The Chemotherapy of Schistosomiasis. Part VIII.[1] 2-Carboxy- and 2-Carbamoyl-4-aminophenyl Ethers

By R. F. Collins and M. Davis

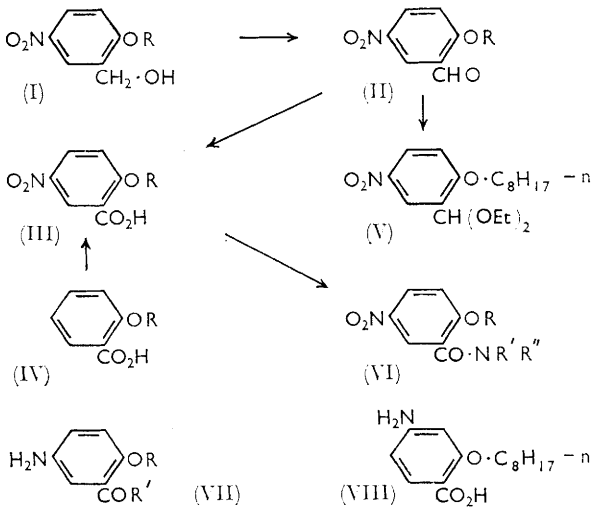
Synthetic work in the series of schistosomicidal *p*-aminophenyl ethers has been continued with the introduction of carboxy-, carbamoyl-, alkylsulphonyl-, and some miscellaneous nuclear substituents for structure–activity studies.

FOLLOWING the discovery that the insertion of a methoxy-group *ortho* to the ether linkage was beneficial in a series of schistosomicidal *p*-aminophenyl ethers,[2] alkyl and substituted alkyl groups were likewise introduced.[1] Extension of the synthetic work to *p*-aminophenyl ethers bearing carboxy-, carbamoyl-, methylsulphonyl-, and several other substituents is now recorded. The biological results are reported separately.[3]

The 2-hydroxymethyl-4-nitrophenyl ethers (I) from earlier work [1] were readily oxidised with chromic acid to the 2-carboxy-ethers (III), alternatively obtained by nitration of the *o*-alkoxybenzoic acid (IV). Use of a limited quantity of chromic acid led also to the aldehyde (II; R = n-C_8H_{17}), which with orthoformic ester yielded the acetal (V). The acids (III) were converted into acid chlorides and thence into a number of aliphatic, aromatic, and heterocyclic amides (VI).

An amino-group *para* to the ether linkage is essential for anthelmintic activity in the simple aminophenyl ethers,[4] and a *meta* isomer (VIII) of an active compound (VII; R = n-C_8H_{17}, R′ = OH) was therefore made to confirm that this relationship held when a carboxyl group was present. It was prepared from ethyl *p*-acetamidosalicylate [5] by alkylation with n-octyl bromide and subsequent hydrolysis of the ester-amide.

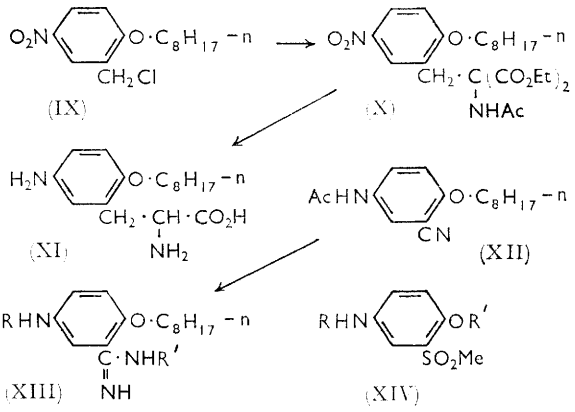
5-Nitro-2-octyloxybenzyl chloride [1] (IX) was utilised for the synthesis of a phenylalanine derivative (XI) by condensation with acetamidomalonic ester, hydrolysis of



the intermediate (XI), and reduction. For the amidine (XIII; R = R′ = H), 2-cyano-4-nitrophenol was condensed with octyl bromide and the nitro-ether was

[1] Part VII, R. F. Collins and M. Davis, *J. Chem. Soc.* (*C*), 1966, 873.
[2] Part IV, R. F. Collins and M. Davis, *J. Chem. Soc.*, 1961, 1863; Part VI, *idem.*, *J. Chem. Soc.* (*C*), 1966, 366.
[3] R. F. Collins, (Mrs.) V. A. Cox, M. Davis, N. D. Edge, J. Hill, K. F. Rivett, and (Miss) M. A. Rust, in preparation.
[4] R. F. Collins, M. Davis, N. D. Edge, and J. Hill, *Brit. J. Pharmacol.*, 1958, **13**, 238.
[5] W. Grimme and H. Schmitz, *Chem. Ber.*, 1954, **87**, 179.

reduced and acetylated. Treatment of the product (XII) with hydroxylamine afforded the amidoxime (XIII; R = Ac, R′ = OH) which was hydrogenated and hydrolysed to the amidine.



The preparation of 5-acetamido-2-methoxybenzenesulphinic acid from *p*-acetamidoanisole was recorded in Part VII,[1] and methylation gave the sulphone (XIV; R = Ac, R′ = Me). Replacement of the methoxy-group by the n-octyloxy-group (which was more potent chemotherapeutically) was effected by hydrolysis with 50% aqueous hydrobromic acid, reacetylation of the aminophenol (XIV; R = R′ = H) to protect the amino-group, and alkylation with octyl bromide. Hydrolysis of the amide (XIV; R = Ac, R′ = n-C_8H_{17}) then gave the desired base (XIV; R = H, R′ = n-C_8H_{17}).

EXPERIMENTAL

Except where stated, light petroleum had b. p. 40—60°.

Nitro-compounds.—The carboxylic acids listed in Table 1 were prepared by one of the following methods.

1-(2-*Carboxy*-4-*nitrophenoxy*)-*n-octane* (*Method A*). 1-(2-Hydroxymethyl-4-nitrophenoxy)-n-octane [1] (108·5 g.) in acetone (2 l.) was oxidised by dropwise addition at room temperature of a solution of chromium trioxide (43·5 g.) in water (220 ml.) and sulphuric acid (38 ml.). After addition the mixture was stirred for 30 min. and poured into water (4 l.) and the solid was collected, washed with 2N-sulphuric acid, and partially dissolved in potassium hydrogen carbonate solution. The insoluble residue was recrystallised from methanol and yielded 1-(2-*formyl*-4-*nitrophenoxy*)-*n-octane* (24 g., 22%), m. p. 47—50° (Found: C, 64·2; H, 7·8; N, 5·1. $C_{15}H_{21}NO_4$ requires C, 64·5; H, 7·6; N, 5·0%).

The alkaline filtrate was acidified and the precipitate was collected and recrystallised from aqueous ethanol to yield the required *acid* (79 g., 69%), m. p. 100—102° (Found: C, 60·8; H, 7·4; N, 4·8. $C_{15}H_{21}NO_5$ requires C, 61·1; H, 7·2; N, 4·7%). Esterification with methanolic hydrogen chloride gave the methyl ester, which was used directly. 1-(2-*Formyl*-4-*nitrophenoxy*)-*n-hexane*, m. p. 66—70° (Found: C, 62·4; H, 7·0; N, 5·6. $C_{13}H_{17}NO_4$ requires C, 61·2; H, 6·8; N, 5·6%) was similarly obtained.

1-(2-*Carboxy*-4-*nitrophenoxy*)-*n-heptane* (*Method B*). A solution of 2-heptyloxybenzoic acid (49 g.) in acetic acid (147 ml.) was added to fuming nitric acid (490 ml.) with stirring at 0°. After 20 min. the mixture was poured into water and the product collected, and crystallised from acetic acid, giving the *acid* (54%), m. p. 93—95° (Found: C, 60·0; H, 6·9; N, 5·0. $C_{14}H_{19}NO_5$ requires C, 59·8; H, 6·8; N, 5·0%).

1-(2-*Carbamoyl*-4-*nitrophenoxy*)-*n-hexane*. 1-(2-Carboxy-4-nitrophenoxy)-n-hexane (15 g.) was refluxed with thionyl chloride (45 ml.) for 1 hr. and excess of reagent removed. The residue in benzene was poured into aqueous ammonia (*d* 0·880, 250 ml.) and ice (200 g.). The product was recrystallised twice from ethanol, giving the *amide* (78%), m. p. 117—122° (Found: N, 10·6. $C_{13}H_{18}N_2O_4$ requires N, 10·5%). The other primary *amides* in Table 3 were prepared similarly. The substituted amides were prepared by adding the acid chloride to a solution of the amine in dry benzene or pyridine.

N-(5-*Nitro*-2-*octyloxybenzoyl*)*aminoacetic acid*. 1-(2-Carboxy-4-nitrophenoxy)-n-octane (20 g.) was converted with thionyl chloride into the acid chloride which was added slowly to a solution of glycine (10·1 g.) in 2N-aqueous sodium hydroxide (200 ml.), with vigorous shaking. The mixture was allowed to stand for 10 min., diluted to 1 l., filtered, and acidified with hydrochloric acid. The product, which separated overnight as a gum which slowly crystallised, was collected and recrystallised from methanol, giving the *amide* (65%), m. p. 119—122° (Found: C, 58·1; H, 6·8; N, 7·9. $C_{17}H_{24}N_2O_6$ requires C, 57·9; H, 6·9; N, 7·95%).

1-(2-*Diethoxymethyl*-4-*nitrophenoxy*)-*n-octane*. 1-(2-Formyl-4-nitrophenoxy)-n-octane (17·4 g.) in ethanol (70 ml.) was treated with ethyl orthoformate (9·3 g.) and concentrated hydrochloric acid (0·04 ml.). After 24 hr. the solution was made just alkaline with ethanolic potassium hydroxide, concentrated, and extracted with ether. The dried extract was distilled to give the *acetal* (72%), b. p. 170—172°/0·04 mm. (Found: C, 64·4; H, 8·7; N, 4·1. $C_{19}H_{31}NO_5$ requires C, 64·6; H, 8·8; N, 4·0%).

Diethyl acetamido-(5-*nitro*-2-*n-octyloxybenzyl*)*malonate*. Diethyl acetamidomalonate (12 g.) and 5-nitro-2-n-octyloxybenzyl chloride [1] (15 g.) were added successively to a cooled, stirred solution of sodium (1·15 g.) in dry ethanol (100 ml.). After 30 min., the mixture was refluxed for 2 hr., diluted with water, and extracted with ether. Evaporation of the extract and crystallisation of the residue from light petroleum yielded the ester (35%), m. p. 69—71° (Found: C, 60·6; H, 7·9; N, 6·2. $C_{24}H_{36}N_2O_8$ requires C, 60·0; H, 7·55; N, 5·8%).

1-[2-(2-*Amino*-2-*carboxyethyl*)-4-*nitrophenoxy*]-*n-octane* [β-(5-*nitro*-2-*octyloxyphenyl*)-α-*alanine*]. The foregoing ester (8 g.) was refluxed with concentrated hydrochloric acid (150 ml.) for 44 hr. The mixture was allowed to cool and the hydrochloride of the product was filtered off, dissolved in water, and treated with aqueous sodium acetate solution. The product was recrystallised from aqueous methanol, yielding the *amino-acid* (80%), m. p. 205—207° (decomp.) (Found: C, 60·1; H, 7·4; N, 8·2. $C_{17}H_{26}N_2O_5$ requires C, 60·3; H, 7·7; N, 8·3%).

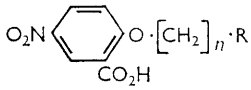
The *compounds* of Table 5 were prepared by condensation of the sodium or potassium salt of the phenol with the appropriate halide.

Amines.—Except where indicated, the amines in Tables 2, 4, and 6 were prepared by catalytic reduction of the corresponding nitro-compounds.

1-[4-*Amino*-2-(*thiazol*-2-*ylcarbamoyl*)*phenoxy*]-*n-octane*. A solution of 1-[4-nitro-2-(thiazol-2-ylcarbamoyl)phenoxy]-n-octane (7·45 g.) in dimethylformamide (15 ml.) was added to a stirred, refluxing mixture of reduced iron powder

TABLE 1

2-Carboxy-4-nitrophenyl ethers

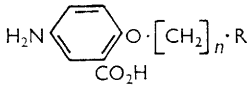


						Found (%)				Required (%)			
n	R	Method	Yield (%)	M. p.	Solvent [a]	C	H	N	Formula	C	H	N	
2	Me	B	67	128—130°	MeOH	53·2	5·1	6·3	$C_{10}H_{11}NO_5$	53·4	4·9	6·3	
3	Me	A	61	117·5—119	AcOH	55·3	5·85	5·9	$C_{11}H_{13}NO_5$	55·2	5·5	5·9	
4	Me	B	55	108—110	EtOAc	57·1	6·1	5·8	$C_{12}H_{15}NO_5$	56·9	6·0	5·5	
5	Me	A	88	117—118·5	MeOH–H_2O	58·7	6·8	5·2	$C_{13}H_{17}NO_5$	58·4	6·4	5·2	
8	Me	B	58	130—131	EtOAc	62·4	7·6	4·9	$C_{16}H_{23}NO_5$	62·1	7·5	4·5	
9	Me	A	66	67—70	Pet	62·9	7·8	5·4	$C_{17}H_{25}NO_5$	63·1	7·8	4·3	
5	Ph	A	54	167—169	EtOH	65·6	5·8	4·45	$C_{18}H_{19}NO_5$	65·7	5·8	4·3	
5	Phthalimido	A [b]	82	153—155	AcOH	60·25	4·6	7·1	$C_{20}H_{18}N_2O_7$	60·3	4·6	7·0	
		[c]	89	119—121	EtOH	61·4	5·0	7·0	$C_{21}H_{20}N_2O_7$	61·2	4·9	6·8	
5	O·C_6H_3(CO_2H)·NO_2–1,2,4	B	61	182—185	AcOH	52·4	4·6	6·4	$C_{19}H_{18}N_2O_{10}$	52·5	4·15	6·45	
		B [d]	14	136—138	EtOAc	54·0	4·8	6·4	$C_{21}H_{22}N_2O_{10}$	54·5	4·8	6·1	

[a] Solvent for crystn.; Pet = light petroleum (b. p. 80—100°). [b] Oxidation carried out at 100°. [c] Methyl ester, prepared using methanolic hydrogen chloride. [d] Dimethyl ester.

TABLE 2

4-Amino-2-carboxyphenyl ethers

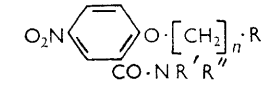


						Found (%)					Required (%)				
n	R	Deriv-ative	Yield (%)	M. p.	Solvent [a]	C	H	N	Hal	Formula	C	H	N	Hal	
2	Me	Base	46	145—148°	EtOAc	61·7	6·5	7·0	—	$C_{10}H_{13}NO_3$	61·5	6·7	7·2	—	
3	Me	Base	82	105—106	EtOH	63·4	7·5	6·8	—	$C_{11}H_{15}NO_3$	63·15	7·2	6·7	—	
4	Me	Base	64	115—117	EtOH	64·2	7·8	6·4	—	$C_{12}H_{17}NO_3$	64·5	7·7	6·3	—	
5	Me	Base	70	103—105	EtOH–H_2O	66·0	8·4	5·7	—	$C_{13}H_{19}NO_3$	65·8	8·1	5·9	—	
6	Me	Base	80	103—105	Pet	67·0	8·4	5·8	—	$C_{14}H_{21}NO_3$	67·0	8·4	5·6	—	
7	Me	Base	83	97—99	MeOH	68·2	8·8	5·3	—	$C_{15}H_{23}NO_3$	67·9	8·75	5·3	—	
		Me ester, HCl	70	173—175	EtOH	—	—	4·5	11·1	$C_{16}H_{25}NO_3$	—	—	4·4	11·3	
8	Me	Base	74	103—105	EtOH	69·05	8·8	5·0	—	$C_{16}H_{25}NO_3$	68·8	9·0	5·0	—	
9	Me	Base	79	109—111	EtOH	69·9	9·5	4·8	—	$C_{17}H_{27}NO_3$	69·6	9·3	4·8	—	
5	Ph	Base	82	99—101	EtOH	72·1	6·9	4·3	—	$C_{18}H_{21}NO_3$	72·2	7·1	4·7	—	
5	Phthalimido	Base	75	165—167	NMe_2·CHO	65·4	5·9	7·7	—	$C_{20}H_{26}N_2O_5$	65·2	5·5	7·6	—	
		Me ester, HCl	83	63 (decomp.)		—	—	6·5	8·5	$C_{21}H_{22}N_2O_5$,HCl	—	—	6·7	8·5	
5	O·C_6H_3(CO_2H)·NH_2–1,2,4	2HCl	39	241—244 (decomp.)	Aq. HCl	—	—	6·1	15·7	$C_{19}H_{22}N_2O_6$,HCl	—	—	6·3	15·85	
		Me_2 ester, 2HCl	90	180 (decomp.)	—[b]	—	—	5·9	15·1	$C_{21}H_{26}N_2O_6$,2HCl	—	—	5·9	14·95	

[a] Solvent for crystn.; Pet = light petroleum. [b] 2-Ethoxyethanol–ethyl ether.

TABLE 3

2-Carbamoyl-4-nitrophenyl ethers

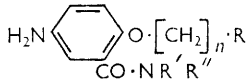


					Yield			Found (%)				Required (%)		
n	R	R′	R″	(%)	M. p.	Solvent [a]	C	H	N	Formula	C	H	N	
7	Me	H	H	74 [b]	140—141°	EtOH	61·2	7·7	9·45	$C_{15}H_{22}N_2O_4$	61·2	7·5	9·5	
9	Me	H	H	85	106—109	EtOH	63·2	8·25	6·9	$C_{17}H_{26}N_2O_4$	63·3	8·1	8·7	
5	Phthalimido	H	H	97	172—175	AcOH	60·2	4·8	10·4	$C_{20}H_{18}N_2O_6$	60·5	4·8	10·6	
7	Me	Et	Et	100	—[c]					$C_{19}H_{30}N_2O_4$				
7	Me		–$[CH_2]_4$–	100	93—95	C_6H_6			8·2	$C_{19}H_{28}N_2O_4$			8·05	
7	Me	H	$[CH_2]_2$·NEt_2,HCl	86	133—135		—	—	9·65	$C_{21}H_{35}N_3O_4$,HCl [d]	—	—	9·8	
7	Me	H	Ph	—	109—111	Pet	67·8	6·95	7·6	$C_{21}H_{26}N_2O_4$	68·1	7·1	7·6	
7	Me	H	Pyrid-2-yl	72	104—105	EtOH	—	—	11·6	$C_{20}H_{25}N_3O_4$	—	—	11·3	
7	Me	H	Thiazol-2-yl	47	121—124	E	—	—	11·1	$C_{18}H_{23}N_3O_4S$ [e]	—	—	11·1	
7	Me	H	5-Methylthiazol-2-yl	76	130—133	EtOH	—	—	10·9	$C_{19}H_{25}N_3O_4S$ [f]	—	—	10·7	
7	Me	H	Pyrimid-2-yl	50	142—145	EtOH				$C_{19}H_{24}N_4O_4$ [g]				
7	Me	H	Pyrazin-2-yl	30	137—139	E–H_2O	—	—	14·6	$C_{19}H_{24}N_4O_4$	—	—	15·0	

[a] Solvent for crystn; E = 2-ethoxyethanol. [b] Also prepared (53%) from the methyl ester and ammonia. [c] Not crystalline. Used without purification. [d] Found: Cl, 8·2; Reqd.: Cl, 8·3%. [e] Found: S, 8·5; Reqd.: S, 8·5%. [f] Found: S, 8·3; Reqd.: S, 8·2%. [g] Not analysed.

TABLE 4

4-Amino-2-carbamoylphenyl ethers

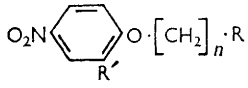


								Found (%)				Required (%)		
n	R	R′	R″	Deriv-ative	Yield (%)	M. p.	Solvent [a]	C	H	N	Formula	C	H	N
5	Me	H	H	Base	86	96—98°	EtOH–H_2O	66·5	8·6	11·5	$C_{13}H_{20}N_2O_2$	66·1	8·5	11·9
				Acetyl [b]		184—185	EtOH	64·7	7·7	10·2	$C_{15}H_{22}N_2O_3$	64·7	8·0	10·1
7	Me	H	H	Base	91	105—106	EtOH–H_2O	67·6	8·8	10·75	$C_{15}H_{24}N_2O_2$	68·1	9·1	10·6
9	Me	H	H	Base	87	103—106	EtOH–H_2O	70·2	9·7	9·7	$C_{17}H_{28}N_2O_2$	69·8	9·7	9·7
5	Phthalimido	H	H	Base	89	150—152	NMe_2·CHO–EtOH	65·3	5·8	11·5	$C_{20}H_{21}N_3O_4$	65·4	5·7	11·4
				Acetyl [b]		198	EtOH	64·8	5·5	10·1	$C_{22}H_{23}N_3O_5$	64·5	5·7	10·3
7	Me	Et	Et	HCl	82	171—174		—	—	8·1	$C_{19}H_{32}N_2O_2$,HCl [c]	—	—	7·9
				Acetyl [b]		74—75	PhMe–Pet (b. p. 60—80°)	70·0	9·4	7·5	$C_{21}H_{34}N_2O_3$	69·6	9·5	7·7
7	Me		–$[CH_2]_4$–	Base	72	—[d]		71·2	9·8	8·8	$C_{19}H_{30}N_2O_2$	71·7	9·5	8·8
				Acetyl [b]		105—106	PhMe–Pet (b. p. 60—80°)	70·1	8·8	8·0	$C_{21}H_{32}N_2O_3$	70·0	9·0	7·8
7	Me	H	CH_2·CO_2H	HCl	71	>310	Aq. HCl	—	—	8·1	$C_{17}H_{26}N_2O_4$,HCl [e]	—	—	7·8
7	Me	H	$[CH_2]_2$·NEt_2	Base	83	75—78	Pet. (b. p. 80—100°)	—	—	11·6	$C_{21}H_{37}N_3O_2$	—	—	11·6
				Acetyl [b]		168—169	EtOH	68·4	9·7	10·6	$C_{23}H_{39}N_3O_3$	68·1	9·7	10·4
7	Me	H	Ph	Base	89	107—109	EtOH	74·2	8·5	8·35	$C_{21}H_{28}N_2O_2$	74·1	8·2	8·2
7	Me	H	Pyrid-2-yl	Base	88	77—79	MeOH–H_2O	70·2	7·9	12·6	$C_{20}H_{27}N_3O_2$	70·3	8·0	12·3

[a] Solvent for crystn.; Pet = light petroleum. [b] Prepared by Mr. D. L. Pain. [c] Found: Cl, 10·0. Reqd.: Cl, 10·0%. [d] B. p. 210—220°/0·03 mm. [e] Found: Cl, 9·3. Reqd.: Cl, 9·9%.

TABLE 5

Miscellaneous 2-substituted 4-nitrophenyl ethers

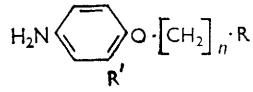


						Found (%)				Required (%)		
n	R	R′	Yield (%)	M. p.	Solvent [a]	C	H	N	Formula	C	H	N
7	Me	Cl	62	24—25°	Pet (b. p. 40—60°)	—	—	4·95	$C_{14}H_{20}ClNO_3$ [b]	—	—	4·9
5	Phthalimido	Cl	46	115—116	AcOH	—	—	7·1	$C_{19}H_{17}ClN_2O_5$ [c]	—	—	7·2
7	Me	NHAc	47	75—78	EtOH	61·6	7·9	9·3	$C_{16}H_{24}N_2O_4$	62·3	7·8	9·1
7	Me	CN	39	45—47 [d]	Pet (b. p. 80—100°)	65·4	7·7	10·2	$C_{15}H_{20}N_2O_3$	65·2	7·3	10·1

[a] Solvent for crystn.; Pet = light petroleum. [b] Found: Cl, 12·5. Reqd.: Cl, 12·4%. [c] Found: Cl, 9·1. Reqd.: Cl, 9·1%. [d] B. p. 165—166°/0·05 mm.

TABLE 6

Miscellaneous 2-substituted 4-aminophenyl ethers



							Found (%)				Required (%)		
n	R	R′	Derivative	Yield (%)	M. p.	Solvent [a]	C	H	N	Formula	C	H	N
7	Me	Cl	Base	58 [b]	57—58°	MeOH	—	—	5·2	$C_{14}H_{22}ClNO$ [c]	—	—	5·5
5	Phthalimido	Cl	Base	68	93—94	EtOH	—	—	7·8	$C_{19}H_{19}ClN_2O_3$ [d]	—	—	7·8
7	Me	$CH(OEt)_2$	Diptolate [e]	44	92—94	Et_2O	66·4	7·3	2·2	$C_{19}H_{33}NO_3$,$C_{20}H_{18}O_8$	66·0	7·25	2·0
7	Me	NHAc	Base	80	71—72	EtOH–H_2O	68·7	9·4	10·0	$C_{16}H_{26}N_2O_2$	69·1	9·4	10·1
7	Me	$CH_2CH(NH_2)$·CO_2H	Base	75	217—219	NMe_2·CHO	—	—	9·2	$C_{17}H_{28}N_2O_3$	—	—	9·1
7	Me	CN	Base	62 [b]	29—31 [f]		—	—	11·2	$C_{15}H_{22}N_2O$	—	—	11·4
			Acetyl	83 [g]	95—97	C_6H_6	70·8	8·5	9·3	$C_{17}H_{24}N_2O_2$	70·8	8·4	9·7
7	Me	COMe	HCl	50 [h]	120—125		—	—	4·9	$C_{16}H_{25}NO_2$,HCl [i]	—	—	4·7
			Acetyl	71 [j]	99—101	EtOH	70·6	9·1	4·7	$C_{18}H_{27}NO_3$	70·8	8·85	4·6
			Thiosemi-carbazone		118—119	C_6H_6	—	—	16·3	$C_{17}H_{28}N_4OS$ [k]	—	—	16·7

[a] Solvent for crystn. [b] Nitro-compound reduced using iron–acetic acid. [c] Found: Cl, 13·65. Reqd.: Cl, 13·9%. [d] Found: Cl, 9·9. Reqd.: Cl, 9·9%. [e] Diptolate = di-*p*-toluoyl-D-tartrate. [f] B. p. 165—175°/0·02 mm. [g] By acetylation of the amine with acetic anhydride–sodium acetate. [h] By hydrolysis of the acetyl derivative with aq. hydrochloric acid. [i] Found: Cl, 11·4. Reqd.: Cl, 11·8%. [j] From potassium 4-acetamido-2-acetylphenoxide and octyl bromide. [k] Found: S, 9·5. Reqd.: S, 9·5%.

(5·35 g.) in water (7·12 ml.), ethanol (25 ml.), and concentrated hydrochloric acid (1 drop). After 18 hr. sodium hydrogen carbonate (0·72 g.) was added, and the mixture stirred and refluxed for a further ¼ hr., then filtered hot, and the residue was washed with hot ethanol. The combined solutions were cooled and filtered, and the product was recrystallised from ethanol, giving the *amine* (58%), m. p. 123—123·5° (Found: C, 62·1; H, 7·3; N, 12·2. $C_{18}H_{25}N_3O_2S$ requires C, 62·2; H, 7·25; N, 12·1%). Similarly prepared were 1-[4-*amino*-2-(5-*methylthiazol*-2-*ylcarbamoyl*)*phenoxy*]-*n*-*octane* (61%), m. p. 104—106° (from light petroleum, b. p. 80—100°) (Found: C, 62·9; H, 7·4; N, 11·7. $C_{19}H_{27}N_3O_2S$ requires C, 63·1; H, 7·5; N, 11·6%); 1-[4-*amino*-2-(*pyrimid*-2-*ylcarbamoyl*)*phenoxy*]-*n*-*octane* (42%), m. p. 136—139° (from benzene) (Found: C, 66·8; H, 7·2; N, 16·2. $C_{19}H_{26}N_4O_2$ requires C, 66·6; H, 7·65; N, 16·4%); and 1-[4-*amino*-2-(*pyrazin*-2-*ylcarbamoyl*)*phenoxy*]-*n*-*octane* (64%), m. p. 135—137° (from ethanol) (Found: C, 66·7; H, 7·7; N, 16·6. $C_{19}H_{26}N_4O_2$ requires C, 66·6; H, 7·65; N, 16·4%).

4-*Acetamido*-2-*n*-*octyloxybenzoic acid*. A mixture of the potassium salt from 5-acetamido-2-methoxycarbonylphenol [5] (23·3 g.) and n-octyl bromide (36 g.) in dimethylformamide (40 ml.) was heated at 150—160° for 30 min., cooled, and poured into water. The oily product, extracted with ether, was dissolved in methanol (150 ml.) and the solution was treated with aqueous 2N-potassium hydroxide (56 ml.). The mixture was heated on a steam-bath (15 min.), cooled, diluted with water (200 ml.), and acidified with hydrochloric acid. The product (55%) was recrystallised from methanol. The *ether* had m. p. 119—121° (Found: C, 66·4; H, 8·4; N, 4·6. $C_{17}H_{25}NO_4$ requires C, 66·4; H, 8·2; N, 4·6%).

1-(4-*Amino*-2-*octyloxy*)*benzoic acid*. A solution of 1-(4-acetamido-2-octyloxy)benzoic acid (15·85 g.) in aqueous 2N-potassium hydroxide (77·4 ml.) and water (75 ml.) was refluxed for 6½ hr., filtered, cooled, and made just acid with dilute acetic acid. The product (52%) was crystallised from carbon tetrachloride; the *amine* had m. p. 67·5—71·5° (Found: C, 68·5; H, 8·8; N, 5·2. $C_{15}H_{23}NO_3$ requires C, 67·9; H, 8·7; N, 5·3%).

5-*Acetamido*-2-*methoxyphenyl methyl sulphone*. 5-Acetamido-2-methoxybenzenesulphinic acid [1] (7 g.) was dissolved in a solution of sodium acetate trihydrate (3·7 g.) in water (10 ml.), and methyl iodide (5 ml.) in acetone (50 ml.) was added. The mixture was refluxed for 2 hr., concentrated, and cooled, yielding the *sulphone* (74%), m. p. 216—218° (Found: N, 5·7; S, 13·3. $C_{10}H_{13}NO_4S$ requires N, 5·8; S, 13·2%).

5-*Amino*-2-*methoxybenzenesulphinic acid hydrochloride* A solution of 5-acetamido-2-methoxybenzenesulphinic acid (6·4 g.) in 11·7N-potassium hydroxide (6 ml.) and water (10 ml.) was refluxed for 3 hr., cooled, and acidified with concentrated hydrochloric acid, giving the *salt* (100%), m. p. 205—215° (decomp.) (Found: Cl, 16·1; N, 5·6. $C_7H_9NO_3S$,HCl requires Cl, 15·9; N, 6·3%).

5-*Amino*-2-*methoxyphenyl methyl sulphone*. 5-Acetamido-2-methoxyphenyl methyl sulphone (3 g.) was refluxed for 2 hr., in a mixture of concentrated hydrochloric acid (7·5 ml.) and water (7·5 ml.). The basic product (56%) was crystallised from ethanol, yielding the *amine*, m. p. 103—104° (Found: N, 6·75; S, 16·3. $C_8H_{11}NO_3S$ requires N, 7·0; S, 15·9%).

o-*Methoxyphenyl methyl sulphone*. The foregoing amine was diazotised (sodium nitrite–aqueous hydrochloric acid) and the diazonium solution was reduced with hypophosphorous acid, giving the sulphone (54%), m. p. 88—90° (Found: C, 51·85; H, 5·65; S, 17·3. Calc. for $C_8H_{10}O_3S$: C, 51·6; H, 5·4; S, 17·2%), not depressed by a sample prepared by methylation of *o*-methoxybenzenesulphinic acid (lit.,[6] m. p. 95°).

5-*Amino*-2-*hydroxyphenyl methyl sulphone hydrobromide*. 5-Acetamido-2-methoxyphenyl methyl sulphone (29·5 g.) was refluxed for 24 hr. with 50% w/v hydrobromic acid (90 ml.). The solution was cooled giving the *salt* (84%), m. p. 160—170° (Found: N, 5·3; S, 12·0. $C_7H_9NO_3S$,HBr requires N, 5·2; S, 11·9%). Acetylation with acetic anhydride–sodium acetate gave 5-*acetamido*-2-*acetoxyphenyl methyl sulphone*, m. p. 172—175° (Found: C, 48·8; H, 4·8; S, 12·0. $C_{11}H_{13}NO_5S$ requires C, 48·7; H, 4·8; S, 11·8%).

5-*Acetamido*-2-*hydroxyphenyl methyl sulphone*. Crude 5-acetamido-2-acetoxyphenyl methyl sulphone (15·5 g.) was warmed and stirred for 1 hr. with 2N-sodium hydroxide (100 ml.); the mixture was filtered and the filtrate was acidified with hydrochloric acid, giving the *phenol* (28%), m. p. 223—224° (Found: C, 47·1; H, 4·4; N, 5·8. $C_9H_{11}NO_4S$ requires C, 47·15; H, 4·8; N, 6·1%). The overall yield from 5-acetamido-2-methoxyphenyl methyl sulphone, without purification of the intermediates, was 74%.

1-(4-*Acetamido*-2-*methylsulphonylphenoxy*)-*n*-*octane*. 5-Acetamido-2-hydroxyphenyl methyl sulphone (2·5 g.), anhydrous potassium carbonate (2·5 g.), n-octyl bromide (1·8 g.), and ethanol (10 ml.) were refluxed for 18 hr. with stirring on the steam-bath. The product was recrystallised from aqueous ethanol, yielding the *octyl ether* (78%), m. p. 106—107° (Found: N, 4·0; S, 9·4. $C_{17}H_{27}NO_4S$ requires N, 4·1; S, 9·4%). Hydrolysis with aqueous hydrochloric acid afforded 1-(4-*amino*-2-*methylsulphonylphenoxy*)-*n*-*octane* (91%), m. p. 68—70° (from aqueous methanol) (Found: N, 4·7; S, 11·0. $C_{15}H_{25}NO_3S$ requires N, 4·7; S, 10·7%).

1-(4-*Dimethylamino*-2-*carbamoylphenoxy*)-*n*-*octane*, m. p. 78—79 [from light petroleum (b. p. 80—100°)] (Found: C, 70·2; H, 10·2; N, 9·6. $C_{17}H_{28}N_2O_2$ requires C, 69·8; H, 9·6; N, 9·6%) was prepared (42%) by pyrolysis of the methiodide, m. p. 110—120° (decomp.) (from acetone), itself obtained (62%) from the primary amine and methyl iodide–sodium carbonate in ethanol.

5-*Acetamido*-2-*octyloxybenzamidoxime*. Sodium hydride (50% suspension in oil, 5·05 g.) was added cautiously to 2-ethoxyethanol (50·5 ml.) cooled in ice, followed by a solution of hydroxylamine hydrochloride (7·71 g.) in 2-ethoxyethanol (150 ml.) and 5-acetamido-2-octyloxyphenyl cyanide (Table 6; 30·3 g.). The mixture was heated at 100° for 18 hr., and evaporated *in vacuo*. The residue was treated with water and the product, isolated with ether, was crystallised twice from ethyl acetate, giving the *amidoxime* (66%), m. p. 145—147° (Found: C, 63·8; H, 8·4; N, 12·9. $C_{17}H_{27}N_3O_3$ requires C, 63·5; H, 8·5; N, 13·1%). The material insoluble in ethyl acetate was 5-*acetamido*-2-*octyloxybenzamide*, m. p. 194—196° (Found: C, 66·9; H, 8·9; N, 9·1. $C_{17}H_{26}N_2O_3$ requires C, 66·6; H, 8·5; N, 9·15%).

5-*Acetamido*-2-*octyloxybenzamidine*. A solution of the foregoing amidoxime (9·3 g.) in methanol (200 ml.) was hydrogenated over Raney nickel at 60°/70 lb. per sq. in. The residue obtained on evaporation was crystallised from aqueous hydrochloric acid, yielding the *amidine hydrochloride* (73%), m. p. 90—95° (Found: N, 12·2. $C_{17}H_{27}N_3O_2$,HCl

[6] M. E. Heppenstall and S. Smiles, *J. Chem. Soc.*, 1938, 899.

requires N, 12·3%). Hydrolysis with hydrochloric acid afforded *5-amino-2-octyloxybenzamidine dihydrochloride* (90%), m. p. 179—183° (Found: N, 12·2; Cl, 21·0. $C_{15}H_{25}N_3O,2HCl$ requires N, 12·5; Cl, 21·2%).

3-Methoxy-4-n-nonyloxyaniline. The corresponding nitro-compound, previously described (Part IV [2]) as an oil, has now been crystallised, m. p. 47·5—49° (Found: C, 65·3; H, 8·6; N, 4·8. Calc. for $C_{16}H_{25}NO_4$: C, 65·1; H, 8·5; N, 4·75%). The amine formed on reduction had m. p. 65·5—67° (lit.,[2] 71—73°) (Found: C, 72·8; H, 10·2; N, 5·5. Calc. for $C_{16}H_{27}NO_2$: C, 72·5; H, 10·2; N, 5·3%).

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