104. *Antituberculous Compounds. Part VII. Some Further N-Substituted Amidines and Analogues.*

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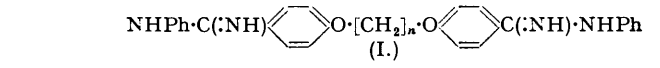
In order to investigate the relation between structure and activity against *Mycobacterium tuberculosis* a number of *N*-substituted aromatic, alicyclic, and aliphatic amidines have been prepared in which the *N*-substituents are in most cases aryl groups of varied type, modified in some compounds as *NN'*-cyclised structures. A few related unsubstituted amidines, dihydroglyoxalines, and *N*-alkyl- or *N-cyclo*alkyl-amidines have also been prepared.

The activity *in vitro* against *Mycobacterium tuberculosis* of di-(*p-N*-arylamidinophenoxy)alkanes (Part II; *J.*, 1949, 2683) and *p*-alkoxy-*N*-arylbenzamidines (Part III; *J.*, 1949, 3043) prompted us to examine a wider range of *N*-substituted amidines in the hope of gaining further insight into the relative importance of the *N*-substituent and of the amidine moiety. Except in a few of the compounds prepared, the *N*-aryl substituent was retained throughout, though of varied type and often considerably modified as an *NN'*-cyclised structure. In a large proportion of

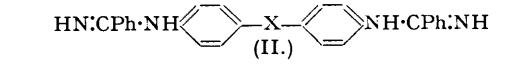
the compounds, however, the aryl radical of the amidine moiety was replaced by an alicyclic or an aliphatic radical, a change frequently resulting in compounds of high activity *in vitro*.

The compounds prepared are enumerated in the accompanying table, together with yields and methods of preparation. The methods were for the most part those developed in these laboratories for the preparation of amidines (Oxley and Short, *J.*, 1946, 147; 1947, 497; 1949, 449; Oxley, Partridge, and Short, *J.*, 1947, 1110) and presented no novel features. In a few cases other methods had to be adopted. These are noted in the discussion below in which the number in parentheses following the name of a compound refers to the number of the compound in the table. Activities *in vitro* are also recorded in the table. Compounds were tested as aqueous solutions of their salts, free bases being in most cases dissolved in an equivalent of aqueous lactic acid. Derivatives unsuitable for testing, such as picrates and reineckates, were first converted into solutions of the base hydrochlorides by standard procedures.

The parent compound *N*-phenylbenzamidine (1) had little activity. The symmetrically substituted *NN'*-diphenylbenzamidine (2) had an even lower activity in agreement with the low activities of the two *NN'*-diphenylbenzamidines described in Part III (*loc. cit.*). The unsymmetrically substituted *NN*-diphenylbenzamidine (3) gave appreciably higher activity and this effect will be referred to again later. A cursory examination of other *N*-phenylbenzamidines (compounds 4—9), substituted in one or both *p*-positions, indicated nothing of promise. *N*-Alkyl substitution as in *N*-methyl-, *N*-octyl-, and *N*-2-diethylaminoethyl-*N*-phenylbenzamidines (10, 11, and 12) gave moderate activity only in the case of the octyl compound.



(I.)



(II.)

An interesting alternation of activity in the odd and even members of the di-(*p*-*N*-phenylamidinophenoxy)alkane series (I; $n = 2$—6) was noted in Part II (*loc. cit.*). No such alternation was shown in a series of di-(*p*-benzimidamidophenoxy)alkanes (20, 21, and 22) (II; X = O·[CH$_2$]$_n$·O where $n = 2$, 3, and 4, respectively) in which nitrogen atoms of two benzamidine residues are linked by the diphenoxyalkane group. All three compounds had comparable high activity, as had also the analogous di-(*p*-benzimidamidophenyl) ether (19) (II; X = O).

In contrast to the low activities of *N*-phenylbenzamidine (1) and *p*-methanesulphonyl-*N*-phenylbenzamidine (6), the corresponding *N*-2-diphenylyl compounds (13 and 14) showed activity of a high order. This powerful activating effect of the 2-diphenylyl group has already been noted in Part III (*loc. cit.*) and is a feature of other 2-diphenylyl derivatives described in the present communication. The corresponding *N*-3-diphenylyl- and *N*-4-diphenylyl-benzamidines (15 and 16) were less active in the absence but of the same order in the presence of serum. The preparation of a series of *N*-4-diphenylyl-amidines, including the latter compound, for antituberculous test has recently been described by Bauer and Cymerman (*J.*, 1950, 1826) who make no reference to the high activity of the analogous *N*-2-diphenylyl compounds here described although the latter author was aware of our results. An increment of activity of a somewhat lower order, especially in the presence of serum, was produced by *N*-1-naphthyl and *N*-2-naphthyl substitution (compounds 17 and 18).

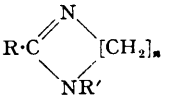
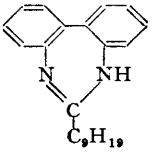
2-Phenylbenziminazole (23), which may be regarded as a cyclised form of *N*-phenylbenzamidine, had moderate activity but a series of 2-phenylbenziminazoles (24—33) substituted in the *p*-position of the 2-phenyl substituent or in the benziminazole nucleus proved of no interest. A number of these compounds were more conveniently prepared by oxidation of a mixture of the appropriate *o*-phenylenediamine and arylaldehyde with copper acetate (Wiedenhagen, *Ber.*, 1936, **69**, 2263) than by the fusion method.

The series of *N*-arylamidino*cyclo*-hexanes and -hexenes (compounds 34—43) presented several points of interest. With the noteworthy exception of 1-*N*-2'-diphenylylamidino*cyclo*hexene (43), replacement of the aromatic nucleus of the benzamidine by *cyclo*hexyl and *cyclo*hexenyl groups if anything enhanced the activity. On the other hand, replacement of the *N*-aryl group by an *N*-*cyclo*hexyl group, as in 1-*N*-*cyclo*hexylamidino*cyclo*hexene (42), led to a compound of low activity. In contrast to the deactivating action of a *p*-chloro-atom in the *N*-phenyl substituent of 1 : 3-di-(*p*-*N*-*p'*-chlorophenylamidinophenoxy)propane (Part II; *loc. cit.*) and its neutral action in *p*-butoxy-*N*-*p'*-chlorophenylbenzamidine (Part III; *loc. cit.*), similar substitution, though not *o*-chloro-substitution, of 1-*N*-phenylamidino*cyclo*hexene appreciably increased the activity (compounds 40 and 41).

The benzamidine moiety may be further modified without loss of activity. Higher members of the series of *N*-phenylamidinoalkanes (compounds 44—50) exhibited high activity in the

absence of serum but both these and the less active lower members were considerably deactivated by serum. Of three analogous *N*-2-diphenylyl compounds, only 1-*N*-2′-diphenylylamidinononane (53) and, to a lesser extent, the heptane analogue (51), showed the expected exaltation of activity. In contrast the corresponding octane analogue (52) was of relatively low activity. All three compounds were, however, reduced to comparable levels of activity by serum.

The analogous series of 1-*N*-2′-naphthylamidinoalkanes (54—62) showed only a uniformly moderate activity in serum comparable with that of the *N*-phenyl analogues. 1-*N*-1′-Naphthylamidinononane (63), the only member which was prepared in the corresponding 1-naphthyl series, was considerably more active than the 2-naphthyl analogue (62). This is the reverse of

(III.)   (IV.)

the observed order of activity of the two naphthylamines themselves (Bloch, Lehr, and Erlenmeyer, *Helv. Chim. Acta*, 1945, **28**, 1406; Doub and Youmans, *Amer. Rev. Tuberc.*, 1950, **61**, 407).

In view of the general high level of activity of the amidinononanes, further examples of compounds containing this grouping were prepared. 1-*NN*-Diphenylamidinononane (64) was of unexpectedly low activity in view of the positive effect of *NN*-diphenyl substitution in benzamidine (cf. compound 3) and was, in fact, no more active than the unsubstituted 1-amidinononane (65).

In 4 : 5-dihydro-2-nonylglyoxaline (66) (III; R = C_9H_{19}, R′ = H, n = 2) a compound of high activity in both the absence and the presence of serum was encountered, but the homologous tetrahydropyrimidine (67) (III; R = C_9H_{19}, R′ = H, n = 3) was feebly active in comparison. Introduction of an *N*-phenyl group into the dihydroglyoxaline (66) gave a compound (68) (III; R = C_9H_{19}, R′ = Ph, n = 2) also of high activity but more susceptible to deactivation by serum. 2-Nonylbenziminazole (69) was about as active as its uncyclised analogue *N*-phenylamidinononane (50), but 2-nonyl-1 : 3-diaza-4 : 5 : 6 : 7-dibenz*cyclo*heptatriene (70) (IV) much less so than its analogue, 1-*N*-(2-diphenylyl)amidinononane (53).

A further example of the potent effect of the dihydroglyoxaline group was furnished by the high activity of 2-heptadecyl-4 : 5-dihydroglyoxaline (72) (III; R = $C_{17}H_{35}$, R′ = H, n = 2) in comparison with the virtual inactivity of 1-amidinoheptadecane (71).

Finally, a few *N*-mono- and -di-alkylated acetamidines were prepared which support the indication observed in the case of the *NN*′- and *NN*-diphenylbenzamidines (2 and 3) that unsymmetrical rather than symmetrical substitution of the amidine group favours activity. Purely aliphatic amidines, mainly *N*-unsubstituted or *N*-monoalkyl-α-alkylated acetamidines, have previously been found active against *M. tuberculosis* (Newbery and Webster, *J.*, 1947, 738). *N*-Octyl-, *NN*-dioctyl-, and *N*-hexadecyl-acetamidines (73, 75, and 76) were prepared by the Pinner route. The usual procedure of treating the imino-ether hydrochloride with the base gave complex mixtures from which it was not possible to isolate the required amidines. However, reaction of a two-fold excess of the base with free acetimido-ether (cf. Ashley *et al.*, *J.*, 1942, 107) for several days (as judged by the rapidity of development of an alkaline reaction to Titan-yellow indicator) provided a practicable method. Attempted preparation of *N*-octylacetamidine from methyl cyanide and octylamine by the aluminium chloride method (Oxley, Partridge, and Short, *loc. cit.*) afforded none of the expected product, but *NN*′-dioctylacetamidine (74) in poor yield. Peak activity was again associated with the unsymmetrically disubstituted *NN*-dioctylacetamidine, both the isomeric *NN*′-dioctyl- and *N*-hexadecyl-acetamidines being considerably less active. The complexity of the factors involving activity is, however, illustrated by the complete reversal of relative activities of the isomeric pair, *N*-octylacetamidine (73) and 1-amidinononane (65), in comparison with the analogous isomeric pair, *N*-heptadecylacetamidine (76) and 1-amidinoheptadecane (71).

Tests *in vivo* on certain of these compounds, selected for favourable activity and toxicity, have already been reported (Croshaw and Dickinson, *Brit. J. Pharm.*, 1950, **5**, 178). The results were uniformly negative.

Experimental

Preparation of Amidines.—The following general methods were used as indicated in the table. The yields recorded in the table refer to the pure compound first isolated.

Compound.	Activity: ‡ in absence of serum.	Activity: ‡ in presence of 10% serum.	Method.	Yield, %.	Derivative.	Solvent.†	Crystal form.	M. p.	Formula.	N, %. Found.	N, %. Reqd.
Benzamidines.											
(1) *N*-Phenyl-	1	—	—	—	—	—	—	—	—	—	—
(2) *NN'*-Diphenyl-	<1 (1)	—	—	—	—	—	—	—	—	—	—
(3) *NN*-Diphenyl-	5 (10)	—	—	—	—	—	—	—	—	—	—
(4) 3 : 4-Dimethoxy-*N*-phenyl-	1	—	—	—	—	—	—	—	—	—	—
(5) *N*-Phenyl-*p*-sulphamyl-	1	—	—	—	—	—	—	—	—	—	—
(6) *p*-Methanesulphonyl-*N*-phenyl-	1	—	—	—	—	—	—	—	—	—	—
(7) *N*-*p*-Methoxyphenyl-	10	—	—	—	—	—	—	—	—	—	—
(8) N-(p-*Methanesulphonyl-phenyl*)-	1	—	D	92	—	Aq. EtOH	Needles	177·5—178°	$C_{14}H_{14}O_2N_2S$	10·1	10·2
					Hydrochloride	EtOH	Cubes	263—265 *	$C_{14}H_{15}O_2N_2ClS$	8·9	9·0
					Picrate	MeOH	Leaflets	137—138	$C_{20}H_{17}O_9N_5S,H_2O$	13·35	13·35
(9) p-*Methanesulphonyl*-N-(p-*methanesulphonyl-phenyl*)-	<1	—	A	60	—	Aq. ethoxy-ethanol	Needles	286—287 *	$C_{15}H_{16}O_4N_2S_2$	7·95	7·95
					Hydrochloride	H_2O	Rosettes, fine needles	270—271 *	$C_{15}H_{17}O_4N_2ClS_2$	7·1	7·2
(10) *N*-Methyl-*N*-phenyl-	1	—	—	—	—	—	—	—	—	—	—
(11) *N*-Octyl-*N*-phenyl-	—	10	D	85	*Reineckate*	H_2O	—	116	$C_{25}H_{29}N_8S_4Cr$	17·6	17·9
(12) *N*-2-Diethylamino-ethyl-*N*-phenyl-	—	1	D	16	*Dipicrate*	MeOH	Needles	109	$C_{31}H_{31}O_{14}N_9$	16·4	16·7
(13) *N*-2-Diphenylyl-	100 (500)	10 (100)	—	—	—	—	—	—	—	—	—
(14) *N*-2-Diphenylyl-*p*-methanesulphonyl-	100	—	—	—	—	—	—	—	—	—	—
(15) N-3-*Diphenylyl*-	50—100	10—50	A	54	—	80% EtOH	Prisms	135—136	$C_{19}H_{16}N_2$	10·15	10·3
(16) *N*-4-Diphenylyl-	50	50	A	57	—	EtOH	Needles	182	$C_{19}H_{16}N_2$	10·3	10·3
(17) *N*-1-Naphthyl-	100	10	A	77	—	80% EtOH	Needles	145	$C_{17}H_{14}N_2$	11·3	11·4
(18) N-2-*Naphthyl*-	10—50	10—50	A	77	—	80% EtOH	Pale yellow plates	123	$C_{17}H_{14}N_2$	11·5	11·4
(19) Di-(*p*-benzimidamido-phenyl) ether	100	10—50	A	40	*Dihydrochloride*	H_2O	Plates	206	$C_{26}H_{24}ON_4Cl_2$	11·9	11·7
(20) 1 : 2-Di-(*p*-benzimid-amidophenoxy)ethane	100	50	A	41	*Dihydrochloride*	H_2O	Plates	280 *	$C_{28}H_{28}O_2N_4Cl_2$	11·0	10·7
(21) 1 : 3-Di-(*p*-benzimid-amidophenoxy)propane	—	50	A	59	*Dihydrochloride*	H_2O	Plates	163—165	$C_{29}H_{30}O_2N_4Cl_2$	10·05	10·4
(22) 1 : 4-Di-(*p*-benzimid-amidophenoxy)butane	—	10—50	A	33	*Dihydrochloride*	H_2O	Small prisms	179—180	$C_{30}H_{32}O_2N_4Cl_2$	10·2	10·2
Benziminazoles.											
(23) 2-Phenyl-	10	1 (10)	C	54	—	—	—	—	—	—	—
(24) 2-*p*-Tolyl-	—	1	C	47	—	60% EtOH	Prisms	269	—	—	—
					Hydrochloride	EtOH	Needles	275	$C_{14}H_{13}N_2Cl$	11·4	11·4

Benziminazoles (contd.)											
(25) 2-p-*Hydroxyphenyl-*	—	5—10	C	60	—	60% EtOH	Prisms	279	$C_{13}H_{10}ON_2$	13·1	13·1
					Hydrochloride	EtOH	Prisms	346	$C_{13}H_{11}ON_2Cl$	11·15	11·4
(26) 2-*p*-Methoxyphenyl-	—	1	E	56	—	Aq. MeOH	Needles	227	$C_{14}H_{12}ON_2$	13·1	12·5
					Hydrochloride	EtOH	Needles	267	$C_{14}H_{13}ON_2Cl$	10·6	10·75
(27) 2-*p*-Nitrophenyl-	—	1	E	51	*Sesquihydrate*	80% EtOH	Minute needles	298—299	$C_{13}H_9O_2N_3,1{\cdot}5H_2O$	15·9	15·8
(28) 2-*p*-Aminophenyl-	—	5	F	90	—	—	—	239	—	—	—
					Dihydrochloride	50% EtOH –aq. HCl	Prisms	351	$C_{13}H_{13}N_3Cl_2$	15·2	14·9
(29) 2-p-*Sulphamylphenyl-*	—	1	A	44	—	Aq. EtOH	Prisms	321	$C_{13}H_{11}O_2N_3S$	15·2	15·4
					Hydrochloride	EtOH	Prisms	335	$C_{13}H_{12}O_2N_3ClS,H_2O$	12·6	12·8
(30) 2-α-Furyl-	—	<1 (10)	E	60	—	EtOH	Needles	284	$C_{11}H_8ON_2$	15·4	15·2
					Hydrochloride	50% EtOH	Needles	299	$C_{11}H_9ON_2Cl,H_2O$	11·8	11·8
(31) 4-Nitro-2-phenyl-	—	—	E	44·5	*Hydrochloride*	EtOH	Prisms	252 *	$C_{13}H_{10}O_2N_3Cl$	15·5	15·3
(32) 4-Amino-2-phenyl-	—	1	F	39	*Dihydrochloride*	80% EtOH	Prisms	264	$C_{13}H_{13}N_3Cl_2$	15·1	14·9
(33) 5-Amino-2-phenyl-	—	<1	F	81	Dihydrochloride	Aq. EtOH–HCl	Prisms	322	$C_{13}H_{13}N_3Cl_2$	15·0	14·9
*Amidino*cyclo*hexanes.*											
(34) *N*-Phenyl-	5 (10)	—	—	—	—	—	—	—	—	—	—
(35) N-p-*Butoxyphenyl-*	100	10—50	B	52	—	Petrol	Plates	90	$C_{17}H_{26}ON_2$	10·1	10·2
					Toluene-p-sulphonate	PrᴵOH	Plates	168·5—169	$C_{24}H_{34}O_4N_2S$	6·4	6·3
1-*Amidino*cyclo*hexenes.*											
(36) *N*-Phenyl-	5 (10)	—	—	—	—	—	—	—	—	—	—
(37) *N*-*p*-Methoxyphenyl-	10	—	A	57	*Benzene-sulphonate*	H_2O	Prisms	171	$C_{20}H_{24}O_4N_2S$	7·3	7·2
(38) N-p-*Ethoxyphenyl-*	50	—	B	62	—	Petrol	Indef.	95	$C_{15}H_{20}ON_2$	11·4	11·5
					Picrate	PrᴵOH	Indef.	136	$C_{21}H_{23}O_8N_5$	15·0	14·8
(39) N-p-*Butoxyphenyl-*	500 (10,000)	100	B	65	—	Petrol	Prisms	69	$C_{17}H_{24}ON_2$	10·5	10·3
					Hydrochloride	H_2O	Plates	143	$C_{17}H_{25}ON_2Cl$	9·1	9·1
(40) N-p-*Chlorophenyl-*	50	10—50	A	92	—	C_6H_6	Prisms	131	$C_{13}H_{15}N_2Cl$	11·9	11·9
					Picrate	PrᴵOH	Indef.	193	$C_{19}H_{18}O_7N_5Cl$	15·2	15·1
(41) N-o-*Chlorophenyl-*	1—5	—	A	41	—	Petrol	Prisms	77	$C_{13}H_{15}N_2Cl$	11·9	11·9
					Picrate	PrᴵOH	Indef.	185	$C_{19}H_{18}O_7N_5Cl$	15·1	15·1
(42) *N-cyclo*Hexyl-	1	—	D	91	*Hydrochloride*	H_2O	Indef.	291 *	$C_{18}H_{23}N_2Cl$	11·6	11·55
(43) *N*-2′-Diphenylyl-	10	—	—	—	—	—	—	—	—	—	—
1-N-*Phenylamidino-alkanes.*											
(44) *-propane*	10	1—5	A	66	—	Petrol	Rhombs	67	$C_{10}H_{14}N_2$	17·2	17·3
					Picrate	PrOH	Rhombic plates	142—142·5	$C_{16}H_{17}O_7N_5$	18·1	17·9
(45) *-butane*	5—10	<1 (10)	A	69	—	Petrol	Flat needles	59	$C_{11}H_{16}N_2$	16·1	15·9
					Picrate	PrᴵOH	Rhombic prisms	139·5—140	$C_{17}H_{19}O_7N_5$	17·3	17·3
(46) *-pentane*	10—100	5—10	A	60	—	Petrol	Flat needles	58	$C_{12}H_{18}N_2$	14·7	14·7
					Picrate	PrᴵOH	Indef.	97	$C_{18}H_{21}O_7N_5$	16·7	16·7

Compound.	Activity : ‡ in absence of serum.	Activity : ‡ in presence of 10% serum.	Method.	Yield, %.	Derivative.	Solvent.†	Crystal form.	M. p.	Formula.	N, %. Found.	N, %. Reqd.
1-N-*Phenylamidino-alkanes* (contd.)											
(47) -*heptane*	500	10	A	80	—	Petrol	Long needles	54	$C_{14}H_{22}N_2$	12·6	12·8
					Picrate	Et_2O	Plates	92—93	$C_{20}H_{25}O_7N_5$	15·9	15·7
					Benzene-sulphonate	$COMe_2$	Plates	96	$C_{20}H_{28}O_3N_2S$	7·6	7·45
(48) -*octane*	100—500	10—50	A	64	—	Petrol	Flat needles	61	$C_{15}H_{24}N_2$	12·0	12·1
					Picrate	Pr^iOH	Small plates	93	$C_{21}H_{24}O_7N_5$	14·7 14·7	15·2
					Benzene-sulphonate	$COMe_2$	Plates	102	$C_{21}H_{30}O_3N_2S$	7·2	7·2
(49) -*nonane*	500	10	A	62	—	Petrol	Needles	70	$C_{16}H_{26}N_2$	11·25	11·4
(50) 1-*N*-*p*-Tolylamidino-butane	50 (100)	—	—	—	—	—	—	—	—	—	—
1-N-2′-*Diphenylylamidino-alkanes.*											
(51) -heptane	500—1000	100	—	—	—	—	—	—	—	—	—
(52) -*octane*	100	50	A	37	—	Petrol (40—60°) or aq. $COMe_2$	Needles	97·5—98	$C_{21}H_{28}N_2$	9·15	9·1
(53) -nonane	5000	50—500	—	—	—	—	—	—	—	—	—
1-N-2′-*Naphthylamidino-alkanes.*											
(54) -*methane*	—	10	A	68	—	Petrol	Prisms	82	$C_{12}H_{12}N_2$	15·5	15·2
					Benzene-sulphonate	Pr^iOH	Prisms	142	$C_{18}H_{18}O_3N_2S$	7·9	8·2
(55) -*ethane*	—	10	A	50·5	—	Petrol	Long prisms	79—80	$C_{13}H_{14}N_2$	14·1	14·1
(56) -*propane*	—	10	A	86	—	Petrol	Prisms	64—66	$C_{14}H_{16}N_2$	13·3	13·2
					Benzene-sulphonate	Aq. EtOH	Plates	133—134	$C_{20}H_{22}O_3N_2S$	7·5	7·6
(57) -*butane*	—	10	A	22	—	Petrol	Plates	62—64	$C_{15}H_{18}N_2$	12·4	12·4
(58) -*pentane*	—	10	A	35	—	Petrol	Plates	72—74	$C_{16}H_{20}N_2$	11·9	11·7
(59) -*hexane*	10	10	B	79	—	Petrol	Prisms	59	$C_{17}H_{22}N_2$	10·8	11·0
					Toluene-p-sulphonate	Aq. EtOH	Plates	138	$C_{24}H_{30}O_3N_2S$	6·7	6·6
(60) -*heptane*	—	10—50	B	69	—	Et_2O–petrol	Prisms	61	$C_{18}H_{24}N_2$	10·45	10·45
					Toluene-p-sulphonate	Aq. EtOH	Plates	151	$C_{25}H_{32}O_3N_2S$	6·25	6·4
(61) -*octane*	—	10	B	83	—	Petrol	Plates	74	$C_{19}H_{26}N_2$	9·75	9·9
					Toluene-p-sulphonate	Aq. EtOH	Plates	156	$C_{26}H_{34}O_3N_2S$	6·4	6·2
(62) -*nonane*	—	5	B	67	—	Petrol	Plates	75	$C_{20}H_{28}N_2$	9·7	9·5
					Toluene-p-sulphonate	Pr^iOH	Plates	158	$C_{27}H_{36}O_3N_2S$	6·05	6·0

Various.											
(63) 1-*N*-1′-Naphthyl-amidinononane	100	100	A	45	*Benzene-sulphonate*	CCl_4	Plates	70—72	$C_{26}H_{34}O_3N_2S$	6·15	6·15
(64) 1-*NN*-Diphenyl-amidinononane	10	1	D	63	*Picrate*	EtOH	Prisms	118·5	$C_{28}H_{33}O_7N_5$	12·6	12·7
					Picrolonate	EtOH	Rods	142—143	$C_{32}H_{38}O_5N_6$	14·2	14·3
(65) 1-Amidinononane	10	—	A	41	*Benzene-sulphonate*	80% EtOH	Plates	92—94	$C_{16}H_{28}O_3N_2S$	8·5	8·5
(66) 4 : 5-*Dihydro*-2-*nonylglyoxaline*	100—500 (1000)	100 (500)	C	60	—	Et_2O–petrol	Plates	74—76	$C_{12}H_{24}N_2$	14·3	14·3
(67) 3 : 4 : 5 : 6-Tetrahydro-2-nonylpyrimidine	—	10	C	90	*Reineckate*	$COMe_2$–$CHCl_3$	Feathery needles	147—148	$C_{17}H_{33}N_8S_4Cr$	21·3	21·2
(68) 4 : 5-*Dihydro*-2-*nonyl*-1-*phenylglyoxaline*	1000	10 (500)	C	18	—	—	—	—	$C_{18}H_{28}N_2$	10·5	10·3
(69) 2-*Nonylbenziminazole*	50	5—10	C	52	—	Aq. EtOH	Indef.	124—126	$C_{16}H_{24}N_2$	11·5	11·5
(70) 2-*Nonyl*-1 : 3-*diaza*-4 : 5 : 6 : 7-*dibenzo*-cyclo*heptatriene*	10	5—10	C	45	—	Petrol	Indef.	73—75	$C_{22}H_{28}N_2$	9·1	8·75
(71) 1-Amidinohepta-decane	<1	—	A	26	*Benzene-sulphonate*	MeOH	Indef.	92—95	$C_{24}H_{44}O_3N_2S$	6·1	6·4
(72) 2-*Heptadecyl*-4 : 5-*di-hydroglyoxaline*	500—1000	100	C	73	—	$COMe_2$	Plates	94	$C_{20}H_{40}N_2$	9·2	9·1
Acetamidines.											
(73) *N*-Octyl-	<1	—	G	67	*Reineckate*	H_2O	Indef.	137	$C_{14}H_{29}N_8S_4Cr$	23·2	23·0
(74) *NN′*-Dioctyl	7·5	—	D	8	*Hydrochloride*	EtOH–$COMe_2$	Indef.	265—268	$C_{18}H_{39}N_2Cl$	9·0	8·8
(75) *NN*-Dioctyl-	50	—	G	85	*Picrate*	Et_2O	Prisms	89	$C_{24}H_{41}O_7N_5$	13·65	13·7
(76) N-*Hexadecyl*-	10	—	G	13	—	Et_2O	Indef.	71·5	$C_{18}H_{38}N_2$	10·3	10·0
					Picrate	Et_2O	Minute needles	114	$C_{24}H_{39}O_7N_5$	13·75	13·7

* With decomposition. † Petrol = light petroleum (b. p. 60—80°).

‡ 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) (Croshaw and Dickinson, *loc. cit.*). Figures in parentheses represent dilutions 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), and (3) Oxley and Short, *J.*, 1946, 147. (4), (5), (6), and (7) Oxley and Short, *J.*, 1949, 449. (8) and (9) Preparations by Dr. M. W. Partridge. (10) Oxley, Partridge, and Short, *loc. cit.* (11) Prepared by precipitation of the crude hydrochloride with ammonium reineckate. (13) and (14) Cymerman and Short, *J.*, 1949, 703. (17) Bernthsen and Trompetter (*Ber.*, 1878, **11**, 1757) give m. p. 141°. (23) Cf. Holljes and Wagner, *J. Org. Chem.*, 1944, **9**, 31. (24) Brücker (*Annalen*, 1880, **205**, 118) and Hübner (*ibid.*, 1881, **210**, 329) record m. p. 268°; Wuyts and Vaerenbergh (*Bull. Soc. chim. Belg.*, 1939, **48**, 329), m. p. 265°; and Holljes and Wagner (*loc. cit.*), m. p. 266—269° for the base. (26) Found for base: C, 74·6; H, 5·4. Calc. for $C_{14}H_{12}ON_2$: C, 75·0; H, 5·4%. Wiedenhagen (*loc. cit.*) gives m. p. 228—230°. (27) Found: C, 58·5; H, 4·4. $C_{13}H_9O_2N_3,1{\cdot}5H_2O$ requires C, 58·8; H, 4·5%. (28) Kym (*Ber.*, 1900, **33**, 2848) records m. p. 235—236°, and Lauth (*Bull. Soc. chim.*, 1897, **17**, 618), m. p. 240° for the base. Miklaszewski and Niementowski (*Ber.*, 1901, **34**, 2953) record m. p. 240° for the base and m. p. 348° for the dihydrochloride. (29) Found for the base: C, 57·3; H, 4·1; S, 12·4. $C_{13}H_{11}O_2N_3S$ requires C, 57·1; H, 4·1; S, 11·7%. (30) Wiedenhagen (*loc. cit.*) gives m. p. 285—286° for the base. (33) Hübner (*loc. cit.*) does not record a m. p. for this compound. (34) and (36) Oxley and Short (*J.*, 1949, 449). (39) The hydrochloride showed dimorphism, m. p. 143° with rapid heating, recrystallising to m. p. 155°; m. p. 155° with slow heating. (43) Cymerman and Short (*loc. cit.*). (45) The hydrochloride could not be crystallised. (49) Preparation by Dr. Cymerman. (50) Oxley and Short (*J.*, 1949, 449). (51) Cymerman and Short (*loc. cit.*). (52) Preparation by Dr. Cymerman. (53) Cymerman and Short (*loc. cit.*). (60) Preparation by Mr. G. S. Ward. (65) and (66) Preparations by Dr. R. P. Hullin. (68) B. p. 144°/1 mm. (73), (74), and (75) Preparations by Dr. R. P. Hullin.

Method A. A mixture of equimolecular quantities of the appropriate cyanide and substituted ammonium benzenesulphonate was heated with stirring (or under pressure if necessary) at temperatures ranging from 180° to 220° (260—265° when ammonium benzenesulphonate was used) for periods of 2—6 hours (Oxley and Short, *J.*, 1946, 147). The product was either isolated as the benzenesulphonate or converted into the free base by dissolving it in water or ethanol and adding an excess of 5N-sodium hydroxide. The crude amidine could be purified by direct crystallisation or by collection in benzene and extraction from the benzene solution with acetic acid–sodium acetate buffer (pH *ca.* 4·6), which did not extract the arylamine. Basification of the buffer extract then gave the amidine in almost pure condition.

Method B. As for method A, but the substituted ammonium toluene-*p*-sulphonate being used.

Method C. For the preparation of cyclic amidines the cyanide was similarly fused with the appropriate diamine mono-benzenesulphonate or -toluene-*p*-sulphonate [or an equivalent mixture of diamine and diamine di-benzenesulphonate or -toluene-*p*-sulphonate (Oxley and Short, *J.*, 1947, 497)].

Method D. A mixture of cyanide and amine was treated with a molecular equivalent of anhydrous aluminium chloride at 160—200° for 20—60 minutes (Oxley, Partridge, and Short, *loc. cit.*). The free base was liberated by aqueous sodium hydroxide solution and isolated as a suitable derivative.

Method E. A mixture of the appropriate *o*-phenylenediamine and arylaldehyde was oxidised with copper acetate in aqueous ethanol or methanol according to Wiedenhagen's method (*loc. cit.*).

Method F. The corresponding nitro-compound was reduced with ammonium sulphide according to Pinnow and Wiskott (*Ber.*, 1899, **32**, 906).

Method G. A mixture of acetimidoethyl ether (2 mols.) and the amine (1 mol.) was kept at room temperature for 6—24 days, alone or diluted with anhydrous ether. During this time the mixture became strongly alkaline to Titan-yellow. Ether and excess of acetimidoether were removed under reduced pressure, and the amidine isolated either as a suitable derivative or by distillation under reduced pressure.

Arylammonium Benzenesulphonates and Toluene-p-*sulphonates.*—The following benzenesulphonates and toluene-*p*-sulphonates used in methods A, B, and C have not previously been described : p-*Butoxyanilinium toluene*-p-*sulphonate*, needles (from *iso*propanol), m. p. 189° (Found : N, 4·3. $C_{17}H_{23}O_4NS$ requires N, 4·15%); 4 : 4′-diaminodiphenyl ether dibenzenesulphonate, m. p. 285° (not analysed); 1 : 2-*di*-(p-*aminophenoxy*)*ethane dibenzenesulphonate*, plates (from water), m. p. 280—281° (Found : N, 5·2. $C_{26}H_{28}O_8N_2S_2$ requires N, 5·0%) [prepared from 1 : 2-di-(*p*-aminophenoxy)ethane, pale buff needles (from aqueous ethanol), m. p. 170—172° (Found : N, 11·5. Calc. for $C_{14}H_{16}O_2N_2$: N, 11·5%). Wagner (*J. pr. Chem.*, 1883, **27**, 206) records m. p. 176°]; 1 : 3-di-(*p*-aminophenoxy)propane dibenzenesulphonate, plates (from ethanol), m. p. 236—238° (not analysed); 1 : 4-*di*-(p-*aminophenoxy*)*butane dibenzenesulphonate*, plates (from ethanol), m. p. 262° (Found : N, 5·0. $C_{28}H_{32}O_8N_2S_2$ requires N, 4·8%); 3-*aminodiphenyl benzenesulphonate*, needles (from water), m. p. 187—188° (Found : N, 4·45. $C_{18}H_{17}O_3NS$ requires N, 4·3%); p-*phenylenediamine dibenzenesulphonate*, needles (from ethanol), m.p. 158° (decomp.) (Found : N, 6·8. $C_{18}H_{20}O_6N_2S_2$ requires N, 6·6%).

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