91. *Antituberculous Compounds. Part VI.* p-(ω-*Alkoxyalkoxy*)-N-*arylbenzamidines and Analogues.*

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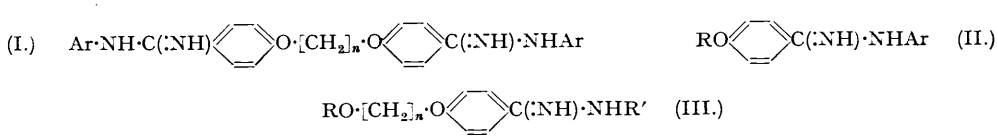
A series of *p*-(ω-alkoxyalkoxy)-*N*-arylbenzamidines and certain analogues have been prepared. Comparison of their activities *in vitro* against *Mycobacterium tuberculosis* with those of the diamidines and of the monoamidines described in Parts II and III respectively (*J.*, 1949, 2683, 3043) has extended the earlier observations on the differences in the relation between structure and activity in analogous monoamidines and diamidines and on the significance of the *N*-aryl substituents. Isosteric replacement of methylene by oxygen in the monoamidines apparently causes a marked decrease in activity.

Marked activity *in vitro* against *Mycobacterium tuberculosis* by di-(*p*-*N*-arylamidinophenoxy)-alkanes (I) and *p*-alkoxy-*N*-arylbenzamidines (II) has been reported in Parts II and III (*J.*, 1949, 2683, 3043) respectively. In these two series, differences were observed in the effects on *in vitro* activity of (*a*) homology in the polymethylene chain of the diamidines and in the alkoxy-group of the monoamidines, (*b*) substitution in the *N*-aryl groups, and (*c*) the presence of serum in the medium during testing. In this communication further experiments on monoamidines are described.

Additional information on the relation between homology and activity was sought through a series of *p*-2-alkoxyethoxy-*N*-phenylbenzamidines (III; $n = 2$, R = alkyl, R′ = Ph). Changes in activity induced by substitution in the *N*-phenyl substituent of the amidine group and by replacement of the *N*-phenyl group by analogous ring systems were also examined in the same series. The preparation of certain analogues of (III) made possible some examination of the significance of the important functional groups in the monoamidine and diamidine series, and of the effect produced by the isosteric replacement of methylene by oxygen.



The 2-alkoxyethanols described in the Experimental section were obtained in satisfactory yield by the method of Palomaa (*Ber.*, 1902, **35**, 3299); in a number of instances, the corresponding diether of ethylene glycol, as would be expected, was formed as a by-product. We find that 2-dodecyloxyethanol, which is claimed by Halasz (*Bull. Soc. chim.*, 1941, **8**, 170) to have been prepared in very low yield and to have m. p. 51°, has m. p. 22—24°. The values said to have been found and required for the elementary analysis correspond to the composition not of 2-dodecyloxyethanol ($C_{14}H_{30}O_2$) but of a compound, $C_{14}H_{30}O$; recalculation of the published results is not possible because of a misprint in the analytical data; it is unlikely that Halasz's material was 1 : 2-*didodecyloxyethane* ($C_{26}H_{54}O_2$) which we find has m. p. 37—38°. Conversion of the 2-alkoxyethanols into the corresponding chlorides or bromides was readily effected by the procedures of Bennett and Heathcoat (*J.*, 1929, 268) and of Palomaa and Kenetti (*Ber.*, 1931, **64**, 797) respectively. It was difficult to obtain consistent elementary analyses of these alcohols and halides; their purity was therefore checked by determination of the molecular refractions.

The preparative work involved in the production of the substituted phenyl cyanides afforded

	Base.					Picrate.				Activity.*	
	Yield, %.	M. p.	Formula.	Found N, %.	Req., N, %.	M. p.	Formula.	Found N, %.	Req., N, %.	In absence of serum.	In presence of serum.
1. p-(2-*Methoxyethoxy*)-N-*phenylbenzamidine* ...	85	124—125°	$C_{16}H_{18}O_2N_2$	10·35	10·35	96—98°	$C_{22}H_{21}O_9N_5$	13·9	14·0	5	1
2. p-(2-*Ethoxyethoxy*)-N-*phenylbenzamidine* ...	73	121—121·5	$C_{17}H_{20}O_2N_2$	9·85	9·85	82—84	$C_{23}H_{23}O_9N_5$	13·3	13·65	10	10
3. p-(2-*Propoxyethoxy*)-N-*phenylbenzamidine* ...	97	104—104·5	$C_{18}H_{22}O_2N_2$	9·45	9·4	84—86	$C_{24}H_{25}O_9N_5$	13·1	13·3	5—10	10
4. p-(2-*Butoxyethoxy*)-N-*phenylbenzamidine*.....	99	98—99	$C_{19}H_{24}O_2N_2$	9·1	8·95	79—81	$C_{25}H_{27}O_9N_5$	13·05	12·95	50	10—50
5. p-(2-*Amyloxyethoxy*)-N-*phenylbenzamidine* ...	85	93—94	$C_{20}H_{26}O_2N_2$	8·65	8·6	83—85	$C_{26}H_{29}O_9N_5$	12·5	12·6	50—100	10
6. p-(2-*Hexyloxyethoxy*)-N-*phenylbenzamidine*...	43	97—98	$C_{21}H_{28}O_2N_2$	8·4	8·25	73—76	$C_{27}H_{31}O_9N_5$	12·4	12·3	50	10—50
7. p-(2-*Heptyloxyethoxy*)-N-*phenylbenzamidine*	44	97—98	$C_{22}H_{30}O_2N_2$	8·05	7·9	78—80	$C_{28}H_{33}O_9N_5$	11·8	12·0	—	10
8. p-(2-*Octyloxyethoxy*)-N-*phenylbenzamidine* ...	49	97—98	$C_{23}H_{32}O_2N_2$	7·9	7·6	76—78	$C_{29}H_{35}O_9N_5$	11·45	11·7	10	10—50
9. p-(2-*Dodecyloxyethoxy*)-N-*phenylbenzamidine*	75	98—99	$C_{27}H_{40}O_2N_2$	6·9	6·6	72—74	$C_{33}H_{43}O_9N_5$	10·75	10·7	—	<1 (10)
10. p-(2-*Hydroxyethoxy*)*benzamidine*	—	—	—	—	—	—	—	—	—	<1	—
11. p-(2-*Hydroxyethoxy*)-N-*phenylbenzamidine* ...	87	158—160	$C_{15}H_{16}O_2N_2$	10·7	10·95	164—165·5	$C_{21}H_{19}O_9N_5$	14·3	14·45	10—50	5—10
12. p-(2-*Ethoxyethoxy*)*benzamidine*	—	—	—	—	—	—	—	—	—	<1—1	<1—1
13. p-(3-*Ethoxypropoxy*-N-*phenylbenzamidine* ...	60	85—87	$C_{18}H_{22}O_2N_2$	9·5	9·4	97—99	$C_{24}H_{25}O_9N_5$	13·0	13·3	50	10—50
14. p-(2-*Phenoxyethoxy*)-N-*phenylbenzamidine* ...	48	203—205	$C_{21}H_{20}O_2N_2$	8·6	8·4	—	—	—	—	<1	—
15. p-(3-*Phenoxypropoxy*)-N-*phenylbenzamidine*	61	128—129	$C_{22}H_{22}O_2N_2$	8·0	8·1	—	—	—	—	500	10
16. p-(2-*Methoxyethoxy*)-N-p′-*propoxyphenyl*-*benzamidine*	95	132—133	$C_{19}H_{24}O_3N_2$	8·8	8·55	97—99	$C_{25}H_{27}O_{10}N_5$	12·7	12·55	—	10
17. p-(2-*Ethoxyethoxy*)-N-p′-*propoxyphenylbenz*-*amidine*	96	122—123	$C_{20}H_{26}O_3N_2$	8·45	8·2	137—139	$C_{26}H_{29}O_{10}N_5$	12·55	12·25	10	10
18. p-(2-*Ethoxyethoxy*)-N-p′-*chlorophenylbenz*-*amidine*	84	115—116	$C_{17}H_{19}O_2N_2Cl$	9·15	8·8	133—134	$C_{23}H_{22}O_9N_5Cl$	13·0	12·8	—	10—50
19. p-(2-*Ethoxyethoxy*)-N-cyclo*hexylbenzamidine*	—	—	—	—	—	—	—	—	—	—	5
20. p-(2-*Ethoxyethoxy*)-N-2′-*pyridylbenzamidine*	—	—	—	—	—	—	—	—	—	—	10
21. p-(2-*Ethoxyethoxy*)-N-*benzylbenzamidine*	—	—	—	—	—	—	—	—	—	10	5—10
22. 3-Ethoxypropanol	—	—	—	—	—	—	—	—	—	—	<1
23. 2-Propoxyethanol	—	—	—	—	—	—	—	—	—	—	<1 (5)
24. 2-Butoxyethanol	—	—	—	—	—	—	—	—	—	—	<1
25. 2-Amyloxyethanol	—	—	—	—	—	—	—	—	—	—	<1
26. 2-*Hexyloxyethanol*	—	—	—	—	—	—	—	—	—	—	1
27. 2-*Heptyloxyethanol*	—	—	—	—	—	—	—	—	—	10	5—10
28. 2-*Octyloxyethanol*	—	—	—	—	—	—	—	—	—	10—50	5—10

* Dilution (in thousands) at which complete inhibition of the growth of *M. tuberculosis* (human virulent strain) was maintained for 4 weeks in modified Long's medium (by the floating-pellicle method). Figures in parentheses represent dilutions (in thousands) at which partial inhibition occurred. Under the same conditions of test 4-aminosalicylic acid gave a value of 10 in the absence of serum.

(1), (2) Colourless needles. (3) Colourless plates. (4) Colourless plates. The *picrate* crystallised as yellow plates from aqueous methanol; from aqueous acetic acid, it separated as solvated needles, m. p. 100—102° after sintering at 84° (Found: loss at 55°/vac., 5·05. Found, on dried material, N, 12·7. $C_{25}H_{27}O_9N_5,0{\cdot}5C_2H_4O_2$ requires $C_2H_4O_2$, 5·25%. $C_{25}H_{27}O_9N_5$ requires N, 12·95%). (5) Colourless plates. (6) Colourless plates. The *benzenesulphonate*, colourless needles from benzene, had m. p. 138—139° (Found: C, 64·75; H, 6·7; N, 5·85. $C_{27}H_{34}O_5N_2S$ requires C, 65·05; H, 6·85; N, 5·6%). (7) Colourless plates. The *picrate* crystallised from aqueous ethanol as thin plates (Found: loss at 55°/vac., 2·8. $C_{28}H_{33}O_9N_5,H_2O$ requires H_2O, 3·0%). (8) Colourless plates. The *benzenesulphonate*, colourless needles from benzene, had m. p. 123—124° (Found: C, 65·8; H, 7·3; N, 5·6. $C_{29}H_{38}O_5N_2S$ requires C, 66·1; H, 7·25; N, 5·3%). (9) Colourless leaflets. The *picrate* crystallised from aqueous ethanol as solvated needles (Found: loss at 20°/vac., 2·6. $C_{33}H_{43}O_9N_5,H_2O$ requires H_2O, 2·7%). (11) Colourless prisms from *iso*propanol. The *amidinium chloride*, colourless prisms from water, had m. p. 143—145° (decomp.) (Found: loss at 100°/vac., 6·4. Found, on dried material, N, 9·45; Cl^-, 11·8; $C_{15}H_{17}O_2N_2Cl,H_2O$ requires H_2O, 5·8%. $C_{15}H_{16}O_2N_2,HCl$ requires N, 9·55; Cl^-, 12·1%). (13), (16) Colourless leaflets. (14) Colourless leaflets from 2-ethoxyethanol. (15) Colourless leaflets from xylene. (17) Colourless plates. The *picrate*, yellow plates from aqueous methanol, melted and effervesced at 110—112°, resolidified, and melted again at 138—139° when not previously dehydrated (Found: loss at 100°/vac., 4·3. $C_{26}H_{29}O_{10}N_5,1{\cdot}5H_2O$ requires H_2O, 4·5%). (18) Plates (Found: Cl, 10·95. $C_{17}H_{19}O_2N_2Cl$ requires Cl, 11·1%).

little new of chemical interest. For the preparation of the *N*-aryl-substituted amidines described in the table, the arylammonium benzenesulphonate method (Oxley and Short, *J.*, 1946, 147) was used; Pinner's method was applied in the preparation of the unsubstituted amidines, and the aluminium chloride method (Oxley, Partridge and Short, *J.*, 1947, 1110) to that of p-(2-*ethoxyethoxy*)-N-cyclo*hexyl*-, -N-2'-*pyridyl*-, and -N-*benzyl*-*benzamidine*. The last compound was also obtained, but only in 3% yield, by interaction of benzylammonium thiocyanate and p-(2-*ethoxyethoxy*)*phenyl cyanide* (Partridge and Short, *J.*, 1947, 390). For the determination of activity *in vitro*, the *N*-substituted amidines were obtained in solution as their lactates.

The activities against *M. tuberculosis in vitro* are recorded in the table. The activity of members of the series of p-(2-*alkoxyethoxy*)-N-*phenylbenzamidines* (III; $n = 2$, R′ = Ph, R = Me, Et, Pr^n, Bu^n, *n*-C_5H_{11}, *n*-C_6H_{13}, *n*-C_7H_{15}, *n*-C_8H_{17}, or *n*-$C_{12}H_{25}$) increases gradually to a maximum when R is C_4—C_6 and then decreases with the higher homologues. In this respect, the series resembles the *p*-alkoxy-*N*-phenylbenzamidines and other series discussed in Part III but differs from the di-(*p*-*N*-arylamidinophenoxy)alkanes (Part II). A large increase in activity in passing from the C_4 to the C_6 homologue, which was observed in the *p*-alkoxy-*N*-phenylbenzamidines, is not apparent here. There is some indication that the presence of serum in the medium during testing inhibits the activity to a lesser extent than in *p*-alkoxy-*N*-phenylbenzamidines, although this inhibiting effect of serum is more pronounced than with the di-(*p*-*N*-arylamidinophenoxy)alkanes. The outstanding feature of the *p*-(2-alkoxyethoxy)-*N*-phenylbenzamidines is their low activity compared with the analogous series described in Part III; this may be ascribed to the replacement of methylene by oxygen. Activities equal to or greater than that shown by 4-aminosalicylic acid, under the same conditions of test, are nevertheless retained.

The dyschemotherapeutic effect of the replacement of methylene by oxygen is best illustrated by a comparison of the isosteres, *p*-hexyloxy-*N*-phenylbenzamidine (Part III) (II; R = *n*-C_6H_{13}, Ar = Ph) and *p*-(2-propoxyethoxy)-*N*-phenylbenzamidine (III; $n = 2$, R = Pr^n, R′ = Ph) which are active at 1 : 5,000,000 and 1 : 5000—10,000 respectively. A similar but much less marked effect of this type of change in structure is to be observed in the series studied by Friedman *et al.* (*J. Pharm. Exp. Ther.*, 1947, **89**, 153). Some significance may possibly be attached to the position of this second ethereal oxygen atom, since the other isostere which was prepared, namely p-(3-*ethoxypropoxy*)-N-*phenylbenzamidine* (III; $n = 3$, R = Et, R′ = Ph) is active at 1 : 50,000. This feature and the 500-fold increase in activity in passing from p-(2-*phenoxyethoxy*)-N-*phenyl*- (III; $n = 2$, R = R′ = Ph) to p-(3-*phenoxypropoxy*)-N-*phenylbenzamidine* (III; $n = 3$, R = R′ = Ph) are reminiscent of the alternation in activity noted in di-(*p*-*N*-phenylamidinophenoxy)alkanes (I; $n = 2$, 3, 4, 5, or 6), in which members having an even number of methylene groups were inactive whereas members with an odd number were active.

A comparison of the activities of *p*-(3-ethoxypropoxy)-*N*-phenylbenzamidine, *p*-(3-phenoxypropoxy)-*N*-phenylbenzamidine, and 1 : 3-di-(*p*-*N*-phenylamidinophenoxy)propane (Part II) (I; $n = 3$, Ar = Ph) indicates that in these monoamidines replacement of the 3-ethyl by 3-phenyl enhances activity *in vitro*, but in order to maintain this activity in the presence of serum, a second *N*-phenyl-substituted amidine group is necessary. Replacement of the 2-ethoxy-group of *p*-(2-ethoxyethoxy)-*N*-phenylbenzamidine by hydroxyl (III; $n = 2$, R = H, R′ = Ph) produces no important change in activity, but the ten-fold decrease in activity which occurs in the corresponding unsubstituted *amidines* (III; $n = 2$, R = Et, R′ = H) and (III; $n = 2$, R = R′ = H) provides evidence additional to that noted in Parts II and III of the importance of the *N*-phenyl substituent in the amidine group. The introduction of *p*-propoxy- (III; $n = 2$; R = Me or Et, R′ = *p*-PrO·C_6H_4) and *p*-chloro- (III; $n = 2$, R = Et, R′ = *p*-C_6H_4Cl) groups into the *N*-phenyl groups of *p*-(2-methoxy- and 2-ethoxy-ethoxy)-*N*-phenylbenzamidines produces no important change in activity. As far as comparison is possible, this effect is in accord with what was found in corresponding *p*-alkoxy-*N*-arylbenzamidines reported in Part III and in contrast with the findings for di-(*p*-*N*-arylamidinophenoxy)alkanes (Part II). The *N*-*cyclo*hexyl (III; $n = 2$, R = Et, R′ = $-\overline{CH{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2}$), *N*-2'-pyridyl (III; $n = 2$, R = Et, R′ = $-\overline{C{:}N{\cdot}CH{:}CH{\cdot}CH{:}CH}$), and *N*-benzyl (III; $n = 2$, R = Et, R′ = $-CH_2{\cdot}C_6H_5$) analogues of *p*-(2-ethoxyethoxy)-*N*-phenylbenzamidine are of about the same order of activity as the parent compound.

From the results obtained with seven ω-alkoxyalkanols, it would appear that no special significance may be assigned to the activities of the *heptyl* and *octyl* homologues. Many similar

instances of long-chain compounds exhibiting activity against *M. tuberculosis in vitro* have been reported (see, *e.g.*, Walker and Sweeney, *J. Infect. Dis.*, 1920, **26**, 238; Stanley *et al.*, *J. Pharm. Exp. Ther.*, 1932, **45**, 121; Barry, *Nature*, 1946, **158**, 863; D'Arcy Hart, *Brit. Med. J.*, 1946, II, 805; 849; Suter, *Schweiz. med. Woch.*, 1948, **78**, 324; Eiseman, *J. Exptl. Med.*, 1948, **88**, 189). The inhibiting effect of serum observed with the octyl homologue and its acute toxicity (2 mg./g. of body-weight by subcutaneous and by oral administration in mice) render it unlikely that any activity could be demonstrated *in vivo*.

Experimental.

2-*Amyloxyethanol*.—The following method derived from that of Palomaa (*loc. cit.*) was employed. Amyl bromide (151 g.) was gradually added to a solution of sodium (23 g., 1 atom) in hot ethylene glycol (200 g., 3·2 mols.), prepared in an atmosphere of nitrogen. The mixture, after boiling under reflux with stirring for 35 minutes, gave on distillation an azeotrope of ethylene glycol and 2-amyloxyethanol, containing 78% of 2-amyloxyethanol and having b. p. 180—182°/750 mm., d_4^{20} 0·9526, d_4^{25} 0·9499, n_D^{20} 1·4260. After being washed five times with water (50 c.c.), dried ($CaSO_4$), and re-fractionated, this material afforded 2-amyloxyethanol (56 g., 42%), b. p. 187—188°/753 mm., d_4^{20} 0·8926, d_4^{25} 0·8902, n_D^{20} 1·4239, $[R_L]_D$ 37·79 (calc., 37·85). Ashburn *et al.* (*J. Amer. Chem. Soc.*, 1936, **58**, 1549) record b. p. 188·3°/751·1 mm., d^{25} 0·8893; Tallman (*ibid.*, 1934, **56**, 126) records d_4^{20} 0·8927; n_D^{20} 1·42233; Cretcher and Pittenger (*J. Amer. Chem. Soc.*, 1924, **46**, 1503) record b. p. 181°/745 mm. Low values for the b. p. (cf. also Berry and Michaels, *Quart. J. Pharm.*, 1947, **20**, 331) are probably attributable to an azeotrope of 2-amyloxyethanol with ethylene glycol.

2-*Hexyloxyethanol*.—Hexyl bromide (165 g.) was brought into reaction with a solution of sodium (23 g., 1 atom) in ethylene glycol (200 g., 3·2 mols.) in the same manner as for the foregoing compound, heating being for 2½ hours. The liquid, obtained free from sodium bromide by distillation under reduced pressure, was washed with water and dried ($CaSO_4$); on fractionation 2-*hexyloxyethanol* (78 g., 53%), b. p. 110—112°/27 mm., was obtained (Found : C, 66·2; H, 12·0. $C_8H_{18}O_2$ requires C, 65·7; H, 12·4%), having d_4^{20} 0·8892, n_D^{20} 1·4291, and $[R_L]_D$ 42·40 (calc. 42·46). Berry and Michaels (*loc. cit.*) record, without further details, b. p. 89—93°/17 mm. for this compound. Interaction of ethylene chlorohydrin and sodium hexyloxide in xylene (cf. Cretcher and Pittenger, *loc. cit.*) failed to yield any material of constant b. p.

2-*Heptyloxyethanol*, prepared in 62% yield by the procedure described for the hexyl homologue, had b. p. 124—125°/28 mm. (Found : C, 66·8; H, 12·6. $C_9H_{20}O_2$ requires C, 67·45; H, 12·6%), d_4^{20} 0·8848, n_D^{20} 1·4325, $[R_L]_D$ 47·04 (calc. 47·15). 1 : 2-*Diheptyloxyethane* (9%), obtained from the end-run of the distillation, had b. p. 174—175°/19 mm. (Found : C, 73·8; H, 12·9. $C_{16}H_{34}O_2$ requires C, 74·35; H, 13·25%), d_4^{20} 0·8437, n_D^{20} 1·4330, $[R_L]_D$ 79·60 (calc. 79·92).

2-*Octyloxyethanol*.—Interaction of octyl bromide (193 g.) with ethylene glycol (200 g., 3·2 mols.) containing sodium (23 g., 1 atom) for 4 hours under conditions described for the amyl homologue, followed by distillation, afforded a two-phase distillate. The upper, water-insoluble layer was washed with water, and the washings were used in the recovery of a small quantity of water-insoluble material from the lower layer. The water-insoluble material, after being dried (K_2CO_3), yielded 2-*octyloxyethanol* (90 g., 52%), b. p. 132—133°/22 mm. (Found : C, 68·55; H, 12·4. $C_{10}H_{22}O_2$ requires C, 68·9; H, 12·75%), d_4^{20} 0·8811, n_D^{20} 1·4357, $[R_L]_D$ 51·69 (calc. 51·74). This compound is referred to in F.P. 44,641 but no details are given. The end-run from the distillation afforded 1 : 2-*dioctyloxyethane* (7%), b. p. 188—191°/14 mm. (Found : C, 75·6; H, 12·85. $C_{18}H_{38}O_2$ requires C, 75·45; H, 13·35%), d_4^{20} 0·8455, n_D^{20} 1·4369, $[R_L]_D$ 88·76 (calc. 89·09).

2-*Dodecyloxyethanol*.—Prepared in 40% yield by the method described for the foregoing compound, this crystallised as colourless plates, which had m. p. 22—24°, depressed to 14—16° by dodecanol, and b. p. 142°/1·8 mm. (Found : C, 72·4; H, 12·3. Calc. for $C_{14}H_{30}O_2$: C, 73·0; H, 13·15%), d_4^{25} 0·8708, n_D^{25} 1·4432, $[R_L]_D$ 70·17 (calc. 70·33). Henkel et Cie (B.P. 401,142) record b. p. 170—174°/15 mm. The residue in the still contained 1 : 2-*didodecyloxyethane* (25%), colourless plates (from ethanol or *iso*propanol), m. p. 37—38° (Found : C, 78·45; H, 13·55. $C_{26}H_{54}O_2$ requires C, 78·3; H, 13·65%).

Halides.—2-Ethoxyethyl bromide was obtained by interaction of phosphorus tribromide, 2-ethoxyethanol, and pyridine by the method of Palomaa and Kenetti (*loc. cit.*) in 53% yield and had b. p. 126—127°/767 mm. (Vogel, *J.*, 1948, 644, records b. p. 128°/768 mm.). The method of *Org. Synth.*, 1943, **23**, 32, in our hands consistently failed to give better than 38% yield either of this compound or of 2-methoxyethyl bromide.

2-*Propoxyethyl chloride*. Interaction of thionyl chloride (78·5 g.), 2-propoxyethanol (62·5 g., 0·91 mol.), and dimethylaniline (87·2 g., 1·1 mols.) by the method of Bennett and Heathcoat (*loc. cit.*) afforded 2-propoxyethyl chloride (51 g., 69%), b. p. 129—131°/760 mm., n_D^{20} 1·4163 (Karvonen, *Ann. Acad. Sci. Fenn.*, 1912, *A*, **3**, No. 7, 1, gives b. p. 130°/756·3 mm., n_D^{20} 1·41756; Sklyarov, *J. Gen. Chem. U.S.S.R.*, 1939, **9**, 2121, gives b. p. 119—120°, n_D^{20} 1·426). The method of Foran (*J. Soc. Chem. Ind.*, 1925, **44**, 173T) failed to give any of the desired product when applied to the preparation of 2-propoxyethyl bromide (cf. Bennett and Heathcoat, *loc. cit.*).

2-Butoxyethyl chloride, prepared in 66% yield by the procedure described for the foregoing compound, had b. p. 153—154°/755 mm., n_D^{20} 1·4220. Palomaa and Kenetti (*loc. cit.*) give b. p. 154·5°/750 mm., and Chalmers (*Canad. J. Research*, 1932, **7**, 464) gives b. p. 153—154°, whereas Sklyarov (*loc. cit.*) records b. p. 139—141° and n_D^{20} 1·431.

2-*Amyloxyethyl chloride*. After interaction of thionyl chloride (49 g.), 2-amyloxyethanol (49·6 g., 0·91 mol.), and dimethylaniline (55 g., 1·1 mols.) according to the method of Bennett and Heathcoat (*loc. cit.*), it was found advantageous to remove sulphur dioxide from the ethereal extract of the product by treatment with sodium hydrogen carbonate before drying, evaporation, and fractional distillation; yield, 37·2 g. (66%); b. p. 83—85°/35 mm., 174—175°/763 mm. (Found : C, 55·95; H, 10·3. $C_7H_{15}OCl$ requires C, 55·8; H, 10·05%); d_4^{20} 0·9363; n_D^{20} 1·4261; $[R_L]_D$ 41·22 (calc. 41·15).

2-*Hexyloxyethyl bromide*, prepared in 61% yield by the procedure of Palomaa and Kenetti (*loc. cit.*), had b. p. 121—122°/44 mm. (Found: C, 46·15; H, 7·45; Br, 37·6. $C_8H_{17}OBr$ requires C, 45·95; H, 8·2; Br, 38·2%), d_4^{20} 1·1558, n_D^{20} 1·4504, $[R_L]_D$ 48·66 (calc. 48·65).

2-*Heptyloxyethyl bromide*, prepared in 43% yield in the same way as the foregoing compound, had b. p. 132—133°/38 mm. (Found: C, 48·1; H, 8·4; Br, 35·6. $C_9H_{19}OBr$ requires C, 48·45; H, 8·6; Br, 35·8%), d_4^{20} 1·1298, n_D^{20} 1·4518, $[R_L]_D$ 53·27 (calc. 53·35).

2-*Octyloxyethyl bromide*, prepared in 51% yield in the same way, had b. p. 126—127°/14 mm. (Found: C, 50·0; H, 8·4; Br, 33·6. $C_{10}H_{21}OBr$ requires C, 50·6; H, 8·9; Br, 33·7%), d_4^{20} 1·1085, n_D^{20} 1·4536, $[R_L]_D$ 57·91 (calc. 57·93). The preparation of this compound is claimed in F.P. 44,641 but no confirmatory data are provided.

2-*Dodecyloxyethyl bromide*. A mixture of 2-dodecyloxyethanol (76·8 g.) and pyridine (5 g., 0·2 mol.) was added dropwise to phosphorus tribromide (36·1 g., 0·4 mol.) at 20—40°. After this had been kept overnight, water and ether were added; the ethereal layer was washed with water, dried ($MgSO_4$), and evaporated. Fractional distillation of the residue afforded 2-*dodecyloxyethyl bromide* (56·7 g., 58%), b. p. 132—133°/1 mm. (Found: C, 56·5; H, 9·9; Br, 26·7. $C_{14}H_{29}OBr$ requires C, 57·3; H, 9·95; Br, 27·25%), d_4^{20} 1·0418, n_D^{20} 1·4576, $[R_L]_D$ 76·75 (calc. 76·52).

p-(ω-*Alkoxyalkoxy*)*phenyl Cyanides*.—The cyanides were prepared from sodium *p*-cyanophenoxide and the appropriate ω-alkoxyalkyl halide by the method described in Part III (*loc. cit.*). In examples involving the use of an alkoxyalkyl chloride, sodium iodide (0·1 mol.) was added and the period of heating was prolonged to 1—3 days. The following substituted *phenyl cyanides* were prepared: p-(2-*methoxyethoxy*)- (72%), colourless plates, m. p. 43·5—44·5° (Found: N, 8·1. $C_{10}H_{11}O_2N$ requires N, 7·9%); p-(2-*ethoxyethoxy*)- (70%), needles, m. p. 29·5—30·5°, b. p. 112—113°/0·5 mm., 161°/6·5 mm., n_D^{35} 1·5209 (Found: N, 7·4. $C_{11}H_{13}O_2N$ requires N, 7·35%); p-(2-*propoxyethoxy*)- (33%), needles, m. p. 23—24°, b. p. 142—143°/0·6 mm., n_D^{35} 1·5132 (Found: N, 6·85. $C_{12}H_{15}O_2N$ requires N, 6·8%), p-(2-*butoxyethoxy*)- (55%), b. p. 150—151°/0·4 mm., n_D^{35} 1·5080 (Found: N, 6·55. $C_{13}H_{17}O_2N$ requires N, 6·4%); p-(2-*amyloxyethoxy*)- (42%), needles, m. p. 30—31°, b. p. 159—162°/0·6 mm., n_D^{35} 1·5057 (Found: N, 6·1. $C_{14}H_{19}O_2N$ requires N, 6·0%); p-(2-*hexyloxyethoxy*)- (73%), needles, m. p. 33·5—34·5°, b. p. 174—175°/1 mm., n_D^{35} 1·5037 (Found: N, 5·9. $C_{15}H_{21}O_2N$ requires N, 5·65%); p-(2-*heptyloxyethoxy*)- (70%), b. p. 171—174°/0·8 mm., n_D^{35} 1·5012 (Found: N, 5·45. $C_{16}H_{23}O_2N$ requires N, 5·35%); p-(2-*octyloxyethoxy*)- (64%), b. p. 186—190°/2 mm., n_D^{35} 1·4991 (Found: N, 5·15. $C_{17}H_{25}O_2N$ requires N, 5·1%); p-(2-*dodecyloxyethoxy*)- (73%), needles (from ethanol), m. p. 40—42° (Found: N, 4·4. $C_{21}H_{33}O_2N$ requires N, 4·25%); p-(3-*ethoxypropoxy*)- (48%), b. p. 128—129°/0·2 mm., n_D^{35} 1·5155 (Found: N, 7·25. $C_{12}H_{15}O_2N$ requires N, 6·8%).

p-(2-*Hydroxyethoxy*)*phenyl Cyanide*.—Ethylene bromohydrin was boiled under reflux in ethanol for 16 hours with an equivalent of sodium *p*-cyanophenoxide; the solvent was evaporated and the residue was stirred with water and ethyl acetate. Unchanged *p*-cyanophenol was removed from the ethyl acetate solution by N-sodium hydroxide and, after removal of the solvent, the product was crystallised from benzene (yield 61%; m. p. 86·5—87·5°) (Found: N, 8·7. Calc. for $C_9H_9O_2N$: N, 8·6%). Boyd and Marle (*J.*, 1914, **105**, 2138) record m. p. 86°.

p-(2-*Phenoxyethoxy*)*phenyl Cyanide*.—Equimolecular quantities of 2-phenoxyethyl bromide and sodium *p*-cyanophenoxide were boiled together for 16 hours in ethanol; the *product* which separated on addition of water crystallised from light petroleum (b. p. 100—120°) in colourless leaflets (70%), m. p. 112—113° (Found: N, 5·9. $C_{15}H_{13}O_2N$ requires N, 5·9%).

p-(3-*Phenoxypropoxy*)*phenyl cyanide*, obtained in a similar manner to the foregoing compound, crystallised from light petroleum (b. p. 100—120°) as leaflets (79%), m. p. 72—73° (Found: N, 5·6. $C_{16}H_{15}O_2N$ requires N, 5·6%).

p-(*Substituted-alkoxy*)-N-*arylbenzamidines*.—The *p*-(substituted-alkoxy)-*N*-arylbenzamidines described in the table were prepared by heating the appropriate *p*-(substituted-alkoxy)phenyl cyanide with one equivalent of an arylammonium benzenesulphonate at 210° for 1—2 hours (Oxley and Short, *loc. cit.*). The experiments were conducted on a 0·04-g.-mol. scale. A solution of the product in ethanol was treated with aqueous ammonia to liberate the amidine which was purified as the free base, usually after separation from non-basic material as the lactate. Except where otherwise indicated in the footnotes, the amidines were crystallised from light petroleum (b. p. 100—120°). The picrates were prepared by double decomposition of solutions of the amidinium lactates and sodium picrate.

p-(2-*Hydroxyethoxy*)*benzamidine*.—The crude imino-ether hydrochloride, obtained by saturating with dry hydrogen chloride a solution of *p*-(2-hydroxyethoxy)phenyl cyanide (16·3 g.) in dry ethanol (40 c.c.) and keeping 10 days, was shaken for 3 days with saturated ethanolic ammonia (180 c.c.). The *hydrochloride* which separated crystallised as prisms (from dilute hydrochloric acid), m. p. 236—238° (decomp.) (13 g.) (Found: N, 12·7. $C_9H_{13}O_2N_2Cl$ requires N, 12·9%). The *base* (2·9 g.), obtained from the mother-liquors, had m. p. 177—178° (decomp.) (Found: N, 15·3. $C_9H_{12}O_2N_2$ requires N, 15·55%).

p-(2-*Ethoxyethoxy*)*benzamidine*.—A mixture of *p*-(2-ethoxyethoxy)phenyl cyanide (9·6 g.) and dry ethanol (3 c.c.) was treated with dry hydrogen chloride (4·3 g.). The crude imino-ether hydrochloride which separated after 5 days was shaken with saturated ethanolic ammonia (35 c.c.) for 6 days. On being worked up in the usual way, the *amidinium chloride* was obtained as colourless needles which crystallised very slowly from *iso*propanol with solvent of crystallisation and had m. p. 74—76° (4·65 g., 38%) (Found, on material dried at 20°: N, 11·35; Cl^-, 14·35. $C_{11}H_{17}O_2N_2Cl$ requires N, 11·45; Cl, 14·5%). The *picrate* (3·1 g., 14%), obtained from the mother-liquors, crystallised as needles from aqueous ethanol; it melted at 95—96° with effervescence, resolidified, and melted again at 149—151° (Found: loss at 20°/vac., 6·0. Found, on dried material: N, 15·95. $C_{17}H_{19}O_9N_5,1\frac{1}{2}H_2O$ requires H_2O, 5·8%. $C_{17}H_{19}O_9N_5$ requires N, 16·0%). The *benzoate*, plates (from water), had m. p. 204·5—205° (Found: N, 8·4. $C_{18}H_{22}O_4N_2$ requires N, 8·5%).

p-(2-*Ethoxyethoxy*)-N-*cyclohexylbenzamidine*.—To *p*-(2-ethoxyethoxy)phenyl cyanide (7·65 g.) and *cyclo*hexylamine (4 g., 1 mol.), finely powdered aluminium chloride (5·3 g., 1 mol.) was added portionwise and the mixture was heated at 180° for 10 minutes. Basic material was extracted as the lactate from the precipitate obtained on the addition of sodium hydroxide to an aqueous solution of the melt. p-(2-

Ethoxyethoxy)-N-cyclo*hexylbenzamidine* (4·45 g., 38%), liberated from the lactate, crystallised as colourless plates, m. p. 79—80°, from light petroleum (b. p. 80—100°) (Found : N, 9·85. $C_{17}H_{26}O_2N_2$ requires N, 9·65%). The *picrate* crystallised as short yellow needles from aqueous acetone and had m. p. 60—62° (Found : N, 13·45. $C_{23}H_{29}O_9N_5$ requires N, 13·5%).

p-(2-*Ethoxyethoxy*)-N-2′-*pyridylbenzamidine* was prepared in a similar manner to the foregoing compound from equimolecular quantities of *p*-(2-ethoxyethoxy)phenyl cyanide, 2-aminopyridine, and aluminium chloride in 36% yield; it crystallised from light petroleum (b. p. 80—100°) as colourless needles, m. p. 101—102° (Found : N, 14·95. $C_{16}H_{19}O_2N_3$ requires N, 14·75%). The *monopicrate*, long yellow needles from aqueous ethanol, had m. p. 183—184° (Found : N, 16·35; $C_6H_3O_7N_3$, 44·4. $C_{16}H_{19}O_2N_3,C_6H_3O_7N_3$ requires N, 16·35; $C_6H_3O_7N_3$, 44·5%).

p-(2-*Ethoxyethoxy*)-N-*benzylbenzamidine*.—(i) *p*-(2-Ethoxyethoxy)phenyl cyanide (9·55 g.), benzylamine (5·35 g., 1 mol.), and aluminium chloride (6·7 g., 1 mol.) were brought into reaction in the usual way at 180° for 30 minutes. Basic material, liberated from an aqueous solution of the melt by sodium hydroxide, was collected in chloroform, recovered, purified *via* the lactate, again liberated, collected in chloroform, and recovered. p-(2-*Ethoxyethoxy*)-N-*benzylbenzamidine* slowly crystallised from a solution of the residue in light petroleum (b. p. 100—120°) as plates (3·6 g., 24%), m. p. 80·5—81° (Found : N, 9·5. $C_{18}H_{22}O_2N_2$ requires N, 9·4%). The *picrate*, m. p. 56—58°, was obtained as clusters of yellow needles from aqueous ethanol (Found : loss at 20°/vac., 2·0. Found, on dried material : N, 13·4. $C_{24}H_{25}O_9N_5,\frac{1}{2}H_2O$ requires H_2O, 1·7%. $C_{24}H_{25}O_9N_5$ requires N, 13·3%).

(ii) A mixture of *p*-(2-ethoxyethoxy)phenyl cyanide (9·6 g.) and benzylammonium thiocyanate (8·3 g., 1 mol.), heated at 180° for 105 minutes, afforded, on being worked up in the usual way (Partridge and Short, *loc. cit.*), the amidinium picrate (0·8 g., 3%), m. p. and mixed m. p. 56—58°.

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