363. *The Chemotherapy of Schistosomiasis. Part IV.*[1] *Some Ethers of 4-Amino-2-methoxyphenol.*

By R. F. Collins and M. Davis.

Numerous alkyl and substituted alkyl ethers of 4-amino-2-methoxyphenol have been prepared, together with some related compounds and *N*-substituted derivatives. Many of the compounds are schistosomicides.

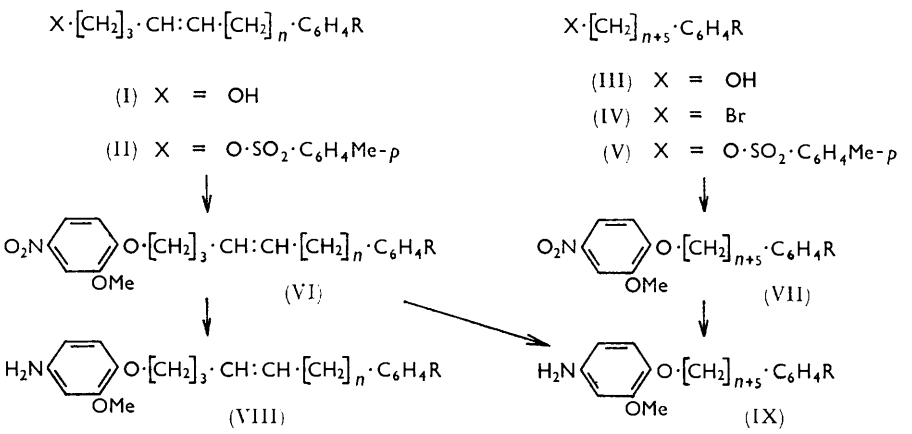
In earlier parts of this series [1,2,3] we have reported alkyl and substituted alkyl ethers of *p*-aminophenol which were effective against *Schistosoma mansoni* infections.[4,5] Some of these compounds produced undesirable ocular effects in cats, but it was noted that this response, which was particularly marked with 1,5-di-(*p*-aminophenoxy)pentane, was absent with the *o,o'*-dimethoxy-derivative.[4] Many more ethers of 4-amino-2-methoxyphenol (4-aminoguaiacol) have therefore been synthesised and tested biologically,[6] the majority being alkyl ethers either unsubstituted or carrying substituents such as hydroxy, alkoxy, alkylthio, aryl, aryloxy, arylthio, arylsulphonyl, etc. For some of these compounds the effects of branching or unsaturation in the chain, and of substitution in the amino-group,

[1] Part III, Ashley, Collins, Davis, and Sirett, *J.*, 1959, 3880.
[2] Ashley, Collins, Davis, and Sirett, *J.*, 1958, 3298.
[3] Ashley, Collins, Davis, and Sirett, *J.*, 1959, 897.
[4] Collins, Davis, Edge, and Hill, *Brit. J. Pharmacol.*, 1958, **13**, 238.
[5] Collins, Davis, Edge, Hill, Reading, and Turnbull, *Brit. J. Pharmacol.*, 1959, **14**, 467.
[6] Collins, Davis, Edge, Hill, and Weston, unpublished work.

have been investigated and a few positional isomers and other related compounds, as well as some further ethers of *p*-aminophenol, have been prepared.

The general method of synthesis used was the condensation of potassium 2-methoxy-4-nitrophenoxide [7] (obtained almost quantitatively by refluxing 4-nitroveratrole with aqueous potassium hydroxide) with the appropriate chloride, bromide, or toluene-*p*-sulphonate, followed by reduction of the nitro-compound to the amine either catalytically or by using sodium sulphide. In some instances 4-acetamido-2-methoxyphenol [8] was used and the condensation product was hydrolysed with acid.

As a homologous series of ω-phenylalkyl halides was required for this work, the Crombie–Harper synthesis [9,10,11] using 2,3-dichlorotetrahydropyran and phenyl or phenylalkyl halides was employed and gave satisfactory overall yields of *trans*-ω-phenylalk-4-en-1-ols (Ia—e). Catalytic reduction afforded the corresponding saturated alcohols (IIIa—e) which were converted into the bromides (IVa—d) or, in one instance, into the toluene-*p*-sulphonate (Ve). Condensation with potassium 2-methoxy-4-nitrophenoxide yielded the



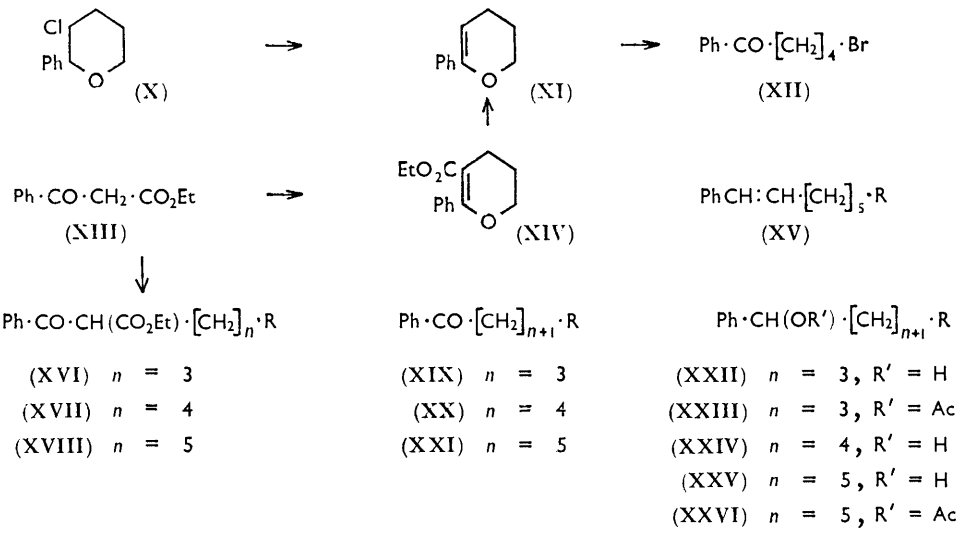
(a) $n = 0$, R = H, (b) $n = 1$—3, R = H, (c) $n = 0$, R = *o*-Me, (d) $n = 0$, R = *p*-Me, (e) $n = 0$, R = *p*-OMe.

nitro-compounds (VII) which were reduced catalytically to the amines (IX). In an alternative procedure, the phenylalkenols (Ia, d, and e) were converted into the toluene-*p*-sulphonates (IIa, d, and e) and thence into the unsaturated nitroguaiacyl ethers (VI), which were reduced either catalytically to the saturated amines (IX) or with sodium sulphide to the unsaturated amine (VIII).

4-Benzoylbutyl bromide (XII) was first prepared by Perkin [12] from benzoylacetic ester (XIII) and 1,3-dibromopropane, the intermediate ethyl 5,6-dihydro-2-phenyl-4*H*-pyran-3-carboxylate (XIV) being hydrolysed and decarboxylated to 3,4-dihydro-6-phenyl-2*H*-pyran (XI), which was then treated with hydrobromic acid. We have found that the key intermediate (XI) is formed in 78% yield by dehydrochlorination of the mixed *cis*- and *trans*-isomers of 3-chlorotetrahydro-2-phenylpyran [13] (X) with sodamide in boiling toluene. The absence of a double-bond isomer of (XI) was shown by almost quantitative conversion of the product into 4-benzoylbutyl bromide. Riobé [11] obtained a mixture of two isomers on heating 3-chlorotetrahydro-2-methylpyran with potassium hydroxide in ethylene glycol, the proportion depending on whether the *cis*- or *trans*-chloro-compound

[7] Pollecoff and Robinson, *J.*, 1918, **113**, 645.
[8] Heidelberger and Jacobs, *J. Amer. Chem. Soc.*, 1919, **41**, 1450.
[9] Crombie and Harper, *J.*, 1950, 1707; Crombie, Gold, Harper, and Stokes, *J.*, 1956, 136.
[10] Ansell and Selleck, *J.*, 1956, 1238; Ansell and Thomas, *J.*, 1957, 3302.
[11] Riobé, *Ann. Chim.* (*France*), 1949, **4**, 630.
[12] Perkin, *J.*, 1887, **51**, 702; cf. Normant, *Compt. rend.*, 1950, **231**, 909; Montaigne, *Ann. Chim.* (*France*), 1954, **9**, 310.
[13] Paul, *Compt. rend.*, 1944, **218**, 122.

was used. Treatment of 3-bromo-2-ethyltetrahydropyran with sodamide in liquid ammonia has been investigated [14] as a route to hept-4-yn-1-ol. Two higher homologues of 4-benzoylbutyl bromide were prepared by a modification of Perkin's method. When benzoylacetic ester (XIII) was condensed with 4-*p*-methoxyphenoxybutyl bromide, and the intermediate ester (XVIIb) was subjected to ketonic hydrolysis, 1-benzoyl-5-*p*-methoxyphenoxypentane (XXb) was obtained; it was converted by aqueous hydrobromic acid



R = (a) Br, (b) O·C_6H_4·OMe-*p*, (c) O·C_6H_4·NO_2-*p*, (d) O·C_6H_3(OMe)·NO_2-3,4.

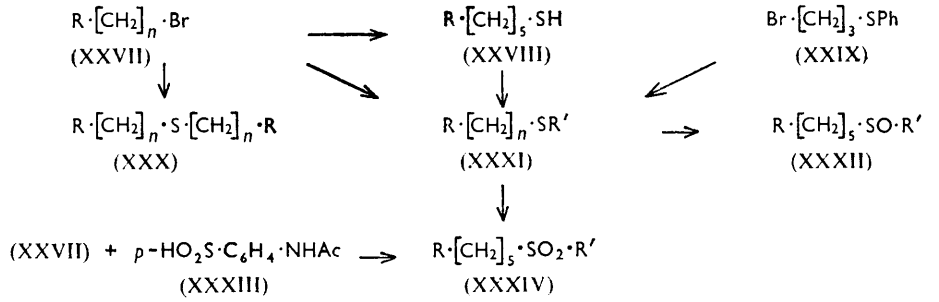
into 5-benzoylpentyl bromide (XXa). Later, it was found that condensation of benzoylacetic ester with an excess of 1,5-dibromopentane and treatment of the crude product (XVIIIa) with hydrobromic acid yielded 6-benzoylhexyl bromide (XXIa) directly.

Reaction of the appropriate benzoylalkyl bromide with potassium 2-methoxy-4-nitrophenoxide or potassium *p*-nitrophenoxide afforded respectively the benzoyl alkyl ethers (XIXd), (XXId), (XIXc),[1] and (XXc). 4-Benzoyl-1-*p*-nitrophenoxybutane (XIXc) and 5-benzoyl-1-*p*-nitrophenoxypentane (XXc) were also obtained directly from benzoylacetic ester by condensation with 3-*p*-nitrophenoxypropyl bromide, or 4-*p*-nitrophenoxybutyl bromide, respectively, followed by alkaline hydrolysis of the intermediate esters (XVIc) and (XVIIc). Reduction of the nitro-ketones by the Meerwein–Ponndorf method, previously described [1] for the preparation of 5-*p*-nitrophenoxy-1-phenylpentane-1-ol (XXIIc), was employed for the nitro-alcohols (XXIId), (XXIVc), and XXVd). Treatment with acetic anhydride in the presence of sulphuric acid at room temperature gave the corresponding acetates (XXIIId) and (XXVId); at a higher temperature the unsaturated compound (XVd) was isolated.

Three methods were used for the preparation of nitroguaiacyl and nitrophenol ethers (XXXIa and XXXIb) containing sulphur in the chains, the most convenient being the condensation of the nitroguaiacyloxyalkyl or *p*-nitrophenoxyalkyl bromide (XXVIIa or XXVIIb) with sodium alkyl, arylalkyl, or aryl sulphide. In a second route, 5-(2-methoxy-4-nitrophenoxy)pentyl bromide (XXVIIa; $n = 5$) was converted successively into the thiouronium salt and the thiol (XXVIIIa), which was alkylated with methyl iodide. Another method is exemplified by the reaction of 1,3-dibromopropane with thiophenol to give 3-phenylthiopropyl bromide (XXIX) and subsequent condensation with potassium nitroguaiacyloxide. Corresponding sulphoxides (XXXIIb) and sulphones (XXXIVa

[14] Eglinton, Jones, and Whiting, *J.*, 1952, 2873.

and b) were obtained by oxidation with hydrogen peroxide in acetic acid, and one sulphone was prepared by condensation of the nitroguaiacyloxypentyl bromide (XXVIIa; $n = 5$) with *p*-acetamidobenzenesulphinic acid (XXXIII). The nitro-sulphones were reduced

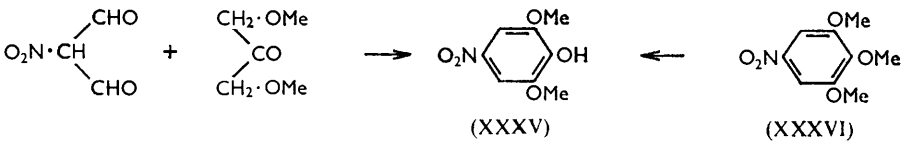


R = (a) O·C_6H_3(OMe)·NO_2-3,4, (b) O·C_6H_4·NO_2-*p*, (c) O·C_6H_3(OMe)·NH_2-3,4, (d) O·C_6H_4·NH_2-*p*.

to the amines (XXXIVc and d) catalytically, but chemical reduction was necessary for the amino-sulphides (XXXIc and d) and amino-sulphoxides (XXXIId). The diamine (XXXc) was formed when 5-(2-methoxy-4-nitrophenoxy)pentyl bromide (XXVIIa; $n = 5$) was heated with sodium sulphide.

Condensation of potassium 2-methoxy-4-nitrophenoxide with acetobromoglucose, followed by hydrolysis of the acetyl groups and reduction, afforded 4-amino-2-methoxyphenyl D-glucoside, presumably the β-isomer.[15]

To examine the effect of introducing a further methoxy-group at $C_{(6)}$ in the aminoguaiacyl ethers, 2,6-dimethoxy-4-nitrophenol (XXXV) was required. It seemed likely that the 2-methoxy-group of the known 5-nitropyrogallol trimethyl ether[16] (XXXVI)



would be sensitive to nucleophilic reagents and it was in fact preferentially attacked by aqueous alkali. The structure of the nitrophenol (XXXV) thus formed was confirmed by its independent synthesis from sodium nitromalondialdehyde and 1,3-dimethoxyacetone.[17] Condensations using this sterically hindered phenol were sluggish and required extended reaction times.

The *N*-substituted amines were for the most part obtained by standard methods, which have been described in earlier papers.[1,2]

Experimental

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

Alcohols, bromides, and related compounds.

1-*Phenylbut-3-yl Bromide*.—Benzylideneacetone was reduced catalytically (Raney nickel) in ethanol to 4-phenylbutan-2-ol (92%), b. p. 119—121°/11 mm. (lit.,[18] 127°/18 mm.), which

[15] Koenigs and Knorr, *Ber.*, 1901, **34**, 957.
[16] Will, *Ber.*, 1888, **21**, 602.
[17] Jones and Kenner, *J.*, 1931, 1842.
[18] Jadot and Braine, *Bull. Soc. roy. Sci. Liége*, 1956, **25**, 62.

was refluxed for 20 hr. with 50% aqueous hydrobromic acid, giving the bromide (75% overall), b. p. 116°/10 mm. (lit.,[19] 116—118°/14 mm.). 4-Phenylbutyl bromide was prepared by the method of Oae and VanderWerf.[20]

Harper–Crombie Method for the Preparation of Phenylalkyl Bromides.—(*a*) A Grignard reagent prepared from benzyl chloride (189·75 g., 1·5 moles) and magnesium (36·45 g., 1·5 g.-atoms) in ether (400 ml.) was cooled and stirred whilst a solution of 2,3-dichlorotetrahydropyran (from 86 g. of dihydropyran *) in ether (200 ml.) was added during 1 hr. The mixture was stirred for a further 5 hr., kept overnight, and decomposed with ammonium chloride solution until the magnesium hydroxide separated as an easily filtrable solid. The suspension was filtered through Hyflo Supercel, the solid was washed with ether, and the ethereal solutions were washed, dried, and distilled, giving a mixture (145·4 g., 67%), b. p. 148—178°/15 mm. (Found: Cl, 14·4. Calc. for $C_{12}H_{15}ClO$: Cl, 16·9%), containing both *cis*- and *trans*-2-benzyl-3-chlorotetrahydropyran. Similar reactions were carried out with bromobenzene,[13] phenethyl bromide,[10] 3-phenylpropyl bromide, *o*-bromotoluene, *p*-bromotoluene, and *p*-bromoanisole, but in these cases the ethereal solutions were treated directly as in (*b*).

(*b*) 2-Benzyl-3-chlorotetrahydropyran (144 g. of crude mixture) was slowly added to a stirred (Hershberg wire stirrer) suspension of finely divided sodium (34·8 g.) in dry ether (500 ml.). Next day, the mixture was treated with ethanol (50 ml.), then water, and the washed and dried ethereal solution was distilled, giving the crude alcohol (107·7 g., 89·5%), b. p. 156—166°/12 mm. A redistilled sample of trans-6-*phenylhex*-4-*en*-1-*ol* had b. p. 152—157°/10 mm., n_D^{12} 1·5380 (Found: C, 81·5; H, 8·9. $C_{12}H_{16}O$ requires C, 81·8; H, 9·2%).

Similarly prepared (yields are for crude alcohol overall from dihydropyran) were *trans*-5-phenylpent-4-en-1-ol (77%), b. p. 102°/0·1 mm., 165—170°/21 mm., n_D^{20} 1·5620 (lit.,[11] b. p. 153—157°/13 mm., n_D^{17} 1·5640); *trans*-7-phenylhept-4-en-1-ol (51%), b. p. 100—105°/0·03 mm., n_D 1·5260 (lit.,[10] b. p. 110—118°/0·7 mm.); trans-8-*phenyloct*-4-*en*-1-*ol* (81%), b. p. 190—194°/15 mm., n_D^{19} 1·5240 (Found: C, 82·5; H, 9·7. $C_{14}H_{20}O$ requires C, 82·3; H, 9·9%); trans-5-o-*tolylpent*-4-*en*-1-*ol* (49%), b. p. 162—170°/15 mm., n_D 1·5505 (Found: C, 81·7; H, 9·25. $C_{12}H_{16}O$ requires C, 81·8; H, 9·1%); trans-5-p-*tolylpent*-4-*en*-1-*ol* (78%), m. p. 40—42°, b. p. 155—173°/14 mm. (Found: C, 82·3; H, 8·9%); and trans-5-p-*methoxyphenylpent*-4-*en*-1-*ol* (71%), m. p. 74—75° (Found: C, 75·1; H, 8·4. $C_{12}H_{16}O_2$ requires C, 75·0; H, 8·3%).

(*c*) Catalytic reduction of the unsaturated alcohols (Raney nickel) gave respectively 5-phenylpentanol (87%), b. p. 133—144°/11 mm., 6-phenylhexanol (93%), b. p. 157—167°/13 mm. (lit.,[21] b. p. 160—161°/13 mm.); 7-phenylheptanol (65%), b. p. 125—135°/0·02 mm., n_D 1·5135 (lit.,[21] b. p. 142—145°/7 mm.); 8-*phenyloctanol* (81%), b. p. 185—189°/12 mm., n_D^{19} 1·5080 (Found: C, 81·9; H, 10·5. $C_{14}H_{22}O$ requires C, 81·5; H, 10·75%); 5-o-*tolylpentanol* (86%), b. p. 155—156°/13 mm., n_D 1·5225 (Found: C, 80·9; H, 9·6. $C_{12}H_{18}O$ requires C, 81·0; H, 10·1%); 5-*p*-tolylpentanol (95%), b. p. 159—162°/14 mm. (lit.,[22] b. p. 158—159°/11 mm.); and 5-p-*methoxyphenylpentanol* (94%), b. p. 110—115°/0·03 mm. (Found: C, 74·5; H, 9·25. $C_{12}H_{18}O_2$ requires C, 74·2; H, 9·3%).

(*d*) The saturated alcohols were converted into the bromides by treatment with 50% aqueous hydrobromic acid (2 ml./g.) and concentrated sulphuric acid (0·67 ml./g.) at 100° for 20 hr. The following were obtained: 5-phenylpentyl bromide, 6-phenylhexyl bromide (used without purification);[20] 7-phenylheptyl bromide, b. p. 110—114°/0·05 mm. (lit.,[21] b. p. 170—175°/15 mm.); 8-*phenyloctyl bromide* (72%), b. p. 185—187°/12 mm. (Found: Br, 27·1. $C_{14}H_{21}Br$ requires Br, 29·7%); 5-o-*tolylpentyl bromide* (84%), b. p. 155—162°/14 mm. (Found: C, 59·45; H, 7·2; Br, 33·3. $C_{12}H_{17}Br$ requires C, 59·7; H, 7·1; Br, 33·2%); 5-p-*tolylpentyl bromide* (84%), b. p. 157—163°/14 mm. (Found: Br, 29·95. $C_{12}H_{17}Br$ requires Br, 33·2%).

5-*Phenylpent*-4-*en*-1-*yl toluene*-p-*sulphonate*, prepared (38%) in the usual way and crystallised from methanol at −80°, had m. p. 42—43° (Found: S, 10·5. $C_{18}H_{20}O_3S$ requires S, 10·1%). The toluene-*p*-sulphonates of 5-*p*-methoxyphenylpent-4-en-1-ol, 5-*p*-tolylpent-4-en-1-ol, and

* On several occasions, when the passage of chlorine through the ethereal solution of dihydropyran was interrupted so that the increase in weight could be measured, a bright flash travelled up the delivery tube leaving a carbonaceous deposit. This occurred with several batches of dihydropyran, all of which had been freshly distilled from sodium, and usually when the uptake was nearly complete.

[19] Bateman, Cunneen, and Lyons, *J.*, 1951, 2290.
[20] Oae and VanderWerf, *J. Amer. Chem. Soc.*, 1953, **75**, 5037.
[21] von Braun, *Ber.*, 1911, **44**, 2867.
[22] von Braun and Kühn, *Ber.*, 1927, **60**, 2557.

5-*p*-methoxyphenylpentanol were similarly prepared, but used without purification. When the toluene-*p*-sulphonate of 5-*p*-tolylpent-4-en-1-ol was prepared in pyridine, but the mixture was left for several days before being worked up, the product was the quaternary *pyridinium salt*, m. p. 68—69° (Found: C, 68·95; H, 6·75; N, 3·4; S, 7·8%; *M*, 409. $C_{24}H_{27}NO_3S,0{\cdot}5H_2O$ requires C, 68·9; H, 6·7; N, 3·3; S, 7·8%; *M*, 418).

5-Phenylpent-4-en-1-yl bromide was obtained from tetrahydro-2-phenylpyran as described by Paul.[23] 1-Methyl-5-phenylpentyl bromide, prepared by catalytic reduction of cinnamylideneacetone [24] and subsequent treatment with 50% aqueous hydrobromic acid, had b. p. 152—156°/14 mm., n_D^{30} 1·5218 (lit.,[25] b. p. 152—156°/10 mm.).

5-Cyclohexylpentan-1-ol was prepared (90%) by reduction of 5-phenylpent-4-en-1-ol over Raney nickel in ethanol at 131°/100 atm. It had b. p. 136—137°/11 mm., n_D^{17} 1·4685 (lit.,[26] b. p. 118—119°/4 mm., n_D^{25} 1·4638). Treatment with hydrobromic–sulphuric acid as described above gave 5-cyclohexylpentyl bromide (91%), b. p. 127°/7 mm., n_D^{20} 1·4838 (lit.,[26] b. p. 113—114°/5 mm., n_D^{25} 1·4814).

3,4-*Dihydro*-6-*phenyl*-2H-*pyran*.—Sodamide (15·6 g.) was ground in a ball-mill under toluene (50 ml.) for 30 hr. and to the resulting cream, stirred and refluxed in toluene (50 ml.), was added during 30 min. a solution of 3-chlorotetrahydro-2-phenylpyran (19·65 g.) in toluene (50 ml.). After a further 17 hr. the cooled mixture was treated with water, and the washed and dried toluene solution was distilled, giving the dihydrophenylpyran (78%), b. p. 119—125°/9 mm., n_D^{17} 1·5703 (lit.,[12] b. p. 125°/11 mm., n_D^{17} 1·5720). When heated with 50% aqueous hydrobromic acid for 15 min. at 100°, it yielded 4-benzoylbutyl bromide (94%), m. p. 58° (lit.,[12] m. p. 61°).

Ethyl α-(4-p-*Methoxyphenoxybutyl*)*benzoylacetate*.—4-*p*-Methoxyphenoxybutyl bromide (67·5 g.), dissolved in ethanol (50 ml.), and benzoylacetic ester (50 g.) were added successively to a solution of sodium (6·1 g.) in ethanol (150 ml.). The mixture was refluxed for 3 hr., then concentrated, diluted with water, and extracted with ether. The residue crystallised on trituration with light petroleum. Recrystallisation of the crude product (62 g., 64%) from ethanol afforded the pure *ester* (50 g.), m. p. 38—40° (Found: C, 71·6; H, 7·05. $C_{22}H_{26}O_5$ requires C, 71·3; H, 7·0%).

1-*Benzoyl*-5-p-*methoxyphenoxypentane*.—A mixture of the foregoing ester (50 g.), potassium hydroxide (20 g.), methanol (300 ml.), and water (200 ml.) was stirred and refluxed for 24 hr., then evaporated. The residue was extracted with ether and the washed and dried ethereal solution was evaporated. Trituration of the residue with light petroleum gave the *ketone* (34·3 g., 88%) (Found: C, 76·3; H, 7·8. $C_{19}H_{22}O_3$ requires C, 76·5; H, 7·4%), m. p. 42° not raised by recrystallisation from light petroleum.

The alkaline mother-liquors on acidification gave 6-p-*methoxyphenoxyhexanoic acid* (1 g.), m. p. 80—82° (Found: C, 65·8; H, 7·6. $C_{13}H_{18}O_4$ requires C, 65·5; H, 7·6%), and benzoic acid.

5-*Benzoylpentyl Bromide*.—A mixture of 1-benzoyl-5-*p*-methoxyphenoxypentane (34·5 g.), phenol (30 g.), and 50% hydrobromic acid (100 ml.) was stirred and refluxed for 2 hr., then cooled, and cautiously added to aqueous sodium hydroxide and ice. The product was extracted with ether and the washed and dried solution was distilled, giving the *bromide* (17·3 g., 59%), b. p. 190—200°/14 mm., m. p. 33—34°. After recrystallisation from light petroleum (b. p. 60—80°), it had m. p. 37·5—38·5° (Found: Br, 30·6. $C_{12}H_{15}BrO$ requires Br, 31·4%).

6-*Benzoylhexyl Bromide*.—1,5-Dibromopentane (46 g.) and benzoylacetic ester (19·2 g.) were added successively to a solution of sodium (2·3 g.) in dry ethanol (70 ml.), and the mixture was refluxed for 1·5 hr., concentrated, diluted with water, and extracted with ether. The extract was evaporated and the residue was stirred with 50% hydrobromic acid (100 ml.) on the steam-bath for 18 hr. The mixture was then diluted and extracted with ether and the washed and dried extract was distilled, giving 6-*benzoylhexyl bromide* (14·7 g., 55%), b. p. 140—150°/0·03 mm. (Found: Br, 27·75. $C_{13}H_{17}BrO$ requires Br, 29·7%).

5-(2-*Methoxy*-4-*nitrophenoxy*)*pentyl Bromide*.—A mixture of potassium 2-methoxy-4-nitrophenoxide (220·5 g., 93·9% pure), 1,5-dibromopentane (1150 g.), and acetone (3 l.) was refluxed for 20 hr., concentrated to low bulk and steam-distilled. The residue was extracted thrice with chloroform and the combined extracts were washed with 2N-sodium hydroxide and water,

[23] Paul, *Bull. Soc. chim. France*, 1935, **2**, 311.
[24] Roblin, Davidson, and Bogert, *J. Amer. Chem. Soc.*, 1935, **57**, 151.
[25] von Braun, Deutsch, and Schmatloch, *Ber.*, 1912, **45**, 1246.
[26] Hiers and Adams, *J. Amer Chem. Soc.*, 1926, **48**, 2388.

concentrated, and diluted with an equal volume of methanol. The crude bromide (252 g.; m. p. 75—76°) was purified by dissolving it in ether and filtering it from 1,5-di-(2-methoxy-4-nitrophenoxy)pentane (8·85 g., m. p. 122—123°). Concentration of the ethereal solution gave the *bromide* (218 g.), m. p. 76—77° (Found: Br, 23·8. $C_{12}H_{16}BrNO_4$ requires Br, 25·1%). 3-(2-*Methoxy*-4-*nitrophenoxy*)*propyl bromide*, m. p. 77·5—79° (from methanol) (Found: N, 4·9; Br, 27·5. $C_{10}H_{12}BrNO_4$ requires N, 4·8; Br, 27·5%), was similarly prepared.

Nitro- and acylamino-compounds.

7-(2-*Methoxy*-4-*nitrophenoxy*)-1-*phenylhepyl Acetate*.—7-(2-Methoxy-4-nitrophenoxy)-1-phenylheptan-1-ol (Table 1) (39 g.) was mixed with acetic anhydride (150 ml.) and treated with one drop of concentrated sulphuric acid. Ice was added after the mixture had been kept for 15 min. at room temperature. When the acetic anhydride had been decomposed the product was extracted with ether, and the extract washed with water, dried, and evaporated. The oil solidified under light petroleum containing a small quantity of ether. The solid was collected and recrystallised from methanol, to give the pure *acetate* (37 g., 89·5%), m. p. 88—89° (Found: C, 65·85; H, 6·8; N, 3·45. $C_{22}H_{27}NO_6$ requires C, 65·8; H, 6·8; N, 3·5%). In an earlier experiment the mixture was refluxed for 1 hr., and the product was recrystallised from ether, yielding 7-(2-*methoxy*-4-*nitrophenoxy*)-1-*phenylhept*-1-*ene* (7·0 g., 35%), m. p. 97—99° (Found: C, 70·05; H, 6·4; N, 4·0. $C_{20}H_{23}NO_4$ requires C, 70·35; H, 6·8; N, 4·1%). Its structure was confirmed by catalytic reduction to the known 1-(4-amino-2-methoxyphenoxy)-7-phenylheptane (Table 2).

Similarly prepared was 5-(2-*methoxy*-4-*nitrophenoxy*)-1-*phenylpentyl acetate* (71%), m. p. 114—115° (Found: C, 64·55; H, 6·35; N, 3·7. $C_{20}H_{23}NO_6$ requires C, 64·3; H, 6·2; N, 3·7%).

5-(2-*Methoxy*-4-*nitrophenoxy*-1-*phenylpentan*-1-*one Diethyl Acetal*.—1-Benzoyl-4-(2-methoxy-4-nitrophenoxy)butane (15 g.) in ethanol (100 ml.) was treated with ethyl orthoformate (5·8 g.) and one drop of concentrated hydrochloric acid. After 3 days at about 35—40° the mixture was filtered from some starting material (4·8 g.) and concentrated. Ether was added and a further quantity of starting material (1·2 g.) was collected. The ether was removed from the filtrate, and the product was recrystallised from ether–light petroleum, to give the *diethyl acetal* (10·2 g., 55·5%), m. p. 62—64° (Found: C, 65·5; H, 7·4; N, 3·55. $C_{22}H_{29}NO_6$ requires C, 65·5; H, 7·2; N, 3·5%).

Ethyl α-(4-p-*nitrophenoxybutyl*)*benzoylacetate* was prepared (62%) from benzoylacetic ester and 4-*p*-nitrophenoxybutyl bromide as described above for the *p*-methoxy-derivative. After crystallisation from methanol it had m. p. 74—75° (Found: C, 65·1; H, 5·9; N, 3·8. $C_{21}H_{23}NO_6$ requires C, 65·5; H, 6·0; N, 3·6%).

6-p-*Nitrophenoxy*-1-*phenylhexan*-1-*one*.—(*a*) The foregoing ester (33·3 g.) was hydrolysed by potassium hydroxide (13 g.) in refluxing methanol (250 ml.) and water (250 ml.) for 24 hr. The *ketone* (80%), recrystallised from ethanol, had m. p. 102° (Found: C, 69·1; H, 6·0; N, 4·5. $C_{18}H_{19}NO_4$ requires C, 69·0; H, 6·1; N, 4·5%). 6-*p*-Nitrophenoxyhexanoic acid (1·8 g.), m. p. 103—104°, not depressed by an authentic sample,[3] was isolated from the alkaline mother-liquors. In an experiment which was similar except that less water was used, the product was largely the acid, with only a small amount of ketone.

(*b*) The same compound was obtained (76%) by condensation of potassium *p*-nitrophenoxide with 5-benzoylpentyl bromide.

5-p-*Nitrophenoxy*-1-*phenylpentan*-1-*one* was similarly obtained from benzoylacetic ester and 3-*p*-nitrophenoxypropyl bromide in 26% overall yield. 5-*p*-Nitrophenoxypentanoic acid (13%) was also formed. The ketone has been previously made from benzoylbutyl bromide.[1]

6-p-*Nitrophenoxy*-1-*phenylhexan*-1-*ol* was prepared (94%) by reduction (Meerwein–Ponndorf method [1]) of the corresponding nitro-ketone. After crystallisation from light petroleum (b. p. 100—120°) it had m. p. 72—74° (Found: C, 68·7; H, 6·75. $C_{18}H_{21}NO_4$ requires C, 68·5; H, 6·7%).

S-5-(2-*Methoxy*-4-*nitrophenoxy*)*pentylthiourea*.—A mixture of 5-(2-methoxy-4-nitrophenoxy)-pentyl bromide (63·6 g.), thiourea (15·2 g.), and ethanol (150 ml.) was refluxed for 20 hr., cooled, and diluted with an equal volume of ether. The *thiouronium bromide* (93%) had m. p. 158—159° (from ethanol) (Found: Br, 18·95; S, 7·9. $C_{13}H_{19}N_3O_4S,HBr$ requires Br, 20·3; S, 8·1%).

5-(2-*Methoxy*-4-*nitrophenoxy*)*pentane*-1-*thiol*.—A mixture of the foregoing thiouronium salt (95 g.) and 1·86N-sodium hydroxide (129 ml.) was refluxed for 3 hr. (under nitrogen), cooled, and extracted with chloroform. The dried extract on evaporation afforded the *thiol* (79%),

m. p. 77—80°. A distilled specimen, b. p. 216°/0·2 mm., was crystallised from ether and had m. p. 84—86° (Found: N, 5·2; S, 11·6%; *M*, 299. $C_{12}H_{17}NO_4S$ requires N, 5·2; S, 11·8%; *M*, 271). On several occasions, samples suddenly decomposed during distillation.

1-(2-*Methoxy*-4-*nitrophenoxy*)-5-*methylthiopentane*.—A mixture of the foregoing thiol (6·15 g.) and a solution from sodium (0·52 g.) in ethanol (30 ml.) was refluxed whilst methyl iodide (3·55 g., 1·1 mol.) in ethanol (10 ml.) was added during 15 min. After a further 4 hr. the mixture was evaporated and the residue was dissolved in chloroform. The washed and dried extract was distilled, giving the *sulphide* (55%), b. p. 185—205°/0·15 mm., m. p. 56—59°. A specimen recrystallised from ether had m. p. 59—61° (Found: C, 55·05; H, 6·85; S, 11·4. $C_{13}H_{19}NO_4S$ requires C, 54·7; H, 6·7; S, 11·2%).

1-2′-*Hydroxyethylthio*-5-(2-*methoxy*-4-*nitrophenoxy*)*pentane*.—2-Mercaptoethanol (15·6 g.) and 5-(2-methoxy-4-nitrophenoxy)pentyl bromide (60·4 g.) were added successively to a solution from sodium (4·6 g.) in ethanol (150 ml.), and the mixture was refluxed for 1 hr., cooled, and filtered. The filtrate was concentrated and diluted with ether. The crystalline product was washed with ether and water, and crystallised from methanol to give the *sulphide* (52%), m. p. 52—54° (Found: N, 4·5; S, 9·95. $C_{14}H_{21}NO_5S$ requires N, 4·4; S, 10·2%).

Similarly prepared were 1-*benzylthio*-3-(2-*methoxy*-4-*nitrophenoxy*)*propane* (80%), m. p. 51—53° (from methanol–ethanol) (Found: N, 4·2; S, 9·3. $C_{17}H_{19}NO_4S$ requires N, 4·2; S, 9·6%), 1-(2-*methoxy*-4-*nitrophenoxy*)-5-*phenylthiopentane* (83%), m. p. 54—55° (from ether–light petroleum) (Found: C, 62·6; H, 6·4; S, 9·35. $C_{18}H_{21}NO_4S$ requires C, 62·2; H, 6·1; S, 9·2%), and 1-p-*chlorophenylthio*-5-(2-*methoxy*-4-*nitrophenoxy*)*pentane* (76%), m. p. 67—69° (from ethanol–ether) (Found: N, 3·7; S, 8·0. $C_{18}H_{20}ClNO_4S$ requires N, 3·7; S, 8·4%).

Similarly prepared, but by using 5-*p*-nitrophenoxypentyl bromide, were 1-p-*nitrophenoxy*-5-*phenylthiopentane* (90%), m. p. 67° (from ethanol) (Found: N, 4·3; S, 10·5. $C_{17}H_{19}NO_3S$ requires N, 4·4; S, 10·1%), 1-p-*nitrophenoxy*-5-p-*nitrophenylthiopentane* (88%), m. p. 83—84° (from acetic acid) (Found: N, 7·7; S, 8·8. $C_{17}H_{18}N_2O_5S$ requires N, 7·7; S, 8·8%), and 5-*benzylthio*-1-p-*nitrophenoxypentane* (77%), m. p. 33—34° (from ethanol) (Found: N, 4·05; S, 9·7. $C_{18}H_{21}NO_3S$ requires N, 4·2; S, 9·7%).

1-(2-*Methoxy*-4-*nitrophenoxy*)-3-*phenylthiopropane*.—Thiophenol (11·0 g.) was added to a solution from sodium (2·3 g.) in dry ethanol (100 ml.), followed by 1,3-dibromopropane (40·4 ml.). After being refluxed for 0·5 hr. the mixture was concentrated and the residue dissolved in ether; the solution was washed with water, dried, and concentrated. Excess of 1,3-dibromopropane was removed by steam-distillation and the residual 3-phenylthiopropyl bromide was condensed with potassium 2-methoxy-4-nitrophenoxide to give the *nitro-compound* (54%), m. p. 87—89° (from ethanol) (Found: N, 4·5; S, 10·15. $C_{16}H_{17}NO_4S$ requires N, 4·4; S, 10·0%).

1-(2-*Methoxy*-4-*nitrophenoxy*)-5-*phenylsulphonylpentane*.—1-(2-Methoxy-4-nitrophenoxy)-5-phenylthiopentane (27 g.) in acetic acid (200 ml.) was treated with 30% w/v hydrogen peroxide (20 ml.); the temperature rose to 50°. After 2·5 hr. the solution was heated at 90° for 1 hr., cooled, and poured into water. The product slowly solidified and recrystallised from ethanol, to give the *sulphone* (88%), m. p. 122—124° (Found: C, 57·6; H, 5·9; S, 8·2. $C_{18}H_{21}NO_6S$ requires C, 57·0; H, 5·6; S, 8·4%).

Similarly prepared were: 1-(2-*methoxy*-4-*nitrophenoxy*)-5-*methylsulphonylpentane* (66%), m. p. 95—97% (from ethanol) (Found: N, 4·5; S, 9·7. $C_{13}H_{19}NO_6S$ requires N, 4·4; S, 10·1%); 1-p-*nitrophenoxy*-5-*phenylsulphonylpentane* (97%), m. p. 85—86° (from ethanol) (Found: C, 58·1; H, 5·8; N, 3·9. $C_{17}H_{19}NO_5S$ requires C, 58·5; H, 5·45; N, 4·0%); 1-p-*nitrophenoxy*-5-p-*nitrophenylsulphonylpentane* (94%), m. p. 129—130° (from acetic acid) (Found: N, 7·1; S, 8·1. $C_{17}H_{19}NO_5S$ requires N, 7·1; S, 8·1%); and 1-*benzylsulphonyl*-5-p-*nitrophenoxypentane* (88%), m. p. 120—121° (from acetic acid) (Found: C, 59·25; H, 6·1; N, 3·8. $C_{18}H_{21}NO_5S$ requires C, 59·5; H, 5·8; N, 3·9%).

1-p-*Acetamidophenylsulphonyl*-5-p-*nitrophenoxypentane*.—A mixture of 5-*p*-nitrophenoxypentyl bromide (28·8 g.), *p*-acetamidobenzenesulphinic acid (19·9 g.), sodium acetate (7·0 g.), sodium iodide (2·0 g.), 2-ethoxyethanol (200 ml.), and water (5 ml.) was refluxed for 2·5 hr., concentrated and diluted with water. Recrystallisation of the product from ethanol afforded the *sulphone* (55%), m. p. 112—113° (Found: C, 56·4; H, 5·5; N, 6·6. $C_{19}H_{22}N_2O_6S$ requires C, 56·2; H, 5·4; N, 6·9%).

5-p-*Nitrophenoxypentyl Phenyl Sulphoxide*.—30% Hydrogen peroxide (14·6 ml.) was added to a solution of 1-*p*-nitrophenoxy-5-phenylthiopentane (40 g.) in acetic acid (400 ml.) at 40°. The solution was heated at 80° for 30 min., cooled, diluted with water, and filtered. The

product was recrystallised from ethanol, giving the *sulphoxide* (98%), m. p. 80—81° (Found: C, 60·6; H, 5·7; N, 4·2. $C_{17}H_{19}NO_4S$ requires C, 61·3; H, 5·7; N, 4·2%). Similarly prepared was *benzyl* 5-p-*nitrophenoxypentyl sulphoxide* (92%), m. p. 97—98° (from aqueous ethanol) (Found: C, 62·0; H, 6·15; N, 4·05. $C_{18}H_{21}NO_4S$ requires C, 62·2; H, 6·05; N, 4·0%).

2-*Methoxy*-4-*nitrophenyl Tetra*-O-*acetyl*-D-*glucoside*.—A mixture of potassium 2-methoxy-4-nitrophenoxide (14·1 g., dried azeotropically with benzene), acetobromoglucose (28 g.), and dimethylformamide (100 ml.) was stirred for 20 hr., then filtered, and the solid was washed with benzene (200 ml.). The combined solutions were evaporated under reduced pressure, and the residue, in benzene, was stirred with activated alumina (7 × 20 g.) to remove free phenol. The filtered solution was evaporated and the residue crystallised from ether, to give the *glucoside* (49%), m. p. 145—147° (Found: C, 50·7; H, 5·2; N, 2·9. $C_{21}H_{25}NO_{13}$ requires C, 50·5; H, 5·05; N, 2·8%). The same compound was obtained in traces on using the free phenol, silver carbonate, quinoline, and acetobromoglucose in ether.

2-*Methoxy*-4-*nitrophenyl* D-*Glucoside*.—The foregoing tetra-acetate (33·2 g.) in methanol (340 ml.) was treated with a solution of sodium hydroxide (11·2 g.) in a small amount of water and methanol (170 ml.) and kept for 30 min. The *product*, which separated, was filtered off and crystallised from methanol; it then had m. p. 212—213° (Found: C, 47·3; H, 4·9; N, 4·4. $C_{13}H_{17}NO_9$ requires C, 47·1; H, 5·2; N, 4·2%).

4-*Acetamido*-2-*methoxyphenol*.—2-Methoxy-4-nitrophenol (31 g.) was reduced over platinum oxide in ethanol (300 ml.). The resulting suspension (still containing catalyst) was evaporated under reduced pressure and the residue was refluxed for 30 min. with acetic anhydride (50 ml.), cooled, and filtered. The solid was washed with ether and crystallised from ethanol, giving the diacetyl derivative (50%), m. p. 150—152° (lit.,[27] 147°).

4-Acetamido-2-methoxyphenyl acetate (54 g.) was shaken with 2N-aqueous sodium hydroxide (242 ml.) containing wetting agent (" Lissapol," 1 drop) until dissolved (10 min.). The solution was filtered (charcoal), cooled in ice, and acidified with concentrated hydrochloric acid (53 ml.). The precipitated 4-acetamido-2-methoxyphenol (98%, m. p. 114—116°), after recrystallisation from ethyl acetate, had m. p. 115—117° (lit.,[8] m. p. 118°).

1-(4-*Acetamido*-2-*methoxyphenoxy*)-5-p-*nitrophenylpentane*.—4-Acetamido-2-methoxyphenol (15·35 g.) and 5-*p*-nitrophenylpentyl bromide [2] (23·1 g. of the crude product from the nitration of 5-phenylpentyl bromide) were added to a solution from sodium (1·95 g.) in ethanol (100 ml.), and the mixture was stirred and refluxed for 20 hr., then evaporated under reduced pressure. The residue was shaken with chloroform and water, and the chloroform solution was separated, dried, concentrated, and treated with ethyl acetate. The *product*, which separated, was recrystallised from methanol (yield 21%), and then had m. p. 115·5—116° (Found: C, 64·65; H, 6·7; N, 7·3. $C_{20}H_{24}N_2O_5$ requires C, 64·5; H, 6·5; N, 7·2%).

1-(2-*Hydroxy*-4-*nitrophenoxy*)-5-*phthalimidopentane*.—4-Nitrocatechol (18·2 g.) and 5-phthalimidopentyl bromide (34·7 g.) were added to 2-ethoxyethanol (100 ml.) and a solution of potassium hydroxide (6·6 g.) in water (20 ml.). The mixture was refluxed for 20 hr., cooled, and diluted with water. Recrystallisation of the product from acetic acid gave the *phthalimide* (41%), m. p. 137—139° (Found: N, 7·7. $C_{19}H_{18}N_2O_6$ requires N, 7·6%).

1-(2-*Methoxy*-4-*nitrophenoxy*)-5-*phthalimidopentane*.—A mixture of the foregoing hydroxy-compound (0·77 g.), anhydrous potassium carbonate (0·3 g.), methyl iodide (4 ml.), and acetone (30 ml.) was refluxed for 20 hr., then evaporated. The residue was treated with aqueous ethanol and the insoluble solid was crystallised from acetic acid. It had m. p. 147·5—148·5°, not depressed by a specimen prepared directly from 2-methoxy-4-nitrophenol (see Table 1).

1-(2-*Methoxy*-5-*nitrophenoxy*)-5-*phenylpentane*, m. p. 73—75° (from ethanol) (Found: C, 68·9; H, 6·9; N, 4·4. $C_{18}H_{21}NO_4$ requires C, 68·5; H, 6·7; N, 4·4%), was prepared (81%) from 2-methoxy-5-nitrophenol,[28] 5-phenylpentyl bromide, and 10N-aqueous potassium hydroxide in 2-ethoxyethanol.

1,2,3-*Trimethoxy*-5-*nitrobenzene*.—Nitric acid (*d* 1·42; 20 ml.) was added fairly slowly to 1,2,3-trimethoxybenzene (30 g.) in acetic acid (60 ml.). When the temperature reached 90—100°, ice-water was added. The product was washed well with water, and (by stirring) with hot dilute sodium hydroxide. It was re-washed with water, and crystallised from ethanol; it then had m. p. 100—102° (lit.,[11] m. p. 100°). The yield (39—41%) was reduced when more dilute nitric acid was employed.

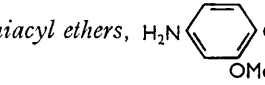
[27] Kehrmann and Hoehn, *Helv. Chim. Acta*, 1925, **8**, 218.
[28] Paul, *Ber.*, 1906, **39**, 2773; Reverdin and Crépieux, *Ber.*, 1906, **39**, 4232.

TABLE 1. *Nitroguaiacyl ethers,* O_2N(OMe)C_6H_3-O-$[CH_2]_n$-R

n	R	Yield (%)	M. p.	Solvent[a]	Formula	Found (%) C	Found (%) H	Found (%) N	Required (%) C	Required (%) H	Required (%) N
4	Me	71	54—55°	EtOH	$C_{12}H_{17}NO_4$	60·4	7·55	5·9	60·4	7·2	5·85
5	Me	69	69·5—70·5	EtOH	$C_{13}H_{19}NO_4$	62·1	7·7	5·45	61·7	7·5	5·5
6	Me	63	53—55	EtOH	$C_{14}H_{21}NO_4$	63·1	8·0	5·0	62·9	7·9	5·3
7	Me	87	37—38	EtOH–H_2O	$C_{15}H_{23}NO_4$	64·2	8·4	5·0	64·0	8·2	5·0
8	Me		[b]		$C_{16}H_{25}NO_4$						
9	Me	73	50	EtOH	$C_{17}H_{27}NO_4$	65·8	8·8	4·05	66·0	8·8	4·5
10	Me	87	49·5—50·5	EtOH	$C_{18}H_{29}NO_4$	66·9	9·2	4·45	66·9	9·0	4·3
11	Me	73	51—52·5	EtOH	$C_{19}H_{31}NO_4$	67·3	9·5	4·3	67·6	9·2	4·2
15	Me	73	57—58·5	EtOH	$C_{23}H_{39}NO_4$	70·55	10·35	3·5	70·2	9·9	3·6
1	$CHEt_2$	45	[c]		$C_{13}H_{19}NO_4$	61·6	7·3	5·7	61·65	7·6	5·5
1	$CHEtBu^n$	44	[d]		$C_{15}H_{23}NO_4$			5·1			5·0
0	$CHMe{\cdot}C_6H_{13}$-n	18	42—43	MeOH	$C_{15}H_{23}NO_4$	64·2	8·2	5·0	64·0	8·25	5·0
1	$CHMe{\cdot}CH_2Bu^t$		[b]		$C_{16}H_{25}NO_4$						
0	$CHMe{\cdot}C_7H_{15}$-n	19[e]	[f]		$C_{16}H_{25}NO_4$	65·3	8·7	4·7	65·1	8·5	4·7
2	$CHMe{\cdot}[CH_2]_2{\cdot}CH_2Pr^i$	29	[g]		$C_{17}H_{27}NO_4$	66·1	8·9	4·6	66·0	8·8	4·5
0	Cyclopentyl	53	83—85	EtOH	$C_{12}H_{15}NO_4$	60·6	6·4	5·8	60·7	6·3	5·9
2	Cyclohexyl	64	78—80	EtOH	$C_{15}H_{21}NO_4$	64·2	7·6	5·1	64·5	7·6	5·0
5	Cyclohexyl	66	57—58	Pet	$C_{18}H_{27}NO_4$	67·5	8·2	4·3	67·3	8·5	4·35
1	$CH{:}CH_2$	85	51—52·5	Et_2O–Pet	$C_{10}H_{11}NO_4$	57·7	5·4	6·6	57·4	5·3	6·7
3	$CH{:}CH_2$	68[h]	65—66	EtOH–H_2O	$C_{12}H_{15}NO_4$	60·8	6·3	5·9	60·7	6·3	5·9
2	$CH{:}CHBu^n$	36[i]	[j]		$C_{14}H_{19}NO_4$	63·8	7·5	5·3	63·4	7·2	5·3
1	COMe	63	116—118	EtOH	$C_{10}H_{11}NO_5$	53·8	4·9	6·2	53·3	4·9	6·2
5	OAc	89[k]	75—76	EtOH	$C_{14}H_{19}NO_6$	56·9	6·65	4·8	56·6	6·4	4·7
1	CO_2Et	79[h]	86—88	MeOH	$C_{11}H_{13}NO_6$	52·0	5·35	5·6	51·8	5·1	5·5
1	CO_2H	91[m]	165·5—167	AcOH–H_2O	$C_9H_9NO_6$	47·1	4·0	6·1	47·6	4·0	6·2
2	NEt_2	49[n]	[o]		$C_{13}H_{20}N_2O_4$	58·35	7·5	10·2	58·2	7·5	10·4
1	Ph	70	80—82	$OH{\cdot}[CH_2]_2{\cdot}OEt$	$C_{14}H_{13}NO_4$	65·0	5·2	5·4	64·9	5·0	5·4
2	Ph	66	97—99	EtOH	$C_{15}H_{15}NO_4$	65·9	5·55	5·3	65·9	5·5	5·1
	Ph	85	72·5—73·5	EtOH	$C_{16}H_{17}NO_4$	67·25	5·75	4·9	66·9	5·9	4·9
4	Ph		[p]		$C_{17}H_{19}NO_4$						
0	$CHMe{\cdot}[CH_2]_2{\cdot}Ph$	55	50—51	EtOH	$C_{17}H_{19}NO_4$	67·7	6·4	4·5	67·75	6·4	4·65
5	Ph	81[q]	75—76[o]	EtOH	$C_{18}H_{21}NO_4$			4·4			4·4
6	Ph		55—57	Pet	$C_{19}H_{23}NO_4$	69·0	6·9	4·3	69·3	7·0	4·3
0	$CHMe{\cdot}[CH_2]_4{\cdot}Ph$	58	65·5—67·5	Et_2O–Pet	$C_{19}H_{23}NO_4$	69·45	7·15	4·3	69·3	7·0	4·3
7	Ph	59	73—74	EtOH	$C_{20}H_{25}NO_4$	69·7	7·4	4·2	69·9	7·3	4·1
8	Ph	62	49—50	$COMe_2$–EtOH	$C_{21}H_{27}NO_4$	70·4	7·6	3·95	70·6	7·6	3·9
5	C_6H_4Me-*o*	82	76—77	EtOH	$C_{19}H_{23}NO_4$	69·4	7·35	4·3	69·3	7·0	4·25
5	C_6H_4Me-*p*	84	76—78	EtOH	$C_{19}H_{23}NO_4$	69·2	7·2	4·3	69·3	7·0	4·25

5	C_6H_4·OMe-*p*	57 [r]	81—82	EtOH	$C_{19}H_{23}NO_5$	66·2	6·9	4·1	66·1	6·7	4·1
5	$C_6H_4NO_2$-*p*	45	84 and 93—94	$COMe_2$–EtOH	$C_{18}H_{20}N_2O_6$	60·1	5·8	7·95	60·0	5·6	7·8
5	$C_6H_3(NO_2)_2$-2,4	58	86—87	EtOAc	$C_{18}H_{19}N_3O_8$	53·1	4·6	10·4	53·3	4·7	10·4
3	·CH:CHPh-*trans*	74	95—97	EtOH	$C_{18}H_{19}NO_4$	69·0	5·9	4·5	69·0	6·1	4·5
3	·CH:CH·C_6H_4Me-*p*-*trans*	57	103—103·5	EtOAc–Pet [s]	$C_{19}H_{21}NO_4$	70·0	6·5	4·3	69·7	6·5	4·3
3	·CH:CH·C_6H_4·OMe-*p*-*trans*	60 [t]	121—121·5	EtOH–EtOAc	$C_{19}H_{21}NO_5$	66·9	6·3	4·2	66·5	6·1	4·1
1	*p*-C_6H_4·SO_2Me	87	195—197	EtOH	$C_{15}H_{15}NO_6S$ [u]			4·2			4·15
1	1-Naphthyl	62	110—111	EtOH–$COMe_2$	$C_{18}H_{15}NO_4$	69·7	5·15	4·7	69·9	4·9	4·5
1	OMe	82 [v]	89—92	EtOH–Pet [w]	$C_9H_{11}NO_5$	50·6	5·35	6·5	50·7	5·2	6·6
5	OMe	66	[x]		$C_{13}H_{19}NO_5$			5·3			5·2
2	O·CH_2Ph	80 [y]	75—77	EtOH	$C_{16}H_{17}NO_5$	63·3	5·8	4·7	63·4	5·6	4·6
5	O·CH_2Ph	71 [z]	90—91	EtOH	$C_{19}H_{23}NO_5$	66·2	7·0	4·15	66·0	6·7	4·05
2	OPh	90	116—117	EtOH	$C_{15}H_{15}NO_5$	62·45	5·3	4·8	62·3	5·2	4·8
3	OPh	73	100—102	EtOH	$C_{16}H_{17}NO_5$	63·8	5·5	4·7	63·4	5·6	4·6
4	OPh	89	90—91·5	EtOH	$C_{17}H_{19}NO_5$	64·5	6·3	4·4	64·3	6·0	4·4
5	OPh	80	67—68	EtOH	$C_{18}H_{21}NO_5$	65·3	6·3	4·2	65·3	6·4	4·2
6	OPh	84	81—82	EtOH	$C_{19}H_{23}NO_5$	66·2	6·7	4·0	66·2	6·7	4·1
7	OPh	70	56—57	EtOH	$C_{20}H_{25}NO_5$	66·7	7·1	4·1	66·9	7·0	3·9
8	OPh	82	58—59	EtOH	$C_{21}H_{27}NO_5$	67·65	7·1	3·8	67·6	7·2	3·8
3	O·C_6H_4·OMe-*p*	32	96—97	EtOH	$C_{17}H_{19}NO_6$	61·6	5·6	4·2	61·2	5·8	4·2
4	O·C_6H_4·OMe-*p*	85	106—107	EtOH	$C_{18}H_{21}NO_6$	62·3	6·1	4·1	62·6	6·1	4·0
5	O·C_6H_4·NHAc-*p*	86	122—123	EtOH	$C_{20}H_{24}N_2O_6$ [aa]			7·3			7·2
5	O·C_6H_4·NO_2-*p*	78	95—96	AcOH	$C_{18}H_{20}N_2O_7$			7·6			7·45
5	Phthalimido	78 [ab]	147·5—148·5	AcOH	$C_{20}H_{26}N_2O_6$			7·3			7·3
6	Phthalimido	61	81—83	EtOH	$C_{21}H_{28}N_2O_6$	63·3	5·9	7·25	63·3	5·5	7·0
8	Phthalimido	79	91—92	AcOH	$C_{23}H_{28}N_2O_6$			6·5			6·6
5	NH·COPh	64 [ac]	131—132	EtOAc	$C_{19}H_{22}N_2O_5$			7·9			7·8
5	NH·CO·CH_2·NH·COPh	95 [ad]	129—130	$COMe_2$	$C_{21}H_{25}N_3O_6$			10·4			10·1
5	NH·CO·$[CH_2]_3$·CO_2H	99 [ae]	94—97	$COMe_2$–Pet	$C_{17}H_{24}N_2O_7$	55·5	6·7	7·6	55·4	6·5	7·6
5	Glutarimido	83 [af]	138—140	EtOH	$C_{17}H_{22}N_2O_6$	58·6	6·2	8·0	58·3	6·3	8·0
1	COPh	84	122—123	OEt·$[CH_2]_2$·OH	$C_{18}H_{19}NO_5$	62·4	4·8	4·7	62·7	4·5	4·9
4	COPh	59	91	OEt·$[CH_2]_2$·OH	$C_{18}H_{19}NO_5$	65·7	5·8	4·2	65·7	5·8	4·3
6	COPh	81	82—84	EtOH	$C_{20}H_{23}NO_5$	67·1	6·4	3·9	67·25	6·45	3·9
4	CHPh·OH	94 [ag]	76—77	Et_2O–Pet	$C_{18}H_{21}NO_5$	65·2	6·6	4·1	65·2	6·4	4·2
6	CHPh·OH	89 [ag]	62—63	Et_2O–Pet	$C_{20}H_{23}NO_5$	67·1	7·0	3·9	66·8	7·0	3·9

[a] Solvent for crystn. Pet = light petroleum (b. p. 40—60°, except where stated). [b] Not obtained crystalline; reduced directly to amine. [c] B. p. 150—170°/0·05 mm. [d] B. p. 164—184°/0·02 mm. [e] Toluene-*p*-sulphonate of alcohol used. [f] B. p. 186—194°/0·8 mm. [g] B. p. 204—215°/0·3 mm. [h] Overall from pent-4-en-1-ol, *via* the toluene-*p*-sulphonate.[3] [i] Overall from hept-3-en-1-ol *via* the toluene-*p*-sulphonate. [j] B. p. 164—186°/0·1 mm. [k] From nitroguaiacyloxypentyl bromide and KOAc (cf. ref. 3). [l] $CH_2Br·CO_2Et$ in acetone used. [m] By hydrolysis of the ethyl ester with 0·8N-aqueous sodium hydroxide. [n] From $CH_2Cl·CH_2·NEt_2$ in acetone. [o] B. p. 175—200°/0·15 mm. [p] Not obtained crystalline; reduced directly to amine. [q] Overall from 5-phenylpentanol. [r] Overall from 5-*p*-methoxyphenylpentanol. [s] B. p. 60—80°. [t] Overall from 5-*p*-methoxyphenylpent-4-en-1-ol. [u] Found: S, 9·4. Required, S, 9·5%. [v] From $CH_2Cl·OMe$. [w] B. p. 60—80°. [x] B. p. 170°/0·1 mm. [y] Toluene-*p*-sulphonate used. [z] From 5-benzyloxypentyl bromide (B.P. 770,870). [aa] Found: OMe, 8·0. Required OMe, 8·0%. [ab] Also prepared by methylation of the 2-hydroxy-compound (see text). [ac] By benzoylation of 5-(2-methoxy-4-nitrophenoxy)pentylamine. [ad] From 5-(2-methoxy-4-nitrophenoxy)pentylamine and 2-phenyloxazolone (cf. ref. 1). [ae] From 5-(2-methoxy-4-nitrophenoxy)pentylamine and glutaric anhydride (cf. ref. 1). [af] By cyclisation of the glutaramic acid with acetyl chloride (cf. ref. 1). [ag] By reduction (Meerwein–Ponndorf) of the ketone (cf. ref. 1).

TABLE 2. *Aminoguaiacyl ethers*, 

			Yield				Found (%)					Required (%)				
n	R	Derivative	(%)	M. p.	Solvent [a]	Formula	C	H	N	S	Hal	C	H	N	S	Hal
1	Me	Base	86	60—61° [b]	Et_2O–Pet	$C_9H_{13}NO_2$			8·2					8·4		
2	Me	Base	87	65—67	Et_2O–Pet	$C_{10}H_{15}NO_2$	66·6	8·4	7·8			66·3	8·3	7·7		
3	Me	Base	77	35—36	Pet	$C_{11}H_{17}NO_2$	67·6	8·6	7·2			67·7	8·8	7·2		
		$Me{\cdot}SO_3H$		173—175	EtOH	$C_{11}H_{17}NO_2,CH_4O_3S$			4·9	10·9				4·8	11·0	
4	Me	Base	92	43—44	Pet	$C_{12}H_{19}NO_2$	69·15	9·3	6·7			68·9	9·15	6·7		
		HCl		185—200	EtOH–Et_2O	$C_{12}H_{19}NO_2$,HCl			5·75		14·3			5·7		14·45
5	Me	Base	91	67—69	EtOH	$C_{13}H_{21}NO_2$	70·1	9·3	6·2		69·9	9·4	6·3			
		HCl		185—200	EtOH–Et_2O	$C_{13}H_{21}NO_2$,HCl			5·2		13·9			5·4		13·7
6	Me	Base	92	72—74	EtOH	$C_{14}H_{23}NO_2$	70·85	9·75	5·9			70·9	9·7	5·9		
7	Me	Base	76	63—64	EtOH	$C_{15}H_{25}NO_2$	72·0	10·0	5·55			71·7	10·0	5·6		
		$Me{\cdot}SO_3H$		120—125 and 200		$C_{15}H_{25}NO_2,CH_4O_3S$			3·6	9·4				4·0	9·2	
		Diptolate [c]		161—162	EtOAc	$C_{15}H_{25}NO_2,C_{20}H_{18}O_8$	65·7	6·8	2·3			65·9	6·8	2·2		
8	Me	Base	64 [d]	71—73	Et_2O–Pet	$C_{16}H_{27}NO_2$	72·4	10·3	5·1			72·5	10·2	5·3		
9	Me	Base	84	61—62	Pet	$C_{17}H_{29}NO_2$	72·9	10·5	4·8			73·1	10·5	5·0		
10	Me	Base	95	66—67	EtOH	$C_{18}H_{31}NO_2$	73·7	10·4	4·8			73·7	10·65	4·8		
11	Me	Base	90	65—66	EtOH	$C_{19}H_{33}NO_2$	74·3	11·0	4·7			74·3	10·7	4·6		
15	Me	Base	85	67—68	Et_2O–Pet	$C_{23}H_{41}NO_2$	76·2	11·35	3·9			76·0	11·3	3·9		
1	$CHEt_2$	HBr	69	214—217	EtOH–Et_2O	$C_{13}H_{21}NO_2$,HBr			4·4		26·0			4·6		26·2
1	$CHEtBu^n$	HBr	55	160—164	Et_2O–C_6H_6	$C_{15}H_{25}NO_2$,HCl			4·9		12·1			4·9		12·3
0	$CHMe{\cdot}C_6H_{13}{\cdot}n$	Base	83	[e]		$C_{15}H_{25}NO_2$	71·7	10·3	5·8			71·7	10·0	5·6		
		HCl		160—180	EtOH–Et_2O	$C_{15}H_{25}NO_2$,HCl			5·0		12·2			4·9		12·3
2	$CHMe{\cdot}CH_2Bu^t$	Base	62 [d]	72—73·5	Et_2O–Pet	$C_{16}H_{27}NO_2$	72·8	10·4	5·35			72·5	10·2	5·3		
0	$CHMe{\cdot}C_7H_{15}{\cdot}n$	Base	49	[f]		$C_{16}H_{27}NO_2$	72·3	10·9	5·35			72·5	10·2	5·3		
		HCl		164—168		$C_{16}H_{27}NO_2$,HCl			4·8		11·6			4·65		11·75
2	$CHMe{\cdot}[CH_2]_2{\cdot}CH_2Pr^i$	HCl	59	158—164	EtOH–Et_2O	$C_{17}H_{29}NO_2$,HCl			4·3		11·4			4·4		11·2
0	Cyclopentyl	Base	83	64—66	EtOH–Pet [g]	$C_{12}H_{17}NO_2$	69·8	8·4	6·8			69·6	8·2	6·8		
2	Cyclohexyl	Base	80	64—65	Pet [g]	$C_{15}H_{23}NO_2$	71·85	9·1	5·65			72·2	9·3	5·6		
5	Cyclohexyl	Base	80	91—91·5	MeOH	$C_{18}H_{29}NO_2$	74·6	9·8	4·85			74·3	10·0	4·8		
3	$CH{:}CH_2$	Base	90 [h]	25—26	Et_2O–Pet	$C_{12}H_{17}NO_2$	69·4	8·3	6·8			69·5	8·2	6·8		
		HBr		195—197	Dil. aq. HBr	$C_{12}H_{17}NO_2$,HBr			4·85		27·5			4·9		27·8
2	$CH{:}CHBu^n$	Base	42 [h]	38—42	Pet	$C_{14}H_{21}NO_2$	71·7	9·3	6·1			71·5	9·0	5·95		
1	$CHMe{\cdot}OH$	Base	78 [i]	125—126	EtOH	$C_{10}H_{15}NO_3$	60·7	7·6	7·0			60·9	7·7	7·1		
5	OAc	Base	71	46—48	EtOH–H_2O	$C_{14}H_{21}NO_4$	62·5	7·75	5·2			62·9	7·9	5·2		
5	OH	Base	93 [j]	70—71	$CHCl_3$–Pet	$C_{12}H_{19}NO_3$	63·9	8·6	6·15			64·0	8·45	6·2		
1	CO_2H	Base	93	200—202	H_2O	$C_9H_{11}NO_4$	54·4	5·6	7·2			54·8	5·6	7·1		
2	NEt_2	2HBr	81	216—218	MeOH–Et_2O	$C_{13}H_{22}N_2O_2$,2HBr			6·7		39·7			6·9		39·6
1	Ph	Base	39	84—85	Pet [k]	$C_{14}H_{15}NO_2$	73·1	6·5	5·95			73·4	6·6	6·1		
		$Me{\cdot}SO_3H$		200—201	EtOH–Et_2O	$C_{14}H_{15}NO_2,CH_4O_3S$			4·05	9·9				4·3	9·8	
2	Ph	Base	78	47—48	Et_2O–Pet	$C_{15}H_{17}NO_2$	73·75	6·85	5·8			74·1	7·0	5·8		
		$Me{\cdot}SO_3H$		159—160	EtOH–Et_2O	$C_{15}H_{17}NO_2,CH_4O_3S$			4·1	9·65				4·1	9·4	
3	Ph	Base	90	103—104	EtOH	$C_{16}H_{19}NO_2$	74·95	7·4	5·5			74·7	7·4	5·4		
		$Me{\cdot}SO_3H$		159—160	EtOH–Et_2O	$C_{16}H_{19}NO_2,CH_4O_3S$			4·1	9·05				4·0	9·1	
4	Ph	$Me{\cdot}SO_3H$	60	123—124	EtOH	$C_{17}H_{21}NO_2,CH_4O_3S$			3·7	8·8				3·8	8·7	

5	Ph	Base	90 [m]	77—78	EtOH	$C_{18}H_{23}NO_2$	76·05	8·4	4·8			75·75	8·1	4·9		
		Me·SO_3H	86 [n]	138·5—139·5		$C_{18}H_{23}NO_2,CH_4O_3S$			3·6	8·5				3·7	8·4	
		HCl		147—149 (clears 158—160)	EtOH–Et_2O	$C_{18}H_{23}NO_2$,HCl			4·3		11·0			4·3		11·1
6	Ph	Base	38 [o]	39—41	Et_2O–Pet	$C_{19}H_{25}NO_2$	76·4	8·35	4·7			76·2	8·4	4·7		
0	CHMe·$[CH_2]_4$·Ph	Base	70	42—44	Et_2O–Pet	$C_{19}H_{25}NO_2$	76·1	8·4	4·7			76·2	8·4	4·7		
7	Ph	Base	80	65	EtOH–Pet	$C_{20}H_{27}NO_2$	76·75	8·9	4·3			76·6	8·7	4·5		
8	Ph	Base	87	52—53	Et_2O–Pet	$C_{21}H_{29}NO_2$	76·7	8·8	4·3			77·0	8·8	4·3		
5	C_6H_4Me-*o*	Base	73	69—71	EtOH–H_2O	$C_{19}H_{25}NO_2$	76·1	8·45	4·5			76·2	8·4	8·7		
5	C_6H_4Me-*p*	Base	91	84—86	EtOH–Pet	$C_{19}H_{25}NO_2$	76·35	8·6	4·7			76·2	8·4	4·7		
5	C_6H_4·OMe-*p*	Base	93	98—100	EtOH	$C_{19}H_{25}NO_3$	72·5	8·0	4·45			72·4	7·9	4·45		
5	C_6H_4·NO_2-*p*	Base	82 [p]	86—87	EtOH	$C_{18}H_{22}N_2O_4$			8·5					8·6		
5	C_6H_4·NH_2-*p*	Base	90	68—69	Et_2O	$C_{18}H_{24}N_2O_2$	72·05	8·15	9·2			72·0	8·05	9·3		
5	$C_6H_3(NH_2)_2$-2,4	Base	71	99—100	EtOH–Pet	$C_{18}H_{25}N_3O_2$	68·9	8·25	13·2			68·5	8·0	13·3		
3	CH:CHPh-*trans*	Base	94 [h]	90—92	EtOH–H_2O	$C_{18}H_{21}NO_2$	76·6	7·45	4·8			76·3	7·5	4·9		
		Me·SO_3H		188—190	EtOH–Et_2O	$C_{18}H_{21}NO_2,CH_4O_3S$			3·6	8·4				3·7	8·4	
3	CH:CH·C_6H_4Me-*p*-*trans*	Base	88 [h]	104—105	EtOH–H_2O	$C_{19}H_{23}NO_2$	76·9	8·1	4·65			76·7	7·8	4·7		
3	CH:CH·C_6H_4OMe-*p*-*trans*	Base	88 [h]	117—118	EtOH	$C_{19}H_{23}NO_3$	76·65	7·7	4·5			72·8	7·35	4·5		
1	1-Naphthyl	Base	65	61—63	Et_2O	$C_{18}H_{17}NO_2$	77·05	6·5	5·3			77·4	6·1	5·0		
		Me·SO_3H		192—194	EtOH	$C_{18}H_{17}NO_2,CH_4O_3S$			3·6	8·5				3·7	8·5	
1	C_6H_4·SO_2Me-*p*	Base	85	130	OH·$[CH_2]_2$·OEt–Et_2O	$C_{15}H_{17}NO_4S$			4·6	10·5				4·6	10·4	
1	OMe	Base	80	61—62	EtOH–Et_2O	$C_9H_{13}NO_3$	58·6	7·2	7·85			59·0	7·15	7·6		
5	OMe	Base	78	[q]		$C_{13}H_{21}NO_3$	65·05	8·95	5·9			65·3	8·8	5·9		
		Me·SO_3H	88	124—126	EtOH–Et_2O	$C_{13}H_{21}NO_3,CH_4O_3S$			4·2	9·4				4·2	9·6	
2	O·CH_2Ph	Base	88	41—42	EtOH–Pet	$C_{16}H_{19}NO_3$	70·1	7·1	5·2			70·3	7·0	5·1		
		Me·SO_3H		138—139	EtOH–Et_2O	$C_{16}H_{19}NO_3,CH_4O_3S$			3·6	8·6				3·8	8·7	
5	OCH_2Ph	Base	80	34—35	Pet [r]	$C_{19}H_{25}NO_3$	72·1	8·0	4·5			72·3	7·9	4·45		
		Me·SO_3H		122—124	EtOH–Et_2O	$C_{19}H_{25}NO_3,CH_4O_3S$			3·1	7·9				3·4	7·8	
2	OPh	Base	84	106—107	EtOH	$C_{15}H_{17}NO_3$	69·3	6·5	5·5			69·5	6·6	5·45		
3	OPh	Base	81	76—78	EtOH	$C_{16}H_{19}NO_3$	70·3	6·85	5·25			70·3	7·0	5·1		
4	OPh	Base	74	115—117	EtOH	$C_{17}H_{21}NO_3$	70·9	7·3	4·9			71·1	7·3	4·9		
5	OPh	Base	81	47—48	$CHCl_3$–Pet	$C_{18}H_{23}NO_3$	71·45	7·5	4·6			71·7	7·7	4·65		
		Me·SO_3H	83	125	EtOH–Et_2O	$C_{18}H_{23}NO_3,CH_4O_3S$			3·5					3·5		
6	OPh	Base	75	104—104·5	EtOH	$C_{19}H_{25}NO_3$	72·55	8·2	4·5			72·4	7·9	4·4		
7	OPh	Base	73	57—58	EtOH	$C_{20}H_{27}NO_3$	73·2	8·5	4·4			73·0	8·2	4·3		
8	OPh	Base	78	76—77	CCl_4	$C_{21}H_{29}NO_3$	73·5	8·5	4·1			73·5	8·5	4·1		
3	O·C_6H_4·OMe-*p*	Base	79	66—67·5	EtOH	$C_{17}H_{21}NO_4$	67·1	7·0	4·9			67·3	7·0	4·6		
4	O·C_6H_4·OMe-*p*	Base	74	105—107	EtOH	$C_{18}H_{23}NO_4$	67·75	7·25	4·5			68·1	7·3	4·4		
5	O·C_6H_4·NHAc-*p*	Me·SO_3H	74	167—169	EtOH	$C_{20}H_{26}N_2O_4,CH_4O_3S$ [s]			6·1	7·3				6·2	7·05	
5	O·C_6H_4·NH_2-*p*	2Me·SO_3H	64	232—234	EtOH	$C_{18}H_{24}N_2O_3,2CH_4O_3S$			5·6	13·05				5·5	12·6	
5	Phthalimido	Base	61	103—105	EtOH	$C_{20}H_{22}N_2O_4$			7·9					7·9		
		Me·SO_3H	92	205—207	EtOH–Et_2O	$C_{20}H_{22}N_2O_4,CH_4O_3S$			6·0					6·2		
6	Phthalimido	Base	98	86—87	EtOH	$C_{21}H_{24}N_2O_4$	68·4	6·75	7·9			68·4	6·6	7·6		
8	Phthalimido	Base	82	70—71	EtOH	$C_{23}H_{28}N_2O_4$	69·6	7·05	7·1			69·7	7·1	7·1		
5	NH·COPh	Base	82	103—104	C_6H_6	$C_{19}H_{24}N_2O_3$	69·6	7·7	8·6			69·5	7·3	8·5		
5	NH·CO·CH_2·NHBz	Base	61	120·5—121·5	C_6H_6	$C_{21}H_{27}N_3O_4$	65·3	7·3	10·8			65·4	7·0	10·9		
5	Glutarimido	Base	83	94—95	EtOH	$C_{17}H_{24}N_2O_4$	63·5	7·0	8·85			63·8	7·5	8·8		
5	Phthalimidino	Base	76 [t]	129—130	EtOH	$C_{20}H_{24}N_2O_3$	70·3	7·0	8·3			70·55	7·1	8·2		
1	CHPh·OH	Base	51 [u]	96—97	EtOH–H_2O	$C_{15}H_{17}NO_3$	69·1	6·3	5·3			69·5	6·6	5·4		
4	CHPh·OH	Base	73 [u]	104—105	EtOH	$C_{18}H_{23}NO_3$	71·8	7·7	4·7			71·7	7·7	4·65		
6	CHPh·OH	Base	89 [u]	108—110	EtOH	$C_{20}H_{27}NO_3$	72·6	8·05	4·2			72·95	8·3	4·3		
4	CHPh·OAc	Base	72	67—68	Et_2O	$C_{20}H_{25}NO_4$	70·15	7·5	4·1			70·0	7·3	4·1		
6	CHPh·OAc	Base	74	36—37	Et_2O–Pet [g]	$C_{22}H_{29}NO_4$	71·4	8·1	3·9			71·15	7·85	3·8		
4	COPh	Base	61 [v]	101—103	MeOH	$C_{18}H_{21}NO_3$	72·1	7·0	4·7			72·3	7·0	4·7		

TABLE 2. (*Continued.*)

							Found (%)					Required (%)				
n	R	Derivative	Yield (%)	M. p.	Solvent [a]	Formula	C	H	N	S	Hal	C	H	N	S	Hal
6	COPh	Base	83 [v]	85—87°	EtOAc–Et_2O	$C_{20}H_{25}NO_3$	73·0	7·9	4·2			73·4	7·65	4·3		
4	$CHPh(OEt)_2$	Base	78	107—109	MeOH	$C_{22}H_{31}NO_4$	71·2	8·65	3·7			70·8	8·3	3·75		
5	SMe	Base	58 [h]	53·5—56	EtOH–H_2O	$C_{13}H_{21}NO_2S$			5·3					5·5		
5	$S[CH_2]_2$·OH	Base	41 [h]	38—40	Et_2O	$C_{14}H_{23}NO_3S$			5·1	11·25				4·9	11·2	
3	$S·CH_2Ph$	$Me·SO_3H$	62 [h]	134—136	MeOH	$C_{17}H_{21}NO_2S,CH_4O_3S$			3·3	15·95				3·5	16·1	
3	SPh	Base	75 [h]	57—58	EtOH–Et_2O	$C_{16}H_{19}NO_2S$			4·7	11·0				4·8	11·1	
5	SPh	Base	74 [h]	72—73	EtOH–H_2O	$C_{18}H_{23}NO_2S$	68·0	7·1		9·9		68·1	7·3		10·1	
5	$S·C_6H_4Cl$-*p*	Base	81 [h]	44—46	Et_2O–Pet	$C_{18}H_{22}ClNO_2S$			4·0		9·9			4·0		10·1
5	SO_2Me	Base	87	84—87	MeOH	$C_{13}H_{21}NO_4S$	54·5	7·2		11·35		54·4	7·3		11·15	
5	SO_2Ph	Base	73	89—90	EtOH	$C_{18}H_{23}NO_4S$	62·0	7·0		9·0		61·8	6·65		9·2	

[a] Solvent for recrystn. Pet = light petroleum (b. p. 40—60°, except where stated) [b] Lit.,[8] m. p. 55°. [c] Diptolate = di-*p*-toluoyl-D-tartrate. [d] Overall from potassium nitroguaiacyl oxide. [e] B. p. 143—146°/0·05 mm. [f] B. p. 160—170°/0·2 mm. [g] B. p. 60—80°. [h] Reduction by sodium sulphide in ethanol. [i] From the corresponding nitro-ketone. [j] By acid hydrolysis of the acetate (cf. ref. 3). [k] B. p. 100—120°. [l] Overall from 4-phenylbutyl bromide. [m] From 1-(2-methoxy-4-nitrophenoxy)-5-phenylpentane. [n] From 1-(2-methoxy-4-nitrophenoxy)-5-phenylpent-4-ene. [o] Overall from 6-phenylhexanol. [p] From the *N*-acetyl derivative by hydrolysis with 2N-aqueous hydrochloric acid in ethanol. [q] B. p. 160—165°/0·1 mm. [r] B. p. 80—100°. [s] Found: OMe, 6·85. Required: OMe, 6·8%. [t] From the corresponding phthalimide by reduction with tin and hydrochloric acid (see Part III [1]). [u] From the corresponding nitro-ketone. [v] By reduction of the nitro-ketone with iron–acetic acid.

TABLE 3. p-*Aminophenyl ethers*, p-$NH_2·C_6H_4·O·[CH_2]_n·R$.

							Found (%)				Required (%)			
n	R	Derivative	Yield (%)	M. p.	Solvent	Formula	C	H	N	S	C	H	N	S
4	COPh	Base	49 [b]	112—114°	EtOH	$C_{17}H_{19}NO_2$	75·9	7·0	5·25		75·9	7·1	5·2	
5	COPh	Base	56 [b]	61—63	C_6H_6–Pet [c]	$C_{18}H_{21}NO_2$	76·2	7·3	5·0		76·4	7·4	4·95	
5	CHPh·OH	Base	89 [d]	86—88	Et_2O–Pet	$C_{18}H_{23}NO_2$	75·8	8·2	4·95		75·8	8·1	4·9	
5	SPh	Base	92 [e]	63	C_6H_6–Pet	$C_{18}H_{21}NOS$			4·75	11·5			4·9	11·2
5	$S·C_6H_4·NH_2$-*p*	2HCl	66 [e]	220—230 (decomp.)	Dil. HCl	$C_{17}H_{22}N_2OS,2HCl$			7·3	8·55			7·5	8·5
5	$S·CH_2Ph$	$Me·SO_3H$	91 [e]	147—149	EtOH–Et_2O	$C_{18}H_{23}NOS,CH_4O_3S$			3·5	16·3			3·5	16·1
5	SOPh	Base	65 [e]	70—71	Et_2O	$C_{17}H_{21}NO_2S$	67·1	7·1	4·5		67·3	6·9	4·6	
5	$SO·CH_2Ph$	Base	66 [e]	89—90	Et_2O	$C_{18}H_{23}NO_2S$			4·5	10·45			4·4	10·1
5	SO_2Ph	Base	82	93—95	EtOH	$C_{17}H_{21}NO_3S$			4·4	9·9			4·4	10·0
5	$SO_2·C_6H_4·NH_2$-*p*	Base	84	136—138	EtOH	$C_{17}H_{22}N_2O_3S$			8·0	9·7			8·4	9·6
		Diacetyl		154		$C_{21}H_{26}N_2O_5S$			6·6				6·7	
5	$SO_2·C_6H_4·NHAc$-*p*	Base	87	126—128	EtOH	$C_{19}H_{24}N_2O_4S$	60·2	6·4	7·4		60·6	6·4	7·45	
5	$SO_2·CH_2Ph$	Base	94	101—102	EtOH	$C_{18}H_{23}N_4O_3S$			4·1	9·9			4·2	9·6

[a] Solvent for recrystn. Pet = light petroleum. [b] Nitro-ketone reduced with iron in 90% acetic acid. [c] B. p. 60—80°. [d] By catalytic reduction of either the nitro-ketone or nitro-alcohol. [e] Reduction by sodium sulphide in ethanol. [f] B. p. 80—100°.

TABLE 4. *N-Substituted amines*, $R''R'N\cdot C_6H_4(OMe)\cdot O\cdot[CH_2]_n\cdot R$

R′	R″	*n*	R	Deriv.	Yield (%)	M. p.	Solvent [a]	Formula	Found (%) C	H	N	Hal	Required (%) C	H	N	Hal
Me	H	5	Ph	Base	63	35° [b]	Et_2O–Pet	$C_{19}H_{25}NO_2$	76·6	8·6	4·7		76·2	8·4	4·7	
Me	H	7	Me	Base	63	[c]		$C_{16}H_{27}NO_2$	72·5	10·2	5·2		72·5	10·2	5·3	
Me	Me	2	Ph	Base	93	32—33	Et_2O	$C_{17}H_{21}NO_2$	75·3	7·7	5·3		75·3	5·75	5·2	
				MeI	89	152—156	H_2O	$C_{18}H_{24}INO_2$			3·5	30·6			3·4	30·8
Me	Me	5	Ph	Base	93	38·5—39·5	Et_2O–Pet	$C_{20}H_{27}NO_2$	76·9	8·5	4·2		76·6	8·7	4·5	
				MeI	93	183—185	H_2O	$C_{21}H_{30}INO_2$			2·8	27·6			3·1	27·9
				p-$C_6H_4Me\cdot SO_3H$		114—116	EtOH–Et_2O	$C_{20}H_{27}NO_2,C_7H_8O_3S$	66·3	7·4	2·6	6·5 [d]	66·8	7·3	2·9	6·6 [d]
Me	Me	7	Me	HBr	80	119—120	EtOH–Et_2O	$C_{17}H_{29}NO_2,HBr$			3·9	22·1			3·9	22·2
				MeI	67	184—186 (decomp.)	H_2O	$C_{18}H_{32}INO_2$			3·0	30·6			3·3	30·1
Me	Me	4	OPh	Base	89	49—51	Et_2O–Pet	$C_{19}H_{25}NO_3$	72·5	8·2	4·5		72·35	8·0	4·4	
				MeI	95	162·5—164 (decomp.)	H_2O	$C_{20}H_{28}INO_3$			3·05	27·1			3·1	27·8
Me	Me	4	COPh	Base	73	82—84	EtOH	$C_{20}H_{25}NO_3$	73·2	7·9	4·3		73·45	7·6	4·3	
				MeI	92	160—163 (decomp.)	H_2O	$C_{21}H_{28}INO_3$			3·0	27·0			3·0	27·1
Me	Me	5	SPh	HBr	26	96—98	Aq. HBr	$C_{20}H_{27}NO_2S,HBr$			3·2	19·0			3·3	18·7
				MeI	100	142—145 (decomp.)	H_2O	$C_{21}H_{30}INO_2S$			2·8	25·95			2·9	26·1
Me	Me	5	*p*-$C_6H_4NMe_2$	Base	74	39—41	Pet	$C_{22}H_{32}N_2O_2$	74·1	9·05	7·8		74·1	9·05	7·9	
				MeI	80	203—204	H_2O	$C_{24}H_{38}I_2N_2O_2$			4·3	39·5			4·4	39·6
Me	Me	5	Phthalimido	Base	92	70—72	EtOH	$C_{22}H_{26}N_2O_4$	69·1	7·0	7·4		69·1	6·85	7·3	
				MeI	100	200—202	H_2O	$C_{23}H_{29}IN_2O_4$			5·1	23·6			5·35	24·2
Et	Et	7	Me	Base	85 [e]			$C_{19}H_{33}NO_2$	74·3	10·8	4·9		74·2	10·8	4·6	
$CO_2\cdot CH_2\cdot CH_2Cl$	H	2	Ph		90	63—65	EtOH	$C_{18}H_{20}ClNO_4$			4·0	10·3			4·0	10·1
$CO_2\cdot CH_2\cdot CH_2Cl$	H	7	Me		100	72—73·5	EtOH	$C_{18}H_{28}ClNO_4$			3·8	9·75			3·9	9·9
$CO_2\cdot CH_2\cdot CH_2Cl$	H	4	OPh		94	109—110	EtOH	$C_{20}H_{24}ClNO_5$			3·5	8·9			3·6	9·0
$CO_2CH_2\cdot CH_2Cl$	H	4	COPh		69	95—97	EtOH	$C_{21}H_{24}ClNO_5$			3·4	8·6			3·45	8·75
$CO_2CH_2\cdot CH_2Cl$	H	5	SPh		86	45—47	EtOH–H_2O	$C_{21}H_{26}ClNO_4S$				8·15				8·4
$[CH_2]_2\cdot OH$	H	2	Ph	HBr	75	147·5—149	MeOH–Et_2O	$C_{17}H_{22}NO_3,HBr$			3·8	21·5			3·8	21·7
$[CH_2]_2\cdot OH$	H	7	Me	Base	75	35—36	Pet	$C_{17}H_{29}NO_3$			4·8				4·75	
$[CH_2]_2\cdot OH$	H	4	OPh	Base	87	62·5—63·5	MeOH	$C_{19}H_{25}NO_4$	68·5	7·8	4·2		68·8	7·6	4·2	
$[CH_2]_2\cdot OH$	H	4	COPh	Base	86	77—78	EtOH–Et_2O	$C_{20}H_{25}NO_4$	70·2	7·45	4·1		70·0	7·3	4·1	
$[CH_2]_2\cdot OH$	H	5	SPh	HBr	67	113—115	EtOH–Et_2O	$C_{20}H_{27}NO_3S,HBr$			3·1	17·85			3·2	18·1
$[CH_2]_2\cdot OH$	$[CH_2]_2\cdot OH$	7	Me	Base	34	62—64	Et_2O	$C_{19}H_{33}NO_4$	67·2	9·9	4·3		67·2	9·8	4·1	
$[CH_2]_2\cdot OH$	$[CH_2]_2\cdot OH$	5	Phthalimido	Base	51	68—69	EtOH	$C_{24}H_{30}N_2O_6$	64·9	6·8	6·2		65·2	6·8	6·3	

[a] Solvent for recrystn. Pet = light petroleum. [b] B. p. 197—228°/0·04 mm. [c] B. p. 161—163°/0·2 mm. [d] Sulphur analysis. [e] Overall from primary amine; intermediate quaternary salt not isolated. [f] B. p. 162—174°/0·05 mm.

2,6-*Dimethoxy*-4-*nitrophenol*.—(*a*) The foregoing nitro-compound (60 g.) was stirred and refluxed for 2 days with potassium hydroxide (60 g.) in water (350 ml.), then cooled. The potassium salt (49·5 g., 74%) was filtered off, washed with chloroform and ethanol, and dried. The mother-liquors were concentrated and refluxed for a further 24 hr., giving a second crop (6·1 g., 9%). The sodium salt was similarly obtained.

(*b*) A mixture of 1,3-dimethoxyacetone (7·14 g.), sodium nitromalondialdehyde (9·5 g.), and a solution of sodium hydroxide (0·9 g.) in water (90 ml.) was kept overnight at room temperature, then concentrated *in vacuo*, cooled, and filtered, giving the sodium salt (8·35 g., 62%) of the phenol. Acidification and recrystallisation from aqueous acetic acid gave 2,6-*dimethoxy*-4-*nitrophenol*, m. p. 136—137° (effervescence) (Found: N, 6·8; OMe, 30·7. $C_8H_9NO_5$ requires N, 7·0; OMe, 31·2%).

1-(2,6-*Dimethoxy*-4-*nitrophenoxy*)-5-*phthalimidopentane*.—A mixture of potassium 2,6-dimethoxy-4-nitrophenoxide (40 g.), 5-phthalimidopentyl bromide (50 g.), and 2-ethoxyethanol (100 ml.) was stirred under reflux at 100° for 7 days. The product crystallised from ethanol, yielding the 5-*phthalimidopentyl ether* (68%), m. p. 105—106° (Found: N, 6·75; OMe, 15·2. $C_{21}H_{22}N_2O_7$ requires N, 6·75; OMe, 14·9%). Similarly obtained (63%) (refluxed for 48 hr.) was 1-(2,6-*dimethoxy*-4-*nitrophenoxy*)-5-*phenylpentane*, m. p. 36—37° (from light petroleum) (Found: C, 66·6; H, 6·9; N, 4·4. $C_{19}H_{23}NO_5$ requires C, 66·1; H, 6·7; N, 4·1%).

The nitro-compounds listed in Table 1 were prepared (except where stated) by condensation of potassium 2-methoxy-4-nitrophenoxide with the appropriate alkyl or substituted alkyl bromide, usually in boiling ethanol or 2-ethoxyethanol.

Amines.

Di-[5-(4-*amino*-2-*methoxyphenoxy*)*pentyl*] *Sulphide*.—A mixture of 5-(2-methoxy-4-nitrophenoxy)pentyl bromide (24 g.), sodium sulphide nonahydrate (48 g.), ethanol (200 ml.), and water (100 ml.) was stirred and refluxed for 24 hr. The ethanol was distilled off and the residue was shaken with ether. The solid (4·55 g., 27%; m. p. 81—89°) which separated was dissolved in chloroform and shaken with 2N-hydrochloric acid. The hydrochloride was reconverted into the *base* which, after recrystallisation from chloroform–ether, had m. p. 90—92° (Found: N, 6·2; S, 7·1. $C_{24}H_{36}N_2O_4S$ requires N, 6·2; S, 7·1%).

3,3′-*Dimethoxy*-4,4′-*di*-n-*octyloxyazoxybenzene*.—This *compound*, m. p. 86—89° (from 2-ethoxyethanol) (Found: C, 70·1; H, 9·1; N, 5·2%; *M*, 490. $C_{30}H_{46}N_2O_5$ requires C, 70·0; H, 8·95; N, 5·45%; *M*, 514), separated (5% yield) on one occasion when a batch of 1-(2-methoxy-4-nitrophenoxy)octane was reduced over Raney nickel in ethanol. The principal product, 3-methoxy-4-octyloxyaniline, was isolated from the filtrate.

4-*Amino*-2-*methoxyphenyl* D-*Glucoside*.—The corresponding nitro-compound (15·6 g.) in ethanol (460 ml.) and water (180 ml.) was reduced over Raney nickel. Concentration of the filtered solution and recrystallisation of the solid from ethanol gave the *amine* (70%), m. p. 202—203°, $[\alpha]_D^{19·5}$ −61° in H_2O (Found: C, 51·7; H, 6·3; N, 4·7. $C_{13}H_{19}NO_7$ requires C, 51·8; H, 6·3; N, 4·65%).

3,5-*Dimethoxy*-4-5′-*phthalimidopentylaniline* was obtained (85%) by catalytic reduction of the nitro-compound over Raney nickel in dimethylformamide. After crystallisation from ethanol, it had m. p. 97° (Found: C, 65·7; H, 6·35; N, 7·45. $C_{21}H_{24}N_2O_5$ requires C, 65·6; H, 6·3; N, 7·3%). 3,5-*Dimethoxy*-, m. p. 85—87° (from ether) (Found: C, 72·5; H, 8·0; N, 4·4. $C_{19}H_{25}NO_3$ requires C, 72·4; H, 7·9; N, 4·4%), and 3-*methoxy*-4-5′-*phenylpentyloxyaniline* (92%), m. p. 59—60° (from ether–light petroleum) (Found: C, 75·7; H, 8·3; N, 4·9. $C_{18}H_{23}NO_2$ requires C, 75·75; H, 8·1; N, 4·9%) [*methanesulphonate*, m. p. 130—131° (from ethanol–ether) (Found: N, 3·55; S, 8·4. $C_{18}H_{23}NO_2,CH_4O_3S$ requires N, 3·7; S, 8·4%)], were obtained (90%) by a similar reduction in ethanol.

The primary amines listed in Tables 2 and 3 were prepared (except where stated) by catalytic reduction of the corresponding nitro-compounds, usually over Raney nickel in ethanol or 2-ethoxyethanol, but occasionally in ethyl acetate or dimethylformamide.

N-*Formyl*-3-*methoxy*-4-5′-*phenylpentyloxyaniline*, prepared (89%) from the primary amine by means of formamide and concentrated hydrochloric acid [1] and recrystallised from methanol, had m. p. 86—88° (Found: C, 72·9; H, 7·2; N, 4·4. $C_{19}H_{23}NO_3$ requires C, 72·8; H, 7·4; N, 4·5%). The 4-*octyloxy*-*derivative* (81%), m. p. 77—78° (from methanol) (Found: C, 68·3; H, 9·1; N, 4·95. $C_{16}H_{25}NO_3$ requires C, 68·8; H, 9·0; N, 5·0%), was similarly prepared.

N-*Methyl Derivatives* (Table 4).—The foregoing formamides were reduced with lithium aluminium hydride in ether–benzene.

NN-*Dimethyl and* NN-*Diethyl Derivatives* (Table 4).—The primary amines were converted into the quaternary iodides, which were pyrolysed under reduced pressure (see Part III [1]).

N-(2-*Chloroethoxycarbonyl*)-3-*methoxy*-4-5′-*phenylpentyloxyaniline*.—2-Chloroethyl chloroformate (8·7 g.) and sodium acetate trihydrate (11·1 g.) were added successively to a suspension of 3-methoxy-4-5′-phenylpentyloxyaniline (20 g.) in water (115 ml.) and acetic acid (3 ml.). The mixture was periodically shaken during 1 hr., then filtered, and the solid was washed with water and recrystallised from aqueous ethanol, giving the *urethane* (85%), m. p. 76—78·5° (Found: N, 3·6; Cl, 8·95. $C_{21}H_{26}ClNO_4$ requires N, 3·6; Cl, 9·1%). The other *urethanes* listed in Table 4 were similarly obtained.

N-(2-*Hydroxyethyl*)-3-*methoxy*-4-5′-*phenylpentyloxyaniline*.—The foregoing urethane (22·4 g.) was added to a solution of sodium hydroxide (12 g.) in water (23 ml.), ethanol (4·9 ml.), and 2-ethoxyethanol (49 ml.), and the mixture was refluxed for 10 min., cooled, diluted with water, and filtered. The product was washed with water and recrystallised from aqueous ethanol, giving the *amine* (68%), m. p. 72—73° (Found: C, 73·05; H, 8·35; N, 4·3. $C_{20}H_{27}NO_3$ requires C, 73·0; H, 8·2; N, 4·3%). The other N-2-*hydroxyethyl derivatives* (Table 4) were similarly prepared.

NN-*Di*-(2-*hydroxyethyl*)-3-*methoxy*-4-5′-*phenylpentyloxyaniline*.—A mixture of 3-methoxy-4-5′-phenylpentyloxyaniline (14·27 g.), calcium carbonate (14·27 g.), ethylene chlorohydrin (14·27 ml.), and water (150 ml.) was stirred and refluxed for 18 hr., cooled, and extracted with chloroform. The extract was evaporated and the residue treated with methanesulphonic acid in ethanol–ether. After recrystallisation from ethanol–ether, the *methanesulphonate* (46%) of the tertiary amine had m. p. 93—94° (Found: N, 2·9; S, 6·8. $C_{22}H_{31}NO_4,CH_4O_3S$ requires N, 3·0; S, 6·8%). The other *di*-(2-*hydroxyethyl*) *derivatives* (Table 4) were similarly prepared.

NN-*Di*-(2-*hydroxypropyl*)-3-*methoxy*-4-5′-*phthalimidopentyloxyaniline*.—A mixture of 3-methoxy-4-5′-phthalimidopentyloxyaniline (20 g.), 1,2-epoxypropane (25 ml.), ethanol (170 ml.), and concentrated hydrochloric acid (1 ml.) was refluxed for 24 hr., diluted with water, and filtered. Recrystallisation of the solid from methanol–ether gave the tertiary *amine* (28%), m. p. 112—114° (Found: C, 66·5; H, 7·3; N, 6·3. $C_{26}H_{34}N_2O_6$ requires C, 66·4; H, 7·7; N, 6·0%).

N-D-*Glucosyl*-3-*methoxy*-4-5′-*phthalimidopentyloxyaniline*.—A mixture of 3-methoxy-4-5′-phthalimidopentyloxyaniline (3·54 g.), D-glucose (1·8 g.), and ethanol (30 ml.) was refluxed for 1·5 hr. (a clear solution was formed after 1 hr.), then concentrated to 15 ml., cooled, and filtered. The *glucosylamine* (53%) had m. p. 121—123° (Found: C, 59·2; H, 6·5; N, 5·35; H_2O, 1·8. $C_{26}H_{32}N_2O_9,0{\cdot}5H_2O$ requires C, 59·4; H, 6·3; H, 5·3; H_2O, 1·7%). Similarly prepared (62%) was the *galactosylamine*, m. p. 96—98° (Found: C, 60·1; H, 6·6; N, 5·7. $C_{26}H_{32}N_2O_9$ requires C, 60·5; H, 6·2; N, 5·4%).

4,6-*Diamino*-1,2-*dihydro*-1-(3-*methoxy*-4-*octyloxyphenyl*)-2,2-*dimethyl*-1,3,5-*triazine*.—A mixture of 3-methoxy-4-octyloxyaniline (30 g.), dicyandiamide (10 g.), concentrated hydrochloric acid (10 ml.), and acetone (300 ml.) was refluxed for 4 hr., cooled, and filtered, and the residue was washed with acetone. The *triazine hydrochloride* had m. p. 210—212° (Found: N, 17·0; Cl, 8·55. $C_{20}H_{33}N_5O_2$,HCl requires N, 17·0; Cl, 8·6%).

The authors thank Dr. H. J. Barber, F.R.I.C., and Dr. J. N. Ashley, F.R.I.C., for their continued interest, and Mr. S. Bance, F.R.I.C., for the analyses.

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[*Received, October 24th*, 1960.]