The Chemotherapy of Schistosomiasis. Part VI.[1] Ethers of 4-Aminocatechol and 4-Aminoresorcinol

By R. F. Collins and M. Davis

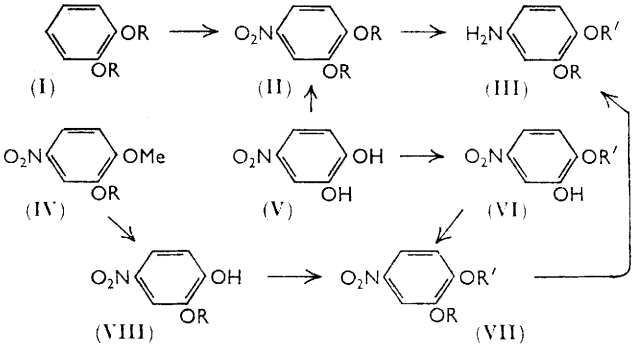
Further nuclear hydroxy- and alkoxy-*p*-aminophenyl ethers (III and XII) have been synthesised for structure-activity studies as schistosomicides.

MANY ethers of *p*-aminophenol have considerable activity against laboratory infections of *Schistosoma mansoni*, but often produce retinotoxicity in experimental animals. The presence of a nuclear 2-methoxy-group [2] reduces the incidence of this side-effect, and we have therefore extended our synthetic work to cover further ethers (III and XII) derived from 4-aminocatechol and 4-aminoresorcinol. The biological results will be reported elsewhere.[3]

Symmetrical ethers (II) of 4-nitrocatechol were obtained either by nitration of catechol diethers (I; R = Et, Bu^n, n-C_5H_{11}, or n-C_8H_{17}) [4] or by dialkylation of 4-nitrocatechol (V) to (II; R = CH_2Ph or CH_2OMe). 4-Nitroveratrole (IV; R = Me) is selectively hydrolysed to 2-methoxy-4-nitrophenol (VIII; R = Me) by alkali,[2] and application of the method to other ethers of 5-nitroguaiacol (IV; R = H) afforded similarly 2-ethoxy-,[5] 2-n-propoxy-, and 2-benzyloxy-4-nitrophenol [6] (VIII). Condensation with the appropriate halide by standard methods previously described then gave the required 1-alkyl and substituted alkyl ethers (VII).

4-Nitrocatechol (V) can be preferentially alkylated in the 1-position [2] and subsequent further alkylation of the 2-hydroxy-compound (VI) provided an alternative route to mixed ethers (VII). Reduction of the nitro-compounds gave the amines (III), in which R′ was usually alkyl or phthalimidopentyl, selected as groups known to be favourable for schistosomicidal activity.[7,8]

For the 3-hydroxy- and 3-alkoxy-compounds similar sequences of reactions were carried out with resorcinol derivatives. Thus, the 3-hydroxy-4-nitrophenyl ether (X; R′ = 5-phthalimidopentyl) was obtained either

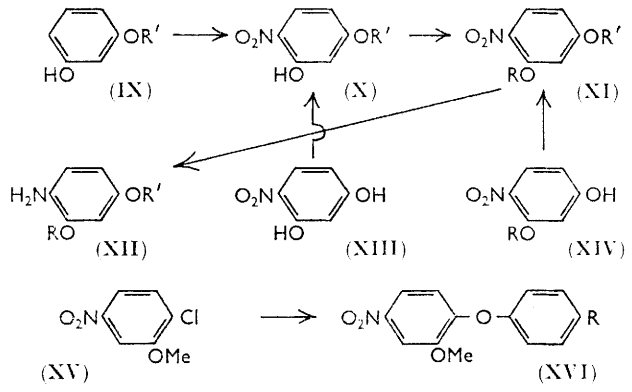


by nitration of the resorcinol monoether (IX) or directly by preferential 1-alkylation of 4-nitroresorcinol (XIII). Further methylation afforded 1-(3-methoxy-4-nitrophenoxy)-5-phthalimidopentane (XI; R = Me, R′ = 5-phthalimodopentyl) which was also prepared from 3-methoxy-4-nitrophenol (XIV; R = Me). Catalytic reduction yielded the amines (XII).

Related ether derivatives were also made for comparison in the biologically active 4-amino-2-methoxyphenyl series (III; R = Me). The diphenyl ether

[1] Part V, M. Davis, *J. Chem. Soc.*, 1962, 178.
[2] Part IV, R. F. Collins and M. Davis, *J. Chem. Soc.*, 1961, 1863.
[3] R. F. Collins, V. A. Cox, M. Davis, N. D. Edge, J. Hill, K. F. Rivott, and M. A. Rust in preparation.
[4] J. Allan and R. Robinson, *J. Chem. Soc.*, 1926, 376.
[5] A. Oliverio, *Gazzetta*, 1943, **73**, 181.
[6] W. Baker, A. W. W. Kirby, and L. V. Montgomery, *J. Chem. Soc.*, 1932, 2876.
[7] R. F. Collins, M. Davis, N. D. Edge, and J. Hill, *Brit. J. Pharmacol.*, 1958, **13**, 238.
[8] R. F. Collins, M. Davis, N. D. Edge, J. Hill, H. W. Reading, and E. R. Turnbull, *Brit. J. Pharmacol.*, 1959, **14**, 467.

(XVI; R = Ph) was obtained from 2-chloro-5-nitroanisole (XV) and 4-hydroxydiphenyl in dimethylformamide, while the symmetrical diphenoxybenzene (XVI; R = O·C_6H_3(OMe)·NO_2-1,2,4) was likewise prepared using quinol. Conversion of the previously described phthalimide (VII; R = Me, R′ = 5-phthalimidopentyl) [2] into the corresponding 3-azaphthalimide



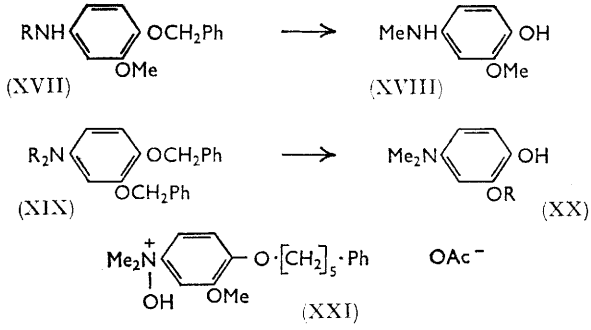
was effected by hydrolysis to the amine with hydrazine and subsequent condensation with quinolinic anhydride.

Removal of the amino-group to other positions is generally dystherapeutic,[7,8] but some isomers were made for comparative tests from 4-methoxy-3-nitrophenol.

The primary amines were converted into *N*-methyl and *N*-hydroxyethyl derivatives by standard methods described in earlier Parts

Among the active amines selected for further biological study was 1-(4-dimethylamino-2-methoxyphenoxy)-5-phenylpentane,[2,3] and several aminocatechol and aminoguaiacol derivatives which could arise by metabolic degradation were synthesised as reference compounds.

4-Aminocatechol [9] and 4-aminoguaiacol [9] were readily obtained by reduction of the nitro-compounds. Synthesis of secondary and tertiary amines required protection of the free hydroxyl groups. For 2-methoxy-4-methylaminophenol (4-methylaminoguaiacol) (XVIII), the 1-benzyl-2-methyl ether of 4-aminocatechol (XVII; R = H) was converted into the ethoxycarbonyl deriv-



ative (XVII; R = CO_2Et) and reduced with lithium aluminium hydride to the secondary amine (XVII; R = Me) and hydrogenolysed.

[9] W. A. Jacobs, M. Heidelberger, and I. P. Rolf, *J. Amer. Chem. Soc.*, 1919, **41**, 458.

For the corresponding tertiary amine (XX; R = Me) 4-aminoguaiacol was methylated and the quaternary iodide was pyrolysed. The preparation of 4-dimethylaminocatechol (XX; R = H) was attempted from the known 3,4-bisbenzyloxyaniline.[10] The corresponding quaternary iodide was pyrolysed to the tertiary amine (XIX; R = Me) and hydrogenolysed, but the product (XX; R = H) could not be isolated pure or adequately characterised.

The *N*-oxide of 1-(4-dimethylamino-2-methoxyphenoxy)-5-phenylpentane was obtained as a crystalline acetate (XXI) by oxidation with perphthalic acid, but was unstable and decomposed on storage.

EXPERIMENTAL

Light petroleum, except where stated, had b. p. 40—60°. Experiments marked (*A*) were by Mr. A. J. Ablewhite, and those marked (*B*) by Mr. S. S. Berg.

Nitro-compounds.—*3,4-Di-n-octyloxynitrobenzene.* Catechol (27·5 g.) in water (50 ml.) under nitrogen was treated with sodium hydroxide (21 g.) in water (50 ml.) and n-octyl bromide (106 g.), and the mixture refluxed for 20 hr. with stirring. 1,2-*Dioctyloxybenzene* was extracted and distilled (35%), b. p. 185—190°/0·35 mm., n_D^{23} 1·484 (Found: C, 79·6; H, 11·8. $C_{22}H_{38}O_2$ requires C, 79·0; H, 11·45%). This (12 g.) in acetic acid (20 ml.) was added slowly to an ice-cooled mixture of concentrated nitric acid (4 ml.) in acetic acid (4 ml.). The solid was collected, washed with water, and recrystallised from methanol to yield the *nitro-compound* (90%), m. p. 59—61° (Found: C, 69·5; H, 9·8; N, 3·7. $C_{22}H_{37}NO_4$ requires C, 69·6; H, 9·8; N, 3·7%). Similarly prepared (Table 1) were 3,4-diethoxy-,[5] 3,4-di-n-butoxy, and 3,4-di-n-pentyloxy-nitrobenzene.

4-Nitro-2-propoxyphenol. 4-Nitro-2-propoxyanisole (31·3 g.) was refluxed with 2N-sodium hydroxide (300 ml.) for 3 days. The hot mixture was filtered, and the filtrate was acidified and extracted with chloroform. The unchanged alkali-insoluble material was further hydrolysed. After three such hydrolyses, the chloroform-soluble products were combined giving 18 g. of crude phenol, used directly for condensation with phthalimidopentyl bromide (Table 1). 12·5 g. of nitro-compound was recovered.

1,2-Bisbenzyloxy-4-nitrobenzene. The disodium salt of 4-nitrocatechol (14 g.) was dissolved in hot dimethylformamide (70 ml.) and benzyl chloride (14·7 ml.) was added. The mixture was heated on the steam-bath for 5 hr., then poured into cold water (*ca.* 500 ml.). The product was filtered off and washed with 2N-aqueous sodium hydroxide and water. Crystallisation from light petroleum (b. p. 60—80°) gave the ether (59%), m. p. 97—99° (lit.,[11] m. p. 97·5°).

1,2-Di(methoxymethoxy)-4-nitrobenzene. The disodium salt of 4-nitrocatechol (42·8 g.) was suspended in dry toluene (1 l.) and chloromethyl methyl ether (84 ml.) was added. The mixture was shaken until the colour disappeared, then washed successively with sodium hydrogen carbonate, sodium hydroxide, and water, dried and evaporated. The residue was triturated with light petroleum, yielding the *bis-methoxymethoxy-derivative* (30 g.), m. p. 58—59° (Found: N, 5·6. $C_{10}H_{13}NO_6$ requires N, 5·8%).

[10] R. H. Hackmann and A. R. Todd, *Biochem. J.*, 1953, **55**, 631.

[11] H. Burton and P. F. G. Praill, *J. Chem. Soc.*, 1951, 522.

2-Methoxymethoxy-4-nitrophenol. The foregoing compound (1·2 g.) was refluxed with N-sodium hydroxide (20 ml.) for 20 hr. The cooled and filtered solution was acidified with acetic acid and the solid product (0·85 g., m. p. 72—73°) was recrystallised from light petroleum (b. p. 100—120°), giving the *phenol* (0·7 g.), m. p. 75—76° (Found: C, 48·25; H, 4·6; N, 6·9. $C_8H_9NO_5$ requires C, 48·25; H, 4·6; N, 7·0%).

1-(2-Hydroxy-4-nitrophenoxy)-5-phthalimidopentane. 1-(2-Methoxymethoxy-4-nitrophenoxy)-5-phthalimidopentane (4 g.) in acetic acid (30 ml.) and water (2 ml.) was treated with 2 drops of concentrated hydrochloric acid, heated for 1 hr. on the steam-bath, and cooled, yielding the hydroxy-compound (3·3 g., 92%), m. p. 138—140°, not depressed by an authentic specimen.[2]

1-(2-Hydroxy-4-nitrophenoxy)-5-phenylpentane. 4-Nitrocatechol (9·1 g.) in 2-ethoxyethanol (50 ml.) was mixed with a solution of potassium hydroxide (3·3 g., 1 equiv.) in water (10 ml.) and 5-phenylpentyl bromide (11·2 g., 1·5 mols.) was added. The mixture was boiled for 24 hr. and added to water (500 ml.). The gum which separated was filtered off, washed with water, and extracted with boiling benzene (200 ml.). The benzene extract was dried by azeotropic distillation with ethanol and concentrated to 50 ml. Addition of light petroleum (150 ml., b. p. 60—80°) to the benzene solution and recrystallisation from cyclohexane (100 ml., charcoal) gave the *nitro-compound* (43%), m. p. 83—84° (Found: C, 67·6; H, 6·7; N, 4·6. $C_{17}H_{19}NO_4$ requires C, 67·8; H, 6·35; N, 4·65%).

1-(3-Hydroxy-4-nitrophenoxy)-5-methoxypentane. A mixture of 4-nitroresorcinol (1·41 g.), 5-methoxypentyl bromide (1·65 g.), 10·4N-potassium hydroxide (0·875 ml.), and 2-ethoxyethanol (5 ml.) was refluxed for 20 hr. and poured into water. The mixture was extracted with chloroform, the extract was washed with warm 2N-sodium hydroxide (the sodium salt separated in the cold), the alkaline solution was acidified with concentrated hydrochloric acid, and the mixture was repeatedly extracted with chloroform. The washed and dried extract was evaporated and the residue triturated with ethanol at −80°. The crystalline product was recrystallised from ethanol at −80°, giving the *nitro-compound* (19%), m. p. 37—38° (Found: C, 56·3; H, 6·65; N, 5·6. $C_{12}H_{17}NO_5$ requires C, 56·5; H, 6·7; N, 5·5%).

1-(3-Hydroxy-4-nitrophenoxy)-5-phthalimidopentane. (*a*) Nitroresorcinol was similarly condensed with phthalimidopentyl bromide. Recrystallised from acetic acid, the *nitro-compound* (46%) had m. p. 164—165° (Found: C, 62·0; H, 5·0; N, 7·6. $C_{19}H_{18}N_2O_6$ requires C, 61·6; H, 4·9; N, 7·6%).

(*b*) 5-Phthalimidopentyl bromide (59 g.) was added to a solution of resorcinol (44 g.) and sodium (4·6 g.) in ethanol (200 ml.) and the mixture was refluxed for 24 hr. The solvent was distilled off and water was added to the residue, which was extracted with chloroform. The washed and dried extract was evaporated, the residue triturated with ether and filtered, and the solid (37%, m. p. 138—140°) recrystallised from toluene, giving 1-m-*hydroxyphenoxy-5-phthalimidopentane*, m. p. 140—142° (Found: C, 70·3; H, 6·2; N, 4·3. $C_{19}H_{19}NO_4$ requires C, 70·1; H, 5·9; N, 4·3%). Nitric acid (*d*, 1·2; 6 ml.) was added rapidly to a solution of 1-*m*-hydroxyphenoxy-5-phthalimidopentane (6 g.) in acetic acid (60 ml.) kept at 50°. After 10 min. water (120 ml.) was added, and the product was filtered off and recrystallised from acetic acid, giving 1-(3-hydroxy-4-nitrophenoxy)-5-phthalimidopentane (2 g.), m. p. 161—162°, not depressed by a specimen prepared as in (*a*).

1-(3-Methoxy-4-nitrophenoxy)-5-phthalimidopentane. A mixture of the foregoing hydroxy-compound (1·55 g.), methyl iodide (3·5 ml.), and anhydrous potassium carbonate (0·6 g.) in acetone (70 ml.) was refluxed for 15 hr., and evaporated. The residue was triturated with aqueous ethanol and the solid filtered off and recrystallised from aqueous acetic acid giving the methoxy-compound (40%), m. p. 122—123°, not depressed by an authentic specimen, m. p. 121—122° (Found: C, 62·5; H, 5·2; N, 7·3. $C_{20}H_{20}N_2O_6$ requires C, 62·5; H, 5·25; N, 7·3%), prepared (47%) from phthalimidopentyl bromide and 3-methoxy-4-nitrophenol.

5-Benzamido-1-(3-hydroxy-4-nitrophenoxy)pentane. A mixture of 1-(3-hydroxy-4-nitrophenoxy)-5-phthalimidopentane (5·6 g.), hydrazine hydrate (80%, 3 ml.), and ethanol (20 ml.) was refluxed for 3 hr., cooled, treated with aqueous hydrochloric acid, and concentrated to remove ethanol. The residue was diluted with water, filtered hot, made alkaline with ammonia, and cooled. The amine (96%), m. p. 205—207° (decomp.), after recrystallisation had m. p. 217—218°. Treatment with benzoyl chloride in pyridine afforded the *benzamide* (26%), m. p. 128—130° (from acetic acid) (Found: C, 62·8; H, 5·8; N, 8·0. $C_{18}H_{20}N_2O_5$ requires C, 62·8; H, 5·9; N, 8·1%).

4-(2-Methoxy-4-nitrophenoxy)biphenyl. To the potassium salt of 4-hydroxybiphenyl (25·2 g.) in dimethylformamide (100 ml.) was added 2-chloro-5-nitroanisole (27·8 g.). The mixture was refluxed for 5 hr., allowed to cool, and diluted with dilute aqueous potassium hydroxide. The product was collected and recrystallised from ethanol. The nitro-compound (58%), m. p. 110—113°, was reduced directly to the amine.

1,4-Di-(2-methoxy-4-nitrophenoxy)benzene. Quinol (11·8 g.) was dissolved in aqueous potassium hydroxide (1·75N, 125 ml.) and water was removed *in vacuo*. The dipotassium salt was dissolved in dimethylformamide (80 ml.), 2-chloro-5-nitroanisole (40 g.) was added, and the solution was refluxed for 7 hr. The nitro-compound (40%), m. p. 226—230°, was obtained on pouring the solution into water and was reduced directly.

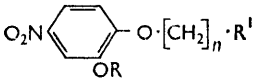
2-Phenyl-2-[4-(2-methoxy-4-nitrophenoxy)butyl]-1,3-dithiolan. To boron trifluoride–ether complex (20 ml.), previously cooled to −80°, was added with stirring 1-(2-methoxy-4-nitrophenoxy)-4-benzoylbutane (10 g.) followed by ethane-1,2-dithiol (2·54 ml.). The mixture was allowed to reach room temperature, stirred for a further 2 hr., kept at room temperature overnight, and then poured into cold, saturated aqueous sodium hydrogen carbonate. The product was extracted into ether, which was dried and concentrated. The residue, crystallised from ethanol, gave the *ditholan* (83%), m. p. 94—96° (Found: N, 3·2; S, 16·1. $C_{20}H_{23}NO_4S_2$ requires N, 3·5; S, 15·8%).

1-(2-Methoxy-4-nitrophenoxy)-5-(3-azaphthalimido)pentane. A solution of 5-(2-methoxy-4-nitrophenoxy)pentylamine [2] (7·6 g.) in acetic acid (60 ml.) was treated with quinolinic anhydride (4·5 g.) and refluxed for 10 min. Acetic anhydride (5 ml.) was added and the solution was refluxed for a further 1 hr., then diluted with acetic acid (60 ml.), and cooled. The *nitro-compound* crystallised and was collected (55%), m. p. 157—158° (Found: C, 59·5; H, 5·9; N, 10·7. $C_{19}H_{19}N_3O_6$ requires C, 59·2; H, 5·0; N, 10·9%).

The following compounds, and those in Table 1, were

TABLE 1

2-Substituted nitrophenyl ethers

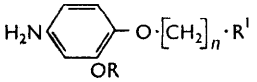


R	n	R¹	Yield (%)	Solvent [a]	M. p.	Formula	Found (%) C	Found (%) H	Found (%) N	Required (%) C	Required (%) H	Required (%) N
Me	8	NH·COPh	68	EtOH–H_2O	102—104°	$C_{22}H_{28}N_2O_5$			6·7			7·0
Et	1	Me	90	EtOH	72—74	$C_{10}H_{13}NO_4$			6·6			6·6
Et	5	Phthalimido	60	AcOH	132—134	$C_{21}H_{22}N_2O_6$	63·4	5·6	6·9	63·3	5·6	7·0
Et	7	Me	23	EtOH	50—51	$C_{16}H_{25}NO_4$ [b]						
Pr^n	5	Phthalimido	60	AcOH	129—130	$C_{22}H_{24}N_2O_6$	63·8	5·9	7·0	64·1	5·9	6·8
Bu^n	3	Me	72	MeOH	51—52	$C_{14}H_{21}NO_4$	63·2	7·95	5·35	62·9	7·9	5·25
n-C_5H_{11}	4	Me	55	MeOH	43—45	$C_{16}H_{25}NO_4$ [b]						
CH_2Ph	5	Phthalimido	61 (also 85 [c])	AcOH	149—150	$C_{26}H_{24}N_2O_6$	67·9	5·5	5·9	67·8	5·3	6·1
CO_2Et	5	Phthalimido	88 [c]	EtOH	106—107	$C_{22}H_{22}N_2O_8$	59·7	5·05	6·2	59·7	5·0	6·3
CH_2OMe	5	Phthalimido	75	EtOH	111—113	$C_{21}H_{22}N_2O_7$	60·9	5·45	6·9	60·8	5·3	6·8

[a] Solvent for crystn. [b] Reduced directly to the amine. [c] From 1-(2-hydroxy-4-nitrophenoxy)-5-phthalimidopentane.

TABLE 2

2-Substituted aminophenyl ethers

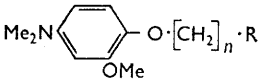


R	n	R¹	Derivative	Yield	M. p.	Solvent [a]	Formula	Found (%) C	Found (%) H	Found (%) N	Found (%) S	Required (%) C	Required (%) H	Required (%) N	Required (%) S
H	5	Phthalimido	Me·SO_3H	73 [b,c]	180—182°	EtOH–Et_2O	$C_{19}H_{20}N_2O_4,CH_4O_3S$			6·45	7·5			6·4	7·3
Me	0	C_6H_4Ph-*p*	Base	88 [c]	112—114	EtOH	$C_{19}H_{17}NO_2$	78·4	6·2	4·7		78·4	5·9	4·8	
Me	4	$CPh(SCH_2)_2$	Base	82·5 [d]	107—109	EtOH	$C_{20}H_{25}NO_2S_2$			3·7	17·0			3·7	17·1
Me	5	3-Azaphthalimido	Base	55 [c]	118—122	NMe_2·CHO–H_2O	$C_{19}H_{21}N_3O_4$			12·0				11·8	
Me	8	NH·COPh	Base	91 [c]	62—65	EtOH–H_2O	$C_{22}H_{30}N_2O_3$	71·3	8·2	7·6		71·3	8·2	7·6	
Et	1	Me	HCl	66 [c]	230—235	EtOH–Et_2O	$C_{10}H_{15}NO_2$,HCl			6·4	16·45 [e]			6·4	16·3 [e]
Et	5	Phthalimido	Base	86 [c]	90	EtOH	$C_{21}H_{24}N_2O_4$	68·4	6·7	7·65		68·4	6·6	7·6	
Et	7	Me	Diptolate [f]	31 [c]	155—159	EtOAc	$C_{16}H_{27}NO_2,C_{20}H_{18}O_8$	66·2	6·9	2·2		66·35	7·0	2·2	
Pr^n	5	Phthalimido	Base	95 [c]	108—109	EtOH	$C_{22}H_{26}N_2O_4$	69·0	7·0	7·2		69·1	6·8	7·3	
Bu^n	3	Me	Base	40 [c]	*g*		$C_{14}H_{23}NO_2$	70·2	9·9	6·1		70·8	9·8	5·9	
			Diptolate [f]		155—157	EtOAc	$C_{14}H_{23}NO_2,C_{20}H_{18}O_8$	65·35	6·9	2·25		65·5	6·6	2·25	
n-C_5H_{11}	4	Me	Diptolate [f]	56 [c]	148—150	EtOAc	$C_{16}H_{27}NO_2,C_{20}H_{18}O_8$	66·0	6·7	2·5		66·4	6·95	2·2	
n-C_8H_{17}	7	Me	Base	85 [c]	*ca.* 30 [h]		$C_{22}H_{39}NO_2$	75·8	11·2	4·05		75·6	11·25	4·0	
CH_2Ph	5	Phthalimido	Me·SO_3H	59 [c]	169—170	EtOH–Et_2O	$C_{26}H_{26}N_2O_4,CH_4O_3S$			5·25	6·2			5·3	6·1
CO_2Et	5	Phthalimido	Base	82 [c]	114—115	EtOH	$C_{22}H_{24}N_2O_6$	63·8	5·9	6·7		64·1	5·9	6·8	
CH_2OMe	5	Phthalimido	Base	87 [c]	89—90	EtOH	$C_{21}H_{24}N_2O_5$	65·5	6·55	7·5		65·6	6·3	7·3	

[a] Solvent for crystn. [b] Nitro compound described by Collins and Davis.[2] [c] Catalytic reduction. [d] Reduction with sodium sulphide. [e] Halogen analysis. M. Heidelberger and W. A. Jacobs (*J. Amer. Chem. Soc.*, 1919, **41**, 1450) give m. p. 47·5—48·5° for the base. [f] Diptolate = di-*p*-toluoyl-D-tartrate. [g] B. p. 120—125°/0·08 mm. [h] G. K. Hughes and F. Lions (*J. Proc. Roy. Soc. New South Wales*, 1938, **71**, 103) gave b. p. 190—200°/0·1 mm.

TABLE 3

4-Dimethylamino-2-methoxyphenyl ethers

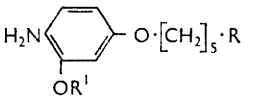


							Found (%)		Calculated (%)	
n	R	Derivative	Yield (%)	M. p.	Solvent [a]	Formula	N	S	N	S
2	Me	Me·SO_3H	67	68—71°	Et_2O	$C_{12}H_{19}NO_2,CH_4O_3S$	4·2	10·7	4·6	10·5
3	Me	Me·SO_3H	38	105—108	Et_2O	$C_{13}H_{21}NO_2,CH_4O_3S$	4·2	10·4	4·4	10·0
4	Me	Me·SO_3H	81	100—102	Et_2O	$C_{14}H_{23}NO_2,CH_4O_3S$	4·35	9·5	4·2	9·6
5	Me	Me·SO_3H	83	106—108	Et_2O	$C_{15}H_{25}NO_2,CH_4O_3S$	3·9	9·4	4·0	9·2
6	Me	Me·SO_3H	86	105—107·5	Et_2O	$C_{16}H_{27}NO_2,CH_4O_3S$	4·1	8·8	3·9	8·9
8	Me	Me·SO_3H	56	92—95	Et_2O	$C_{18}H_{31}NO_2,CH_4O_3S$	4·0	8·1	3·6	8·2
3	Ph	Base	80	43—45	EtOH	$C_{18}H_{23}NO_2$ [b]	4·95		4·9	
4	Ph	Me·SO_3H	51	98—100	Et_2O–Pet[c]	$C_{19}H_{25}NO_2,CH_4O_3S$	3·5	8·6	3·55	8·1
4	CHPh·OH	HCl	53 [d]	158—161	EtOH–Et_2O	$C_{20}H_{27}NO_2,HCl$	4·1	9·95 [e]	3·8	9·7 [e]
5	NH·COPh	Base	68	82—84	EtOH	$C_{21}H_{28}N_2O_3$	7·8		7·9	
		MeI	75	192—195	H_2O	$C_{22}H_{31}IN_2O_3$		26·2 [e]		25·5 [e]

[a] Solvent for crystn. [b] Found: C, 76·0; H, 8·2. Required: C, 75·8; H, 8·1%. [c] Pet = light petroleum. [d] By catalytic reduction of 1-(4-dimethylamino-2-methoxyphenoxy)-5-phenylpentan-5-one.[2] [e] Halogen analysis.

TABLE 4

3-Substituted aminophenyl ethers



							Found (%)			Required (%)		
R^1	R	Derivative	Yield (%)	M. p.	Solvent [a]	Formula	C	H	N	C	H	N
H	OMe	Me·SO_3H	60	122—123°	EtOH–Et_2O	$C_{12}H_{19}NO_3,CH_4O_3S$			4·3			4·35
H	NH_2	2 HCl	32	210—215 [c]	EtOH–Et_2O	$C_{11}H_{18}N_2O_2,2HCl$ [d]			9·9			9·9
H	Phthalimido	Base	71	150—152	EtOH	$C_{19}H_{20}N_2O_4$	66·7	5·9	8·1	67·2	5·9	8·2
Me	Phthalimido	Base	35	105—106	MeOH	$C_{20}H_{22}N_2O_4$	68·0	6·6	7·8	67·8	6·3	7·9
H	NH·COPh	Base	77	101—103	EtOH–H_2O	$C_{18}H_{22}N_2O_3$	68·95	7·2	8·9	68·7	7·0	8·9

[a] Solvent for crystn. [b] Found: S, 9·9. Required: S, 10·0%. [c] With decomp. [d] Found: Cl, 25·1. Required: Cl, 25·0%.

prepared (except where stated) by condensation of the substituted nitrophenol (as sodium or potassium salt) with the appropriate substituted alkyl halide, usually in boiling 2-ethoxyethanol:[2] 1-(5-*methoxy*-2-*nitrophenoxy*)-5-*phthalimidopentane* (15%), m. p. 119—120° (from ethanol) (Found: C, 62·2; H, 5·4; N, 7·3. $C_{20}H_{20}N_2O_6$ requires C, 62·5; H, 5·25; N, 7·3%); 1-(6-*chloro*-2-*methoxy*-4-*nitrophenoxy*)-*n*-*octane* (84%), m. p. 38·5—39·5° (from ethanol) (Found: N, 4·4; Cl, 11·2. $C_{15}H_{22}ClNO_4$ requires N, 4·4; Cl, 11·2%); 1-(4-methoxy-3-nitrophenoxy)-n-butane (92%), an oil, which was reduced directly; and 1-(4-methoxy-3-nitrophenoxy)-n-octane (86%), an oil, which was reduced directly.

Amines.—4-*Aminoguaiacol hydrochloride* (*A*). 4-Nitroguaiacol (7 g.) was catalytically hydrogenated in dimethylformamide and the filtered solution acidified with concentrated hydrochloric acid and evaporated. The residue crystallised from ethanol–ether to give the *salt* (69%), m. p. *ca.* 340° (Found: N, 8·3; Cl, 20·1. $C_7H_9NO_2$,HCl requires N, 8·0; Cl, 20·2%). The base has been reported.[9]

4-*Dimethylaminoguaiacol methiodide* (*A*). 3-Methoxy-4-methoxymethoxyaniline [2] was methylated with methyl iodide and sodium carbonate in ethanol. The methoxymethyl group was lost and the product after recrystallisation from ethanol was dimethylaminoguaiacol methiodide (78%), m. p. 215—216° (Found: N, 4·3; I, 41·2. Calc. for $C_{10}H_{16}INO_2$: N, 4·5; I, 41·1%). 4-*Dimethylaminoguaiacol*, prepared by the pyrolysis (water pump pressure) of the foregoing methiodide, darkened rapidly in air and had m. p. 71—74° (Found: C, 64·2; H, 7·5; N, 8·3. $C_9H_{13}NO_2$ requires C, 64·6; H, 7·8; N, 8·4%). The hydrochloride had m. p. 174—176°.

4-*Aminocatechol hydrochloride* (*A*). 1,2-Di(methoxymethoxy)-4-nitrobenzene was catalytically reduced to the amine. This was treated with concentrated hydrochloric acid, the acid was evaporated off, and the resiue crystallised from ethanol–ether to give the *hydrochloride* (44%), m. p. 224—227° (Found: C, 44·3; H, 5·1. $C_6H_7NO_2$,HCl requires C, 44·6; H, 5·0%). The base and hydrobromide have been reported.[9]

1,2-*Bisbenzyloxy*-4-*dimethylaminobenzene methiodide* (*A*). 3,4-Bisbenzyloxyaniline [10] (2·6 g.) (prepared by catalytic hydrogenation of 1,2-bisbenzyloxy-4-nitrobenzene), methyl iodide (4·8 ml.), sodium carbonate (0·9 g.), and ethanol (39 ml.) were refluxed together overnight and cooled. The *methiodide* (84%), recrystallised from ethanol, had m. p. 183—184° (Found: I, 26·9. $C_{23}H_{26}INO_2$ requires I, 26·7%). The methocarbonate has been reported.[12]

4-*Ethoxycarbonylamino*-2-*methoxyphenyl benzyl ether*. The benzyl ether of 4-nitroguaiacol (prepared as for 4-nitrocatechol dibenzyl ether) was catalytically reduced to the amine; the latter (2·3 g.) was dissolved in dry acetone (10 ml.) and dry pyridine (0·78 ml.) was added. Ethyl chloroformate (1·0 ml.) was then run in and the mixture refluxed on the steam-bath for 30 min. The acetone was evaporated off and the residue stirred with water. Extraction with ethyl acetate and recrystallisation from benzene–light petroleum (b. p. 60—80°) gave the *urethane*, m. p. 110—113° (Found: N, 4·7. $C_{17}H_{19}NO_4$ requires N, 4·65%).

2-*Methoxy*-4-*methylaminophenyl benzyl ether*. 4-Ethoxycarbonylamino-2-methoxyphenyl benzyl ether (1 g.) was dissolved in dry tetrahydrofuran and the solution added dropwise to a stirred solution of lithium aluminium hydride (0·3 g.) in dry tetrahydrofuran (10 ml.). The mixture was stirred under reflux for 45 min. and then cooled. Ethyl acetate (10 ml.) was added dropwise with stirring, followed by water (*ca.* 10 ml.). The precipitate was filtered off and washed with ethyl acetate and with water, and the combined filtrate and washings extracted with chloroform. The chloroform extract was dried and evaporated to give the methylamino-compound as a brown oil (400 mg.).

4-*Methylaminoguaiacol hydrochloride* (*A*). The foregoing benzyl ether was hydrogenolysed with palladised charcoal. The mixture was filtered under nitrogen, ethereal hydrogen chloride was added to the filtrate, and the solution evaporated. The residue was triturated with sodium-dried ether and recrystallised from dry ethanol–dry ether to give the *amine hydrochloride* (150 mg., 55%), m. p. 171—172° (Found: Cl, 18·3. $C_8H_{11}NO_2$,HCl requires Cl, 18·7%).

1-(4-*Amino*-2-*hydroxyphenoxy*)-5-*phenylpentane hydrochloride* (*B*). 1-(2-Hydroxy-4-nitrophenoxy)-5-phenylpentane was dissolved in hot 50% aqueous acetic acid (20 ml.). Reduced iron (0·5 g.) was added portionwise. When the addition was completed (*ca.* 8 min.) the mixture was heated a further 10 min., filtered, and treated with concentrated hydrochloric acid (10 ml.). The product crystallised from the ice-cooled solution and was washed with water–concentrated hydrochloric acid (1 : 1). It was recrystallised from ethanol–concentrated hydrochloric acid, washed with water, and dried to give the *amine hydrochloride* (59%), m. p. 191—194° (decomp.), darkening above 170° (Found: Cl, 11·7; N, 4·6. $C_{17}H_{21}NO_{21}$HCl requires Cl, 11·5; N, 4·55%).

1-(4-*Acetamido*-2-*methoxyphenoxy*)-5-*hydroxy*-5-*phenylpentane*. 1-(4-Amino-2-methoxyphenoxy)-5-hydroxy-5-phenylpentane [2] was acetylated with acetic anhydride in dry dioxan, giving the *acyl derivative* (48%), m. p. 104—105° (Found: C, 69·5; H, 7·3; N, 4·0. $C_{20}H_{25}NO_4$ requires C, 69·9; H, 7·2; N, 4·1%).

1-(4-*Dimethylamino*-2-*methoxyphenoxy*)-5-*phenylpentane* N-*oxide acetate*. To a solution of 1-(4-dimethylamino-2-methoxyphenoxy)-5-phenylpentane (20 g.) in sodium-dried ether (250 ml.) was added dropwise monoperphthalic acid in ether (127 ml., 10·1% w/v) with stirring during ½ hr., the temperature being kept at 16—19° by an ice-bath. The mixture was stirred for a further 3½ hr. at room temperature. The product separated as an oil which slowly hardened, the ether was decanted and the solid was dissolved in 2N-aqueous sodium carbonate (500 ml.). This solution was extracted three times with chloroform (500, 100, and 100 ml.). The combined chloroform extracts were adjusted to pH 6 with acetic acid, then washed with water and dried, and the chloroform was distilled off *in vacuo* at <40°. The residue was dissolved in a little ethyl acetate and the solution was treated with dry ether. The N-*oxide acetate* (65%) crystallised on cooling and was collected and washed with dry ether. It had m. p. 69—74° (Found: C, 67·0; H, 7·9; N, 3·6; acetyl, 10·8. $C_{20}H_{27}NO_3$,$C_2H_4O_2$ requires C, 67·8; H, 8·0; N, 3·6; acetyl, 11·05%) but on storing in a desiccator over phosphoric oxide for about 1 month it decomposed to an almost black tar with a fishy odour.

1-(4-*Amino*-2-*methoxyphenoxy*)-5-o-*carboxybenzamidopentane*. 1-(4-Amino-2-methoxyphenoxy)-5-phthalimidopentane [2] (8·8 g.) was suspended in water (37·5 ml.) and 2N-aqueous sodium hydroxide (12·5 ml.) was added. The mixture was heated on the steam-bath for 15 min., filtered,

[12] J. Iwao and M. Kawazu, *J. Pharm. Soc. Japan*, 1956, **76**, 811.

cooled, and treated with the calculated amount of 2N-aqueous hydrochloric acid; the *acid* (80%) separated and had m. p. 142—145° (Found: C, 64·5; H, 6·7; N, 7·6. $C_{20}H_{24}N_2O_5$ requires C, 64·5; H, 6·45; N, 7·5%).

The following amines, and those in Tables 2 and 4, were obtained (except where stated) by catalytic reduction of the nitro-compounds: 1-(4-*Amino*-6-*chloro*-2-*methoxyphenoxy*)-*n*-*octane* (58%), m. p. 37—39° (from aqueous methanol) (Found: Cl, 12·4; N, 5·05. $C_{15}H_{24}ClNO_2$ requires Cl, 12·4; N, 4·9%); 1-(3-*amino*-4-*methoxyphenoxy*)-*n*-*butane methanesulphonate* (53%), m. p. 138—140° (from ethanol–ether) (Found: N, 5·1; S, 11·1. $C_{11}H_{17}NO_2,CH_4O_3S$ requires N, 4·8; S, 11·0%); 1-(3-*amino*-4-*methoxyphenoxy*)-*n*-*octane methanesulphonate* (96%), m. p. 95·5—100° (from ethanol–ether) (Found: N, 4·1; S, 8·9. $C_{15}H_{25}NO_2,CH_4O_3S$ requires N, 4·0; S, 9·2%); 1,4-*di*-(4-*amino*-2-*methoxyphenoxy*)*benzene* (50%), m. p. 179—184° (from chlorobenzene) (Found: C, 68·4; H, 5·6; N, 7·9. $C_{20}H_{20}N_2O_4$ requires C, 68·1; H, 5·7; N, 8·0%).

The *NN*-dimethyl compounds of Table 3 were obtained by quaternisation of the primary amine with methyl iodide and subsequent pyrolysis.[13]

1-(4-*Chloroethoxycarbonamido*-2-*methoxyphenoxy*)*butane*. A solution of 1-(4-amino-2-methoxyphenoxy)butane [2] (25 g.) and sodium acetate (28 g.) in acetic acid (100 ml.) was treated with chloroethyl chloroformate (35·4 ml.). An exothermic reaction took place and the product crystallised on standing and cooling. After recrystallisation from acetic acid, the *ester* (85%) had m. p. 77—78° (Found: Cl, 12·0; N, 4·6. $C_{14}H_{20}ClNO_4$ requires Cl, 11·8; N, 4·6%). Similarly prepared was 5-*benzamido*-1-(4-*chloroethoxycarbonamido*-2-*methoxyphenoxy*)*pentane* (69%), m. p. 132·5—134° (from aqueous acetic acid) (Found: Cl, 8·0; N, 6·2. $C_{22}H_{27}ClN_2O_5$ requires Cl, 8·15; N, 6·4%).

1-(4-2′-*Hydroxyethylamino*-2-*methoxyphenoxy*)*butane*. 1-(4-Chloroethoxycarbonamido-2-methoxyphenoxy)butane (28 g.) was suspended in a mixture of 2-ethoxyethanol (70 ml.), ethanol (70 ml.), and a solution of sodium hydroxide (20 g.) in water (35 ml.). The mixture was refluxed for 10 min., cooled, and diluted with water. The product (19·5%) crystallised from aqueous 2-ethoxyethanol and had m. p. 49—51° (Found: C, 65·3; H, 9·0; N, 5·7. $C_{13}H_{21}NO_3$ requires C, 65·3; H, 8·9; N, 5·85%).

Similarly prepared was 5-*benzamido*-1-(4-2′-*hydroxyethylamino*-2-*methoxyphenoxy*)*pentane* (74%), m. p. 102—103° (from aqueous ethanol) (Found: N, 7·4. $C_{21}H_{28}N_2O_4$ requires N, 7·5%).

1-[4-*Bis*-(2-*hydroxyethyl*)*amino*-2-*methoxyphenoxy*]*butane*. 1-(4-Amino-2-methoxyphenoxy)butane [2] (25 g.), ethylene chlorohydrin (21 ml.), and calcium carbonate (14 g.) were suspended in water (150 ml.) and the mixture was refluxed for 18 hr. The product was then extracted into chloroform, which was dried and concentrated. Crystallisation from benzene afforded the *amine* (38%), m. p. 69—71° (Found: C, 63·7; H, 8·9; N, 5·0. $C_{15}H_{25}NO_4$ requires C, 63·6; H, 8·9; N, 4·9%).

Similarly prepared was 5-*benzamido*-1-[4-*bis*-(2-*hydroxyethyl*)*amino*-2-*methoxyphenoxy*]*pentane* (69%), m. p. 80—82° (from benzene) (Found: N, 6·5. $C_{23}H_{32}N_2O_5$ requires N, 6·7%).

1-(2-*Methoxy*-4-p-*nitrobenzamidophenoxy*)-*n*-*octane*. A solution of 1-(4-amino-2-methoxyphenoxy)-n-octane (20 g.) and sodium acetate (10 g.) in acetic acid (100 ml.) was treated with *p*-nitrobenzoyl chloride (14·3 g.) and gently warmed until a solution was obtained. On standing and cooling the product separated and was recrystallised from ethanol. The *nitrobenzamide* (39%) had m. p. 146—150° (Found: C, 65·9; H, 7·3; N, 6·75. $C_{22}H_{28}N_2O_5$ requires C, 66·0; H, 7·05; N, 7·0%). Catalytic reduction afforded 1-(4-p-*aminobenzamido*-2-*methoxyphenoxy*)-*n*-*octane* (75%), m. p. 122—123° (from benzene) (Found: C, 71·7; H, 8·35; N, 7·5. $C_{22}H_{30}N_2O_3$ requires C, 71·2; H, 8·2; N, 7·6%).

1-(4-*Acetamido*-2-*methoxyphenoxy*)-5-*phenylpentane* (47%), m. p. 83—85° (from light petroleum) (Found: N, 4·5. $C_{20}H_{25}NO_3$ requires N, 4·3%), and 1-(4-*acetamido*-2-*methoxyphenoxy*)-5-*phthalimidopentane* (73%), m. p. 150—153° (from ethanol) (Found: N, 6·9. $C_{22}H_{24}N_2O_5$ requires N, 7·1%) were prepared by acetylation of the corresponding amines.[2]

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[13] J. N. Ashley, R. F. Collins, M. Davis, and N. E. Sirett, Part I, *J. Chem Soc.*, 1958, 3298; Part III, *ibid.*, 1959, 3880.