requires C, 67·8; H, 6·6; N, 6·6%); and 1-p-*nitrophenoxy*-6-*phthalimidohex*-3-*ene* (55%) (from 6-phthalimido-1-toluene-*p*-sulphonyloxyhex-3-ene; B. P. 769,706), m. p. 118—119° (from aqueous acetic acid) (Found: C, 65·7; H, 5·2; N, 7·5. $C_{20}H_{18}O_5N_2$ requires C, 65·6; H, 4·9; N, 7·65%).

1-*Amino*-5-p-*nitrophenoxypentane*.—1-*p*-Nitrophenoxy-5-phthalimidopentane was treated with aqueous hydrazine in ethanol as already described,[1] but the amine was more conveniently liberated by shaking the resulting complex with chloroform and warm 2N-sodium hydroxide. The *amine* had b. p. 160—165°/0·02 mm. (partial decomp.) (Found: N, 12·9. $C_{11}H_{16}O_3N_2$ requires N, 12·5%). Similarly prepared were: 1-*amino*-5-p-*aminophenoxypentane* (94%), m. p. 67—69° [from light petroleum (b. p. 100—120°)] (Found: N, 14·1. $C_{11}H_{18}ON_2$ requires N, 14·4%) [*dimethanesulphonate*, m. p. 244—246° (from ethanol) (Found: N, 7·4; S, 16·8. $C_{11}H_{18}ON_2,2CH_4O_3S$ requires N, 7·25; S, 16·6%)]; and 1-p-*acetamidophenoxy*-5-*aminopentane* (91%), m. p. 137—139° (from benzene) (Found: C, 65·7; H, 8·45; N, 11·9. $C_{13}H_{20}O_2N_2$ requires C, 66·1; H, 8·5; N, 11·85%) [*methanesulphonate*, m. p. 155—157° (from ethanol) (Found: N, 8·4. $C_{13}H_{20}O_2N_2,CH_4O_3S$ requires N, 8·4%)].

[11] Belotsvetov, *J. Gen. Chem. U.S.S.R.*, 1944, **14**, 226.

1-p-*Nitrophenoxy*-5-*tetrachlorophthalimidopentane*.—A mixture of 5-amino-1-*p*-nitrophenoxypentane (22·4 g.) and tetrachlorophthalic anhydride (28·6 g.) was heated at 180—190° for 2 hr., cooled somewhat, and dissolved in hot 2-ethoxyethanol (150 ml.). The cooled solution deposited the *tetrachlorophthalimide* (96%), m. p. 165—167° (Found: N, 5·7; Cl, 28·5. $C_{19}H_{14}O_5N_2Cl_4$ requires N, 5·7; Cl, 28·8%). Similarly prepared were: 1-p-*nitrophenoxy*-5-3′-*nitrophthalimidopentane* (84%), m. p. 163—164·5° (from 2-ethoxyethanol) (Found: N, 10·45. $C_{19}H_{17}O_7N_3$ requires N, 10·5%); 1-p-*acetamidophenoxy*-5-3′-*nitrophthalimidopentane* (67%), m. p. 132—134° (from ethanol) (Found: N, 10·2. $C_{21}H_{21}O_6N_3$ requires N, 10·3%); and 1-*homophthalimido*-5-p-*nitrophenoxypentane* (65%), m. p. 144—145° (from acetone) (Found: C, 65·2; H, 5·6; N, 7·5. $C_{20}H_{20}O_5N_2$ requires C, 65·2; H, 5·4; N, 7·6%).

1-(5-p-*Nitrophenoxypentyl*)*barbituric Acid*.—A mixture of 1-*p*-nitrophenoxy-5-ureidopentane [1] (61 g.), malonic acid (24 g.), and acetic acid (55 ml.) was heated to 70—80° and treated dropwise with acetic anhydride (45 ml.). After a further 8 hr. at 90°, the mixture was cooled, diluted with water (84 ml.), and filtered from some solid [m. p. 178·5—180° (from acetone), which was possibly an acetyl derivative (Found: C, 54·0; H, 5·3; N, 11·1. Calc. for $C_{17}H_{19}O_7N_3$: C, 54·1; H, 5·0; N, 11·1%)]. Further dilution with water (240 ml.) gave the substituted *barbituric acid*, m. p. 149—151° (from ethanol) (Found: C, 53·85; H, 5·1; N, 12·5. $C_{15}H_{17}O_6N_3$ requires C, 53·7; H, 5·1; N, 12·5%).

1-p-*Nitrophenoxy*-5-*salicylylamidopentane*.—A mixture of 5-amino-1-*p*-nitrophenoxypentane (45 g.) and methyl salicylate (15·2 g.) was heated at 120° for 5 hr., cooled, and dissolved in chloroform. The solution was washed with 2N-hydrochloric acid and water, dried, and evaporated. The residue was crystallised from benzene, yielding the *amide* (73%), m. p. 123—125° (Found: N, 8·2. $C_{18}H_{20}O_5N_2$ requires N, 8·15%).

3,4-*Dihydro*-3-(5-p-*nitrophenoxypentyl*)-2,4-*dioxo*-5,6-*benz*-1,2-*oxazine*.—Ethyl chloroformate (12 g.) was slowly added to a cooled solution of the foregoing nitro-compound (35 g.) in dry pyridine (120 ml.). The mixture was heated at 100° for 2 hr., cooled, and diluted with water, and the product was crystallised from acetic acid and from ethanol, giving the *benzoxazinedione* (86%), m. p. 145—146° (Found: C, 61·8; H, 5·1; N, 7·5. $C_{19}H_{18}O_6N_2$ requires C, 61·6; H, 4·9; N, 7·6%).

1-*Camphorimido*-5-p-*nitrophenoxypentane*.—A mixture of 5-*p*-nitrophenoxypentyl bromide (16·15 g.), (±)-camphorimide (10·15 g.), 10·4N-potassium hydroxide (5·4 ml.), and 2-ethoxyethanol (25 ml.) was refluxed for 2 hr., cooled, and diluted with water. The solid was recrystallised from aqueous ethanol, giving the *camphorimide* (71%), m. p. 66—67° (Found: C, 64·9; H, 7·5; N, 7·4. $C_{21}H_{28}O_5N_2$ requires C, 64·9; H, 7·3; N, 7·2%). N-(5-p-*Nitrophenoxypentyl*)*phthalhydrazide* (23%), m. p. 160—162° (from toluene) (Found: C, 61·95; H, 5·35; N, 11·7. $C_{19}H_{19}O_5N_5$ requires C, 61·8; H, 5·2; N, 11·4%), was similarly made (in dimethylformamide).

1-β-*Carboxyacrylamido*-5-p-*nitrophenoxypentane*.—A solution of 1-amino-5-*p*-nitrophenoxypentane (22·4 g.) in chloroform (100 ml.) was slowly added to a suspension of maleic anhydride (9·8 g.) in chloroform (100 ml.). When the exothermic reaction was over, the solution was refluxed for 1 hr., cooled, washed with 2N-hydrochloric acid and water, dried, and evaporated. Crystallisation of the residue from ethanol gave the *maleamic acid* (53%), m. p. 91—93° (Found: C, 55·6; H, 5·8; N, 8·3. $C_{15}H_{18}O_6N_2$ requires C, 55·9; H, 5·6; N, 8·7%). Similarly prepared were: 1-p-*acetamidophenoxy*-5-β-*carboxyacrylamidopentane* (63%), m. p. 161—163° (from aqueous acetic acid) (Found: C, 60·4; H, 6·8; N, 8·7. $C_{17}H_{22}O_5N_2$ requires C, 61·1; H, 6·6; N, 8·4%); 1-(β-carboxymethyl-β-methylvaleramido)-5-*p*-nitrophenoxypentane (not obtained crystalline); and 1-*γ-carboxybutyramido*-5-p-*nitrophenoxypentane* (92%), m. p. 116—117° (also obtained by hydrolysis of the corresponding ethyl ester as described below).

1-*Maleimido*-5-p-*nitrophenoxypentane*.—A mixture of the foregoing maleamic acid (17·2 g.), acetic anhydride (18 ml.), and freshly fused sodium acetate (1·8 g.) was stirred at 100° for 1 hr., and excess of the anhydride was removed *in vacuo*. The residue was triturated with water, and the solid product crystallised from aqueous ethanol and from light petroleum (b. p. 100—120°), giving the *maleimide* (51%), m. p. 105—107° (Found: C, 59·1; H, 5·1; N, 9·2. $C_{15}H_{16}O_5N_2$ requires C, 59·2; H, 5·3; N, 9·2%).

1-*Glutarimido*-5-p-*nitrophenoxypentane*.—A mixture of the glutaramic acid (37·3 g.) and acetyl chloride (100 ml.) was refluxed for 20 min., then evaporated, and the residue was crystallised from methanol, yielding the *glutarimide* (84%), m. p. 87—88° (Found: C, 59·7; H, 6·2; N, 8·9. $C_{16}H_{20}O_5N_2$ requires C, 60·0; H, 6·3; N, 8·75%). 1-(β-Ethyl-β-methylglutarimido)-5-*p*-nitrophenoxypentane was made similarly, but was not obtained crystalline.

1-*γ-Ethoxycarbonylbutyramido*-5-p-*nitrophenoxypentane*.—Glutarimide (11·3 g.) and 5-*p*-nitrophenoxypentyl bromide (28·8 g.) were added to a solution of sodium (2·3 g.) in ethanol (150 ml.), and the mixture was refluxed for 20 hr., cooled, diluted with water, and extracted with chloroform. The washed and dried extract was evaporated and the residue was crystallised from benzene, giving the *ethyl ester* (39%), m. p. 90—91·5° (Found: C, 59·0; H, 7·3; N, 7·3; OEt, 12·3%; *M*, 300. $C_{18}H_{26}O_6N_2$ requires C, 59·0; H, 7·15; N, 7·6; OEt, 12·3%; *M*, 366). Hydrolysis with 2N-sodium hydroxide (1 equiv.) afforded the corresponding *acid* (93%), m. p. 118—119° (Found: C, 56·9; H, 6·8; N, 8·3. $C_{16}H_{22}O_6N_2$ requires C, 56·8; H, 6·6; N, 8·3%) not depressed by a specimen prepared as described above.

When a similar condensation was carried out by using sodium hydroxide (1 equiv.) in aqueous ethanol, the product (33%) was 5-p-*nitrophenoxypentyl glutaramate*, m. p. 93—95° (from benzene) (Found: C, 56·9; H, 6·3; N, 8·3%; *M*, 330. $C_{16}H_{22}O_6N_2$ requires C, 56·8; H, 6·6; N, 8·3%; *M*, 338), identical with a specimen, m. p. 93—94°, prepared (34%) from 5-*p*-nitrophenoxypentyl bromide and silver glutaramate in dry dioxan. Its structure was confirmed by catalytic reduction to 5-p-*aminophenoxypentyl glutaramate* (81%), m. p. 116—118° (from ethanol) (Found: N, 9·0. $C_{16}H_{24}O_4N_2$ requires N, 9·1%), and subsequent hydrolysis to 5-*p*-aminophenoxypentanol, m. p. 94—96° (Found: N, 7·2. Calc. for $C_{11}H_{17}O_2N$: N, 7·2%) not depressed by an authentic specimen (see Part II).

The amides (listed in Table 1) were prepared from 1-*p*-acetamidophenoxy-5-aminopentane, 1-amino-4-*p*-nitrophenoxybutane, 1-amino-5-*p*-nitrophenoxypentane or 1-amino-8-*p*-nitrophenoxyoctane with the appropriate acid chloride or anhydride either in pyridine or under Schotten–Baumann conditions (in some instances the yields quoted are overall from the phthalimide). NN′-*Di*-(5-p-*nitrophenoxypentyl*)*terephthalamide* (58%), m. p. 154—157° (from ethanol) (Found: N, 9·7. $C_{30}H_{34}O_8N_4$ requires N, 9·6%), and NN′-*Di*-(5-p-*nitrophenoxypentyl*)*glutaramide* (39%), m. p. 127—129° (from acetone) (Found: N, 10·4. $C_{27}H_{36}O_8N_4$ requires N, 10·3%), were prepared similarly.

1-*Cyanoacetamido*-5-p-*nitrophenoxypentane* was prepared (68%) from 1-amino-5-*p*-nitrophenoxypentane and ethyl cyanoacetate in boiling ethanol. After recrystallisation from aqueous ethanol, it had m. p. 85—86° (Found: C, 57·55; H, 5·8; N, 14·3. $C_{14}H_{17}O_4N_3$ requires C, 57·75; H, 5·9; N, 14·4%). Similarly obtained (in the absence of a solvent) was NN′-*di*-(5-p-*nitrophenoxypentyl*)*oxamide* (73%), m. p. 163·5—164·5° (from chloroform–ethanol) (Found: C, 57·25; H, 5·8; N, 11·2. $C_{24}H_{30}O_8N_4$ requires C, 57·4; H, 6·0; N, 11·1%).

1-*Ethoxalylamino*-5-p-*nitrophenoxypentane*.—Ethoxalyl chloride (13·65 g.) was slowly added to a cooled solution of 1-amino-5-*p*-nitrophenoxypentane (21·4 g.) in pyridine (100 ml.). The solution was kept overnight at room temperature, diluted with water and ether, and filtered from the insoluble oxamide (2·15 g.). The ether solution was separated, washed with 2N-hydrochloric acid and water, dried, and evaporated. The residue was repeatedly extracted with boiling light petroleum (b. p. 100—120°). The cooled extracts deposited the *ethoxalyl derivative* (27%), m. p. 85—87° (Found: C, 55·9; H, 5·95; N, 8·8. $C_{15}H_{20}O_6N_2$ requires C, 55·55; H, 6·2; N, 8·6%).

1-*Formamido*-5-p-*nitrophenoxypentane*.—A mixture of 1-*amino*-5-p-*nitrophenoxypentane* (36·4 g.), concentrated hydrochloric acid (13·95 ml.), and formamide (64·5 ml.) was heated at 145° for 30 min., cooled, and evaporated under reduced pressure. Water (100 ml.) was added to the residue, and the solid product was filtered off, dried, and recrystallised from benzene. The crude nitro-compound was extracted with ether (Soxhlet), and the extract was cooled and filtered, giving the *formamide* (78%), m. p. 71—72° (Found: C, 57·25; H, 6·4; N, 11·3. $C_{12}H_{16}O_4N_2$ requires C, 57·15; H, 6·35; H, 11·1%).

1-*Hippuramido*-5-p-*nitrophenoxypentane*.—2-Phenyloxazolone (8·6 g.) was added to a solution of 1-amino-5-*p*-nitrophenoxypentane (12·0 g.) in chloroform, the solution was evaporated, and the residue was heated at 100° for 30 min. Crystallisation of the residue from ethanol gave the *hippuramide* (80%), m. p. 145—147° (Found: N, 10·7. $C_{20}H_{23}O_5N_3$ requires N, 10·9%).

1-o-*Carboxybenzamido*-5-p-*nitrophenoxypentane*.—1-*p*-Nitrophenoxy-5-phthalimidopentane (17·7 g.) was refluxed with N-sodium hydroxide (50 ml.) for 15 min. The yellow solution was filtered and the filtrate was acidified with acetic acid. The *acid* was filtered off, washed with dilute acetic acid and water, dried, and recrystallised from chloroform–light petroleum. Its m. p., 118—122°, varied with the rate of heating (Found: C, 61·4; H, 5·5; N, 7·4. $C_{19}H_{20}O_6N_2$ requires C, 61·3; H, 5·4; N, 7·5%).

1-p-*Acetamidobenzamido*-5-p-*nitrophenoxypentane*.—(*a*) Tetraethyl pyrophosphite (2·7 ml.)

was added to a solution of 1-amino-5-*p*-nitrophenoxypentane (2·24 g.) and *p*-acetamidobenzoic acid (1·79 g.) in diethyl phosphite (7 ml.), and the mixture was heated at 100° for 1 hr., diluted with water, and cooled. Recrystallisation of the product from 2-ethoxyethanol gave the *amide* (55%), m. p. 187—188° (Found: N, 10·95. $C_{20}H_{23}O_5N_3$ requires N, 10·9%).

(*b*) 1-Amino-5-*p*-nitrophenoxypentane (11·2 g.) was added to a solution of *p*-acetamidobenzoic acid (17·9 g.) and toluene-*p*-sulphonyl chloride (9·52 g.) in pyridine (40 ml.). After 30 min. at room temperature, the mixture was treated with a solution of sodium hydroxide (10 g.) and sodium metabisulphite (5 g.) in water (200 ml.), and the precipitate was filtered off, washed, dried, and recrystallised. The amide (60%) had m. p. 185—186°.

1-*Dibenzoylamino*-5-p-*nitrophenoxypentane*.—A solution of 1-amino-5-*p*-nitrophenoxypentane (2·54 g.) in pyridine (10 ml.) was refluxed with benzoyl chloride (5 ml.) for 1·5 hr., cooled, and diluted with water. After recrystallisation from ethanol, the *dibenzoyl derivative* (83%) had m. p. 119—120° (Found: N, 6·8. $C_{25}H_{24}O_5N_2$ requires N, 6·5%).

1-(N-*Benzyloxycarbonyl*-β-*alanyl*)*amino*-5-p-*nitrophenoxypentane*.—A solution of benzyloxycarbonyl-β-alanine [12] (24 g.) and 1-amino-5-*p*-nitrophenoxypentane (24 g.) in diethyl phosphite (75 ml.) was heated with tetraethyl pyrophosphite (30 ml.) at 100° for 30 min., diluted with water, cooled, and filtered. The product was recrystallised from aqueous ethanol; the *benzyloxycarbonyl compound* (90%) had m. p. 137—138° (Found: N, 9·65. $C_{22}H_{27}O_6N_3$ requires N, 9·8%).

1-β-*Alanylamino*-5-p-*nitrophenoxypentane*.—33% Hydrogen bromide–acetic acid (60 ml.) was added to the foregoing benzyloxycarbonyl derivative (35·05 g.) in a flask fitted with a guard tube ($CaCl_2$). Evolution of carbon dioxide began at once. After 20 min. the clear solution was treated with dry ether, and the hydroscopic hydrobromide was filtered off, washed with dry ether, and dissolved in water. The solution was basified and extracted with chloroform, the washed and dried extract was evaporated, and the residue was triturated with ether. The solid product (m. p. 85—92°) proved difficult to purify and was used directly for the next stage. A small amount was recrystallised from benzene, giving the β-*alanyl compound*, m. p. 93—95° (Found: C, 57·6; H, 7·2; N, 13·6. $C_{14}H_{21}O_4N_3$ requires C, 56·9; H, 7·2; N, 14·2%).

1-p-*Nitrophenoxy*-5-DL-*pantothenamidopentane*.—A solution of the foregoing amine (10·36 g.) and DL-pantolactone [13] (4·56 g.) in absolute ethanol (50 ml.) was refluxed for 20 hr., then evaporated. The residue, in ethyl acetate, was washed with 2N-sodium hydroxide, 2N-hydrochloric acid, and water, dried, and evaporated, and the residual oily *product* (14·6 g.) (Found: N, 9·2. $C_{20}H_{31}O_7N_3$ requires N, 9·9%) was reduced directly to the amine.

1-*Cyclohexylamino*-5-p-*nitrophenoxypentane*.—A solution of 5-*p*-nitrophenoxypentyl bromide (43·2 g.) and cyclohexylamine (19·8 g.) in ethanol (50 ml.) was refluxed for 19 hr., cooled, and filtered. The *amine hydrobromide* (76%), after recrystallisation from ethanol, had m. p. 221—223° (Found: C, 53·1; H, 7·2; N, 7·35. $C_{17}H_{26}O_3N_2$,HBr requires C, 52·7; H, 7·0; N, 7·2%). The *benzoyl derivative* had m. p. 78—79° (from aqueous ethanol) (Found: N, 7·0. $C_{24}H_{30}O_4N_2$ requires N, 6·8%).

1-N-*Benzyloxybenzamido*-5-p-*nitrophenoxypentane*.—5-*p*-Nitrophenoxypentyl bromide (44·5 g.) and *N*-benzyloxybenzamide [14] (35 g.) were added to a solution from sodium (3·5 g.) and dry ethanol (300 ml.), and the mixture was refluxed for 24 hr., filtered from sodium bromide, and concentrated. The residue was dissolved in chloroform, and the solution was washed with 2N-sodium hydroxide and water, dried, concentrated, and diluted with ether, giving the *nitro-ether* (46%), m. p. 77—78° (Found: C, 69·1; H, 6·1; N, 6·4. $C_{25}H_{26}O_5N_2$ requires C, 69·1; H, 6·0; N, 6·45%).

1-*Anilino*-5-p-*nitrophenoxypentane*.—A mixture of 5-*p*-nitrophenoxypentyl bromide (57·6 g.), aniline (50 ml.), and ethanol (200 ml.) was refluxed for 20 hr., concentrated, and diluted with water. Crystallisation of the product from ethanol gave the *anilino-derivative* (98%), m. p. 87—89° (Found: C, 67·7; H, 6·4; N, 9·1. $C_{17}H_{20}O_3N_2$ requires C, 68·0; H, 6·7; N, 9·3%). The acetyl derivative was not obtained crystalline and was reduced directly to the amine (see Table 2). The *methanesulphonyl derivative* (64%) had m. p. 73—74° [from benzene–light petroleum (b. p. 80—100°)] (Found: N, 7·0; S, 8·3. $C_{18}H_{22}O_5N_2S$ requires N, 7·4; S, 8·5%).

1-N-*Methylmethanesulphonamido*-5-p-*nitrophenoxypentane*.—1-Methanesulphonamido-5-*p*-nitrophenoxypentane (42·7 g.), water (5 ml.), and methyl iodide (17·4 ml.) were added successively to a solution from sodium (3·5 g.) and ethanol (300 ml.). The mixture was refluxed for 3 hr.,

[12] Sifferd and du Vigneaud, *J. Biol. Chem.*, 1935, **108**, 753.
[13] Stiller, Harris, Finkelstein, Keresztesy, and Folkers, *J. Amer. Chem. Soc.*, 1940, **62**, 1785.
[14] Beckman, *Ber.*, 1893, **26**, 2631.

concentrated, and diluted with water, and the solid product was crystallised from ether, giving the N-*methylmethanesulphonamide* (78%), m. p. 61—63° (Found: N, 8·6; S, 9·9. $C_{13}H_{20}O_5N_2S$ requires N, 8·9; S, 10·1%).

N-*Benzoyldi*-(4-p-*nitrophenoxypentyl*)*amine*.—A solution of 5-*p*-nitrophenoxypentyl bromide (28·8 g.) and 1-amino-5-*p*-nitrophenoxypentane (22·4 g.) in ethanol (250 ml.) was refluxed for 20 hr., cooled, and filtered. The crude hydrobromide (68%) was shaken with benzoyl chloride in acetone–2N-sodium hydroxide, and the product was crystallised from acetone–ether, giving the *benzoyl derivative* (66%), m. p. 114—115·5° (Found: C, 65·1; H, 6·3; N, 7·8. $C_{29}H_{33}O_7N_3$ requires C, 65·05; H, 6·2; N, 7·8%).

1-*Benzoyl*-4-p-*nitrophenoxybutane* was obtained (89%) by condensation of potassium *p*-nitrophenoxide with 4-benzoylbutyl bromide [10] in 2-ethoxyethanol; after crystallisation from acetic acid, it had m. p. 122—123° (Found: C, 68·3; H, 6·0; N, 4·7. $C_{17}H_{17}O_4N$ requires C, 68·2; H, 5·7; N, 4·7%).

1-*Hydroxy*-5-p-*nitrophenoxy*-1-*phenylpentane*.—A solution of the foregoing nitro-ketone (63 g.) and aluminium isopropoxide (25·2 g.) in propan-2-ol (3 l.) was slowly distilled until no more acetone was obtained (2 hr.). The solution was evaporated, the residue was treated with dilute hydrochloric acid, and the solid was recrystallised from aqueous ethanol, giving the *hydroxy-compound* (94%), m. p. 61—62° (Found: C, 67·7; H, 6·2; N, 4·75. $C_{17}H_{19}O_4N$ requires C, 67·8; H, 6·3; N, 4·65%).

5-p-*Nitrophenoxy*-1-*phenyl*-1-*phthalimidopentane*.—Phosphorus tribromide (21·6 ml.) was slowly added to a solution of the foregoing hydroxy-compound (54 g.) in benzene (500 ml.), stirred and cooled to 10°; the mixture was then kept overnight at room temperature and treated with water, the benzene layer was separated, and the aqueous layer was extracted with ether. The combined benzene and ether solutions were washed, dried, and evaporated. A mixture of the residual bromo-compound, potassium phthalimide (54 g.), and dry acetone (250 ml.) was stirred and refluxed for 48 hr. The product (34 g.) was isolated in the usual way. Unchanged bromide recovered from the mother-liquors was re-treated with potassium phthalimide in acetone, giving more of the required product (total 51 g., 66%). After recrystallisation from ethanol, the *phthalimido-derivative* had m. p. 131—132° (Found: C, 69·8; H, 4·7; N, 6·6. $C_{25}H_{22}O_5N_2$ requires C, 69·8; H, 5·1; N, 6·5%). Hydrolysis with hydrazine and subsequent benzoylation afforded 1-*benzamido*-5-p-*nitrophenoxy*-1-*phenylpentane* (69% overall), m. p. 116—118° (from benzene) (Found: C, 71·6; H, 5·9. $C_{24}H_{24}O_4N_2$ requires C, 71·8; H, 5·9%).

1-p-*Nitrophenoxy*-5-2′-*phthalimidoethoxypentane*.—1-2′-Hydroxyethoxy-5-*p*-nitrophenoxypentane [15] was converted by toluene-*p*-sulphonyl chloride in pyridine into the *toluene*-p-*sulphonyl derivative* (81%), m. p. 49—50° (Found: C, 56·95; H, 5·8; N, 3·4. $C_{20}H_{25}O_7NS$ requires C, 56·7; H, 5·9; N, 3·3%), which was condensed with potassium phthalimide in the usual way, giving the *phthalimido-derivative* (65%), m. p. 78—79° (from methanol) (Found: C, 63·5; H, 5·9; N, 6·9. $C_{21}H_{22}O_6N_2$ requires C, 63·3; H, 5·5; N, 7·0%).

1-(1,2-*Dihydro*-2-*oxo*-*pyrid*-1-*yl*)-5-p-*nitrophenoxypentane*.—A mixture of 5-*p*-nitrophenoxypentyl iodide (Part II) (102 g.), the sodium derivative (36 g.) of 2-pyridone, ethanol (400 ml.), and water (200 ml.) was refluxed for 24 hr., ethanol was distilled off, and the residue was diluted with water. The solid product was recrystallised from acetone, giving the *nitro-ether* (47%), m. p. 103° (Found: C, 63·7; H, 6·2; N, 9·1. $C_{16}H_{18}O_4N_2$ requires C, 63·6; H, 6·0; N, 9·3%). From the mother-liquors a small amount of 1-*p*-nitrophenoxy-5-pyrid-2′-yloxypentane (Part II) was obtained.

1-(2,3-*Dihydro*-3-*oxobenzisothiazol*-2-*yl*)-5-p-*nitrophenoxypentane*.—A mixture of 5-*p*-nitrophenoxypentyl bromide (2·88 g.), the sodium derivative (1·73 g.) of 2,3-dihydro-3-oxobenzisothiazole,[16] and 2-ethoxyethanol (10 ml.) was refluxed for 20 hr., cooled, and diluted with water. The solid product was dissolved in chloroform, the solution was washed with dilute sodium hydroxide and water, dried, and evaporated, and the residue was triturated with ether. Recrystallisation of the solid from ethanol yielded the *nitro-ether* (39%), m. p. 109—111° (Found: N, 7·5; S, 9·0. $C_{18}H_{18}O_4N_2S$ requires N, 7·8; S, 8·9%). Oxidation with 30% hydrogen peroxide in acetic acid at 100° gave the known saccharin derivative,[1] m. p. and mixed m. p. 126—127°.

1-p-*Acetamidophenoxy*-5-(2,3-*dihydro*-3-*oxobenzisothiazol*-2-*yl*)*pentane* (42%), m. p. 170—171° (from ethanol) (Found: C, 61·7; H, 6·6; N, 7·05; S, 8·4. $C_{20}H_{22}O_4N_2S$ requires C, 62·1;

[15] May and Baker Ltd., B.P. 770,870.
[16] McClelland and Gait, *J.*, 1926, 923.

H, 5·7; N, 7·25; S, 8·3%) was similarly prepared. When 5-*p*-nitrophenoxypentyl bromide (3·15 g.) was condensed with 2,3-dihydro-3-oxobenzisothiazole (1·65 g.) by using potassium carbonate (0·76 g.) in acetone (50 ml.), the product (1·9 g.) had m. p. 97—99° (from acetic acid) (Found: C, 59·7; H, 5·0; N, 7·5; S, 9·0%; *M*, 350. $C_{18}H_{18}O_4N_2S$ requires C, 60·3; H, 5·1; N, 7·8; S, 8·9%; *M*, 358), depressed to below 90° by the foregoing nitro-compound, and was probably 1-p-*nitrophenoxy-5-benzisothiazol-3′-yloxypentane*.

3-(5-p-*Nitrophenoxypentyl*)*rhodanine*.—Carbon disulphide (8·4 ml.) and dimethylformamide (60 ml.) were added successively to a solution of 5-amino-1-*p*-nitrophenoxypentane (32 g.) in dry toluene (100 ml.). After 30 min. the solution was cooled, treated with mercuric oxide (32 g.), and shaken for 30 min., then filtered from black mercuric sulphide, and the filtrate was treated with 90% mercaptoacetic acid (7·3 g.). The solution was heated at 100° for 30 min., concentrated, and diluted with water, and the solid product was recrystallised from ethanol, giving the *rhodanine* (68%), m. p. 112—113° (Found: C, 49·6; H, 5·1; S, 18·8. $C_{14}H_{16}O_4N_2S_2$ requires C, 49·4; H, 4·7; S, 18·8%). The *5-benzylidene-derivative*, prepared (96%) by heating the rhodanine (30 g.) with benzaldehyde (20 ml.), acetic acid (200 ml.), and concentrated sulphuric acid (40 ml.) at 100° for 3 hr., crystallised from acetic acid and had m. p. 143—144° (Found: N, 6·4; S, 14·9. $C_{21}H_{20}O_4N_2S_2$ requires N, 6·5; S, 14·95%).

3-(5-p-*Nitrophenoxypentyl*)*thiazolidine-2,4-dione*.—Thiazolidine-2,4-dione (14·1 g.) and 5-*p*-nitrophenoxypentyl iodide (49·7 g.) were added successively to a solution from sodium (3·43 g.) and dry ethanol (200 ml.), and the mixture was refluxed for 20 hr., cooled, and filtered. The solid was washed with cold ethanol and water, and recrystallised from ethanol, giving the *thiazolidine-2,4-dione* (46%), m. p. 118—119° (Found N, 8·55; S, 9·7. $C_{14}H_{16}O_5N_2S$ requires N, 8·6; S, 9·8%).

N-(5-p-*Nitrophenoxypentyl*)*butane-1,4-sultam*—Butane-1,4-sultam[17] (2 g.) was dissolved in a solution from sodium (0·35 g.) and dry ethanol (10 ml.), and a solution from 5-*p*-nitrophenoxypentyl bromide (4·3 g.) in dry ethanol (10 ml.) was added. The mixture was refluxed for 3 hr., concentrated, diluted with water, and filtered. Recrystallisation of the solid from methanol yielded the *sultam* (79%), m. p. 89—90° (Found: C, 53·0; H, 6·5; N, 8·2; S, 9·0. $C_{15}H_{22}O_5N_2S$ requires C, 52·6; H, 6·4; N, 8·2; S, 9·35%). N-(5-p-*Nitrophenoxypentyl*)*naphthalene-1,8-sultam* (59%), m. p. 119° (from ethanol) (Found: N, 6·9; S, 8·0. $C_{21}H_{22}O_5N_2S$ requires N, 6·8; S, 7·8%), was similarly prepared from naphthalene-1,8-sultam.[18]

Primary amines.

1-p-*Aminophenoxy-7-hexahydrophthalimidoheptane*.—When 1-*p*-nitrophenoxy-7-phthalimidoheptane (43·8 g.) was reduced in ethanol (350 ml.) over 2% platinum dioxide at 70° and 56 lb. per sq. inch hydrogen pressure, the uptake reached 133% of theory for $NO_2 \longrightarrow NH_2$. The cooled solution deposited 1-*p*-aminophenoxy-7-phthalimidoheptane (55%), m. p. 107—109° [after recrystallisation from chloroform–light petroleum (b. p. 60—80°)]. Concentration of the mother-liquors afforded the *hexahydro-compound* (27%) which, after recrystallisation from chloroform–light petroleum, had, m. p. 73—75° (Found: C, 70·2; H, 7·9; N, 7·8. $C_{21}H_{30}O_3N_2$ requires C, 70·3; H, 8·4; N, 7·8%).

1-p-*Aminophenoxy-5-maleimidopentane*.—1-Maleimido-5-*p*-nitrophenoxypentane (5·9 g.) was added to a solution of stannous chloride dihydrate (18 g.) in warm concentrated hydrochloric acid (27 ml.). The solution was kept for 5 min. at 100°, then slowly poured into a stirred mixture of 50% aqueous sodium hydroxide (50 ml.) and chloroform (100 ml.) maintained at 0°. The chloroform solution was immediately separated, washed, dried, concentrated, and diluted with light petroleum. Recrystallisation of the crystalline product from ethyl acetate–light petroleum gave the *amine* (71%), m. p. 122—124° (Found: C, 64·7; H, 7·2; N, 10·0. $C_{15}H_{18}O_3N_2$ requires C, 65·7; H, 6·6; N, 10·2%). The *methanesulphonate* had m. p. 194—195° (Found: C, 51·4; H, 5·9; N, 7·75; S, 9·1. $C_{15}H_{18}O_3N_2,CH_4O_3S$ requires C, 51·9; H, 6·0; N, 7·6; S, 8·65%) (from ethanol). Both the base and the methanesulphonate gave consistently low carbon analyses.

3-(5-p-*Aminophenoxypentyl*)*rhodanine* (40%), m. p. 104—106° (from ethanol) (Found: C, 54·1; H, 5·9; N, 8·9. $C_{14}H_{18}O_2N_2S_2$ requires C, 54·1; H, 5·8; N, 9·0%), and 3-(5-p-*aminophenoxypentyl*)-*5-benzylidenerhodanine* (73%) (acetic acid used as solvent), m. p. 133—135°

[17] Dirscherl and Weingarten, *Annalen*, 1951, **574**, 137.
[18] Dannerth, *J. Amer. Chem. Soc.*, 1907, **29**, 1319.

(from 2-ethoxyethanol) (Found: C, 63·1; H, 5·4; N, 6·7. $C_{21}H_{22}O_2N_2S_2$ requires C, 63·3; H, 5·5; N, 7·0%), were similarly prepared. 3-(5-p-*Aminophenoxypentyl*)*thiazolidine*-2,4-*dione*, m. p. 107—109° (from ethanol) (Found: C, 57·3; H, 6·1; N, 9·2. $C_{14}H_{18}O_3N_2S$ requires C, 57·2; H, 6·1; N, 9·5%), was prepared (54%) by reducing the corresponding nitro-compound with stannous chloride or, preferably, with reduced iron powder and aqueous acetic acid.

1-p-*Aminophenoxy*-5-*cyanoacetamidopentane*.—A mixture of 1-amino-5-*p*-aminophenoxypentane (14·55 g.), ethyl cyanoacetate (8·36 g.), and methanol (20 ml.) was kept for 5 days in a stoppered flask. The solid was recrystallised from ethanol, giving the *cyanoacetamide* (81%), m. p. 92—93° (Found: C, 64·4; H, 7·2; N, 16·0. $C_{14}H_{19}O_2N_3$ requires C, 64·35; H, 7·2; N, 16·1%). The *acetyl derivative*, m. p. 173—175° (from ethanol) (Found: N, 13·8. $C_{16}H_{21}O_3N_3$ requires N, 13·85%), was also obtained directly from 1-*p*-acetamidophenoxy-5-aminopentane and ethyl cyanoacetate.

Similarly prepared were 1-p-*aminophenoxy*-5-*dichloroacetamidopentane* (experiment by Mr. D. E. Wright) (13%), m. p. 81—82° (from benzene–light petroleum) (Found: N, 9·0; Cl, 23·0. $C_{13}H_{18}O_2N_2Cl_2$ requires N, 9·2; Cl, 23·2%), and 1-p-*aminophenoxy*-5-*trichloroacetamidopentane* (66%), m. p. 97—99° (from ether) (Found: N, 7·9; Cl, 31·65. $C_{13}H_{17}O_2N_2Cl_3$ requires N, 8·2; Cl, 31·4%).

1-p-*Aminophenoxy*-5-*phthalimidinopentane*.—Concentrated hydrochloric acid (100 ml.) was added during 1 hr. to a stirred, refluxing mixture of 1-*p*-aminophenoxy-5-phthalimidopentane (32·4 g.), tin (25 g.) and ethanol (200 ml.). After a further 17 hr. the solution was filtered and the cooled filtrate was slowly added to 50% aqueous sodium hydroxide (200 ml.). The precipitate was filtered off, washed with water, and extracted with boiling ethanol (400 ml.). The cooled extract afforded the *phthalimidine* (63%), m. p. 143—144° (Found: C, 73·7; H, 7·1; N, 8·9. $C_{19}H_{22}O_2N_2$ requires C, 73·5; H, 7·15; N, 9·0%).

Except where stated, the amines in Table 2 were prepared by catalytic reduction of the corresponding nitro-compounds, usually over Raney nickel in ethanol, 2-ethoxyethanol, or dimethylformamide.

N-*Substituted amines*.

1-p-*Dimethylaminophenoxy*-3-*phthalimidopropane*.—1-*p*-Aminophenoxy-3-phthalimidopropane, m. p. 92—93° (prepared by reduction of the nitro-compound; lit.,[19] m. p. 92—94°), was converted by methyl iodide and sodium carbonate in ethanol into the quaternary iodide (100%), m. p. 203—206° (from water), which was pyrolysed under reduced pressure, giving 1-*p*-dimethylaminophenoxy-3-phthalimidopropane (100%), m. p. 121—122° (from ethanol) (Found: C, 70·7; H, 6·3; N, 8·4. Calc. for $C_{19}H_{20}O_3N_2$: C, 70·4; H, 6·2; N, 8·6%) (lit.,[11] m. p. 159·6—160·9°).

1-*Benzenesulphonamido*-5-p-*dimethylaminophenoxypentane*, m. p. 71—72·5° (from ether) (Found: N, 7·5; S, 8·9. $C_{19}H_{26}O_3N_2S$ requires N, 7·7; S, 8·8%), was similarly obtained (96%) from its *methiodide* (96%), m. p. 183—185° (from water) (Found: N, 5·5; I, 25·4. $C_{20}H_{29}O_3N_2SI$ requires N, 5·55; I, 25·15%).

1-(p-N-*Methylacetamidophenoxy*)-5-*phthalimidopentane*, prepared (53%) from *p*-*N*-methylacetamidophenol, 5-phthalimidopentyl bromide, and sodium ethoxide in ethanol, had m. p. 83—85° (from chloroform–ether) (Found: N, 7·6. $C_{22}H_{24}O_4N_2$ requires N, 7·4%). 1-(p-N-*Methylbenzamidophenoxy*)-5-*phthalimidopentane*, m. p. 121—124° (from methanol) (Found: N, 6·2. $C_{27}H_{26}O_4N_2$ requires N, 6·3%), was similarly obtained.

1-*Amino*-5-p-*methylaminophenoxypentane*, prepared by refluxing the foregoing acetyl derivative with concentrated hydrochloric acid, had m. p. 76—79° [from light petroleum (b. p. 60—80°)], b. p. 200—205°/15 mm. (Found: C, 69·2; H, 10·1; N, 13·3. $C_{12}H_{20}ON_2$ requires C, 69·2; H, 9·7; N, 13·4%). It decomposed on storage.

1-*Benzamido*-5-(p-N-*methylacetamidophenoxy*)*pentane*.—The corresponding 5-phthalimido-compound was treated with aqueous-alcoholic hydrazine, as previously described, and the amine formed was benzoylated, yielding the *benzamide* (61% overall), m. p. 110—112° (from acetone–light petroleum) (Found: N, 7·95. $C_{21}H_{26}O_3N_2$ requires N, 7·9%). 1-*Benzamido*-5-(p-N-*methylformamidophenoxy*)*pentane*, m. p. 115—116° (from acetone–ether) (Found: C, 71·05; H, 7·0; N, 8·3. $C_{20}H_{24}O_3N_2$ requires C, 70·4; H, 7·0; N, 8·2%), was similarly prepared (12% overall). Partial hydrolysis of either the *N*-formyl or the *N*-acetyl derivative, with aqueous hydrochloric acid (1 equiv.) in acetic acid, then afforded 1-*benzamido*-5-p-*methylaminophenoxypentane* (60%), m. p. 91—92° (from acetone–light petroleum) (Found: C, 73·5; H, 7·7; N, 8·9.

[19] Matejka and Robinson, *J.*, 1934, 1324.

$C_{19}H_{24}O_2N_2$ requires C, 73·45; H, 7·7; N, 9·0%). The N-*benzoyl derivative* had m. p. 111—113° (from benzene–ether) (Found: C, 75·0; H, 6·3; N, 6·6. $C_{26}H_{28}O_3N_2$ requires C, 75·0; H, 6·8; N, 6·7%).

1-*Benzenesulphonamido*-5-(p-N-*methylacetamidophenoxy*)*pentane*, m. p. 109—111° (from toluene–light petroleum) (Found: N, 7·05; S, 8·4. $C_{20}H_{26}O_4N_2S$ requires N, 7·2; S, 8·2%), was similarly prepared and was hydrolysed to 1-*benzenesulphonamido*-5-p-*methylaminophenoxypentane* (62% overall), m. p. 83—85° (from ethanol) (Found: N, 7·8; S, 9·6. $C_{18}H_{24}O_3N_2S$ requires N, 8·0; S, 9·2%). The latter base, on treatment with ethylene chlorohydrin and calcium carbonate in boiling water, yielded 1-*benzenesulphonamido*-5-[p-(2-*hydroxy*-N-*methylethylamino*)*phenoxy*]*pentane* (76%), m. p. 76—78° (from benzene–light petroleum) (Found: N, 6·95; S, 8·3. $C_{20}H_{28}O_4N_2S$ requires N, 7·1; S, 8·2%).

1,2-*Di*-(p-5-*benzamidopentyloxyanilino*)*ethane*.—A mixture of 1-*p*-aminophenoxy-5-benzamidopentane (14·9 g.), ethylene dibromide (4·7 g.), and ethanol (25 ml.) was refluxed for 20 hr., cooled, and filtered. The solid was extracted with water and boiling ethanol. The insoluble residue was the piperazine derivative (3·3 g., see below). The ethanolic extract yielded the *dianilinoethane* (24%), m. p. 155—157° (from ethanol) (Found: C, 73·1; H, 7·5; N, 8·9. $C_{38}H_{46}O_4N_4$ requires C, 73·3; H, 7·45; N, 9·0%).

1,4-*Di*-(p-5-*benzamidopentyloxyphenyl*)*piperazine*.—The foregoing dianilinoethane (8·1 g.), ethylene dibromide (4·7 g.), and sodium hydrogen carbonate (4·2 g.) were refluxed in 2-ethoxyethanol (30 ml.) for 20 hr. The *piperazine* formed (96%) had m. p. 231—233° (from 2-ethoxyethanol) (Found: C, 74·15; H, 7·3; N, 8·6. $C_{40}H_{48}O_4N_4$ requires C, 74·1; H, 7·45; N, 8·6%).

1-p-*Di*-(2-*chloroethyl*)*aminophenoxy*-5-*phthalimidopentane*.—Phosphorus oxychloride (2·74 ml.), was added to 1-*p*-di-(2-hydroxyethyl)aminophenoxy-5-phthalimidopentane (B.P. 769,706) (4·12 g.) in dry benzene (15 ml.) and the mixture was refluxed for 2 hr., poured on ice and extracted with benzene. The washed and dried extract was evaporated and the residue was triturated with ether. Crystallisation of the product from ethanol gave the *chloroethyl derivative* (81%), m. p. 107—108° (Found: N, 6·2; Cl, 15·5. $C_{23}H_{26}O_3N_2Cl_2$ requires N, 6·2; Cl, 15·8%).

1-(3-*Chloro*-p-*tolyl*)-4-(p-5-*phthalimidopentyloxyphenyl*)*piperazine*.—A mixture of the foregoing chloroethyl compound (17·96 g.), 3-chloro-*p*-toluidine (5·66 g.), sodium carbonate (4·24 g.), and 2-ethoxyethanol (75 ml.) was refluxed for 20 hr., cooled, and filtered. The solid product was washed with water and crystallised from chloroform–ethanol, yielding the *piperazine* (63%), m. p. 149—150° (Found: N, 8·2; Cl, 6·7. $C_{30}H_{32}O_3N_3Cl$ requires N, 8·1; Cl, 6·8%).

1-p-(2-*Amino*-6-*methylpyrimid*-4-*ylamino*)*phenoxy*-5-*phthalimidopentane*.—A mixture of 2-amino-4-chloro-6-methylpyrimidine (14·35 g.), 1-*p*-aminophenoxy-5-phthalimidopentane (32·4 g.), N-hydrochloric acid (100 ml.), and water (500 ml.) was refluxed for 1 hr., cooled, and made just alkaline to phenolphthalein. Recrystallisation of the solid product from 2-ethoxyethanol gave the *pyrimidine derivative* (67%), m. p. 211—213° (Found: C, 66·9; H, 5·8; N, 15·9. $C_{24}H_{25}O_3N_5$ requires C, 66·8; H, 5·8; N, 16·2%). Treatment with methyl sulphate in nitrobenzene for 1 hr. at 100° afforded the 1-*metho*(*methyl sulphate*) (75%), m. p. 186—188° (from ethanol) (Found: N, 12·8; S, 6·2. $C_{26}H_{31}O_7N_5S$ requires N, 12·5; S, 5·8%).

4-*Amidino*-4′-(5-*phthalimidopentyloxy*)*diazoaminobenzene*.—A solution of sodium nitrite (1·43 g.) in water (24 ml.) was added slowly at 0—5° to a mixture of *p*-aminobenzamidine dihydrochloride (4·16 g.) and concentrated hydrochloric acid (2·9 ml.) in water (17 ml.). The resulting solution was stirred whilst a solution of 1-*p*-aminophenoxy-5-phthalimidopentane (6·28 g.) in acetic acid (20 ml.) (at 20°) was quickly added, followed immediately by saturated sodium acetate. The red precipitate was filtered off, washed with water, and recrystallised from ethanol, giving the *amidine acetate* (68%), m. p. 210—212° (Found: C, 63·3; H, 6·4; N, 15·8. $C_{26}H_{26}O_3N_6,C_2H_4O_2$ requires C, 63·4; H, 5·7; N, 15·8%).

5-*Benzamido*-1-p-*carbamoylmethylaminophenoxypentane*.—A mixture of 1-*p*-aminophenoxy-5-benzamidopentane (19·7 g.), chloroacetamide (6·18 g.), sodium carbonate (3·5 g.), and ethanol (200 ml.) was refluxed for 20 hr., cooled, diluted with water, and filtered. Crystallisation of the product from ethanol gave the *amide* (61%), m. p. 161—163° (Found: C, 68·0; H, 6·6; N, 11·6. $C_{20}H_{25}O_3N_3$ requires C, 67·6; H, 7·1; N, 11·8%).

1-p-D-*Glucosylaminophenoxy*-5-*phthalimidopentane*.—A solution of 1-*p*-aminophenoxy-5-phthalimidopentane (3·24 g.), D-glucose (1·8 g.), and 5% ethanolic calcium chloride (0·5 ml.) in ethanol (20 ml.) was refluxed for 1·5 hr., cooled, and filtered. The *glucosylamine* (86%) had m. p. 110—115° (Found: C, 60·1; H, 6·55; N, 5·6; H_2O, 3·7. $C_{25}H_{30}O_8N_2,H_2O$ requires C, 59·5; H, 6·4; N, 5·55; H_2O, 3·6%).

1-*Benzamido*-5-p-D-*glucosylaminopentane* (83%), m. p. 119—120° (from aqueous methanol) (Found: C, 61·25; H, 7·3; N, 6·0; H_2O, 2·0. $C_{24}H_{32}O_7N_2,0{\cdot}5H_2O$ requires C, 61·4; H, 7·1; N, 6·0; H_2O, 1·9%), was similarly prepared.

Miscellaneous compounds.

4-(3-*Chloro*-p-*tolyl*)-1-(5-p-*nitrophenoxypentyl*)*piperazine*.—A mixture of 5-*p*-nitrophenoxypentyl bromide (14·6 g.), 1-(3-chloro-*p*-tolyl)piperazine [20] (10·65 g.), and ethanol (75 ml.) was refluxed for 40 hr., cooled, and filtered from the *hydrobromide* (76%), m. p. 170—172° (from ethanol) (Found: N, 8·3. $C_{22}H_{28}O_3N_3Cl,HBr$ requires N, 8·4%), of the product. The free *base* had m. p. 101—103° (from ethanol) (Found: N, 10·1; Cl, 8·6. $C_{22}H_{28}O_3N_3Cl$. requires N, 10·05; Cl, 8·5%). Reduction with sodium sulphide gave 1-(5-p-*aminophenoxypentyl*)-4-(3-*chloro*-p-*tolyl*)*piperazine* (86%), m. p. 95—96° (from ethanol) (Found: N, 10·9; Cl, 9·0. $C_{22}H_{30}ON_3Cl$ requires N, 10·8; Cl, 9·15%).

1,4-*Di*-(5-p-*nitrophenoxypentyl*)*piperazine*.—A mixture of 5-*p*-nitrophenoxypentyl bromide (5·76 g.) and piperazine hexahydrate (1·94 g.) was heated for 40 hr. at 100°. Refluxing the residue with ethanol afforded the sparingly soluble *dihydrobromide* (92%), m. p. 253—255° (Found: N, 8·3; Br, 24·5. $C_{26}H_{36}O_6N_4,2HBr$ requires N, 8·45; Br, 24·2%). The light-sensitive *base* had m. p. 122—123° (from ethanol) (Found: C, 62·2; H, 7·6; N, 11·2. $C_{26}H_{36}O_6N_4$ requires C, 62·4; H, 7·25; N, 11·2%). Catalytic reduction yielded 1,4-*di*-(5-p-*aminophenoxypentyl*)*piperazine* (92%), m. p. 124—126° [from ethanol–light petroleum (b. p. 100—120°)] (Found: C, 70·3; H, 9·5; N, 12·5. $C_{26}H_{40}O_2N_4$ requires C, 70·85; H, 9·2; N, 12·7%).

A further group of compounds, prepared by standard methods, and not described previously, is recorded in Table 3.

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[20] Farbwerke Hoechst A.G., Belgian Patent 539,950.