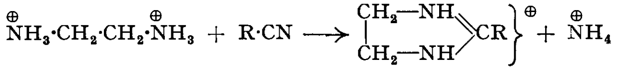
96. *Amidines. Part VI. Preparation of 2-Substituted 4 : 5-Dihydroglyoxalines and Ring Homologues from Cyanides and Alkylenediamines.*

By P. Oxley and W. F. Short.

2-Substituted 4 : 5-dihydroglyoxalines are produced in good yield by heating cyanides with a salt of ethylenediamine. Ring homologues containing 6 and 7 atoms can be prepared similarly, but not those containing 8 and 9 atoms.

Derivatives of 4 : 5-dihydroglyoxaline substituted in position 2 have recently come into prominence owing to their influence on the circulatory system. Thus, 2-benzyldihydroglyoxaline is a powerful vasodilator (Hartmann and Isler, *Arch. exp. Path.*, 1939, **192**, 141) and replacement of the phenyl by a naphthyl radical affords 2-α-naphthylmethyldihydroglyoxaline which is a strong vasoconstrictor (Hartmann and Isler, *loc. cit.*; Hild, *Schweiz. med. Wschr.*, 1941, **71**, 557; Babel, *ibid.*, p. 561). 2-(2′ : 3′ : 4′-Trimethoxybenzyl)dihydroglyoxaline has a pressor action and has been used to combat the fall of blood pressure in spinal anæsthesia and for the treatment of post-operative shock (Jones and Wilson, *Lancet*, 1938, **234**, 195; Hartmann and Isler, *loc. cit.*; Elmes and Jefferson, *Brit. Med. J.*, 1942, ii, 65; Burn, *Brit. Med. Bull.*, 1946, **4**, 95). Since relatively few methods are available for the preparation of dihydroglyoxalines (see Chitwood and Reid, *J. Amer. Chem. Soc.*, 1935, **57**, 2424; Scholtz, *Ind. Eng. Chem.*, 1945, **37**, 120) we were led to inquire whether these compounds could be obtained by adapting and extending the methods for the preparation of amidines described in previous parts of this series.

It was shown in Part I (Oxley and Short, *J.*, 1946, 147) that amidines can be prepared by heating a cyanide with an ammonium sulphonate, and we now find that 2-substituted dihydroglyoxalines are obtained from a cyanide and a neutral sulphonate of ethylenediamine at 220—250° :



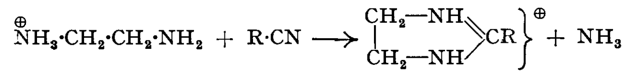
$$\overset{\oplus}{N}H_3\cdot CH_2\cdot CH_2\cdot\overset{\oplus}{N}H_3 + R\cdot CN \longrightarrow \left\{\begin{array}{l} CH_2-NH \\ | \\ CH_2-NH \end{array}\!\!>CR\right\}^{\oplus} + \overset{\oplus}{N}H_4$$

When two molecular proportions of the cyanide are used, a considerable quantity of an amidinium salt $\mathrm{R{\cdot}C({:}NH){\cdot}NH_3\}^{\oplus}\ R'{\cdot}SO_3^{\ominus}}$ is simultaneously produced by the reaction between the cyanide and the ammonium salt formed in the ring closure. The heterocyclic nucleus is formed so readily that attempts to isolate the intermediate amidinium salt,

$$\mathrm{R{\cdot}C({:}NH){\cdot}NH{\cdot}CH_2{\cdot}CH_2{\cdot}NH_3\}^{\oplus}\ R'{\cdot}SO_3^{\ominus}},$$

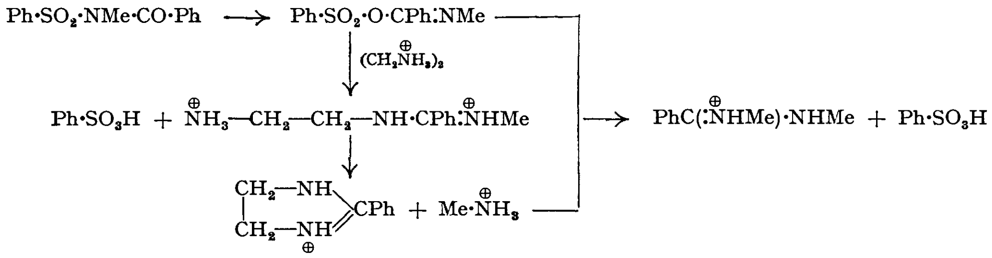
were unsuccessful. Ring formation is prevented by the introduction of alkyl groups, and Mr. J. Miller obtained the *toluene*-p-*sulphonates* of *N*-β-diethylaminoethylbenzamidine and *N*-β-diethylaminoethyl-*p*-amidinophenyl methyl sulphone by heating β-diethylaminoethylammonium toluene-*p*-sulphonate with phenyl cyanide and *p*-cyanophenyl methyl sulphone respectively.

In a subsequent communication it will be shown that the production of amidines by the addition of ammonia or an amine to a cyanide is facilitated by (*a*) structural influences which enhance the kationoid properties of the carbon atom of the cyano-group, and (*b*) increase in the strength of the basic addendum. Owing to the instability of unsubstituted amidines, only exceptional cyanides yield amidines by combination with ammonia in absence of a stabilising agent (cf. Part I, *loc. cit.*). However, *N*-alkylamidines are known to be less readily decomposed to cyanides than the corresponding unsubstituted amidines (cf. Part III, this vol., p. 382) and it is clear that combination of a cyanide with ethylenediamine to give an amidine, $\mathrm{NH{:}CR{\cdot}NH{\cdot}CH_2{\cdot}CH_2{\cdot}NH_2}$, would be favoured by the strongly basic character of the diamine and by the presence of the methylene chain. Since ring closure by loss of the elements of ammonia would almost certainly be irreversible it seemed probable that dihydroglyoxalines would be formed by boiling cyanides with ethylenediamine. It is now found that reactive cyanides, such as *p*-cyanophenyl methyl sulphone, rapidly yield dihydroglyoxalines with boiling ethylenediamine but the slow reaction which occurs with less active cyanides cannot conveniently be accelerated by raising the temperature owing to the low boiling point of the diamine (117°) and the evolution of ammonia. In such cases it is advantageous to use the mono-acid salt of the diamine which reacts rapidly with cyanides at 100—200° to give dihydroglyoxalinium salts and ammonia :

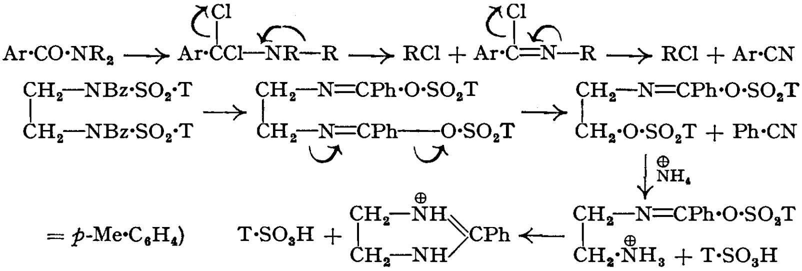


The use of sulphonic acid salts facilitates reaction with the cyanides since a homogeneous melt is formed, and, although the corresponding chlorides ultimately afford good yields of dihydroglyoxalines, the initial reaction mixture is usually heterogeneous, the reaction is slower, and the resulting hydrochlorides are not so tractable as the sulphonates. The scope of the method is illustrated by the examples collected in the Table (Nos. 1—25) and it will be observed that bases containing two dihydroglyoxaline nuclei are readily prepared from dicyanides (Nos. 18—25). The yields are so good that the method could be used for the identification of cyanides.

Mixed imides, $\mathrm{Ar{\cdot}SO_2{\cdot}NX{\cdot}CO{\cdot}R}$, and ammonium salts, $\mathrm{YZ\overset{\oplus}{N}H_2\}\overset{\ominus}{A}}$, afford salts of amidines, $\mathrm{R{\cdot}C({:}NX){\cdot}NYZ}$ (Part III, *loc. cit.*), and we now find that *N*-benzoylbenzenesulphonmethylamide and ethylenediammonium dichloride yield 2-phenyldihydroglyoxaline and *NN'*-dimethylbenzamidine :



The potassium salt of αβ-bistoluene-*p*-sulphonamidoethane (Howard and Marckwald, *Ber.*, 1899, **32**, 2041) and benzoyl chloride afford *NN'-dibenzoyl-*αβ-*bistoluene-*p-*sulphonamidoethane*, and 2-phenyldihydroglyoxaline (93%) and phenyl cyanide are obtained when this mixed imide is heated with ammonium toluene-*p*-sulphonate. We suggest that in this reaction the toluene-*p*-sulphonyloxy-radical simulates the behaviour of the chlorine atom in v. Braun's method for the preparation of aryl cyanides and chloroparaffins (or αω-dichloroparaffins) from the *N*-disubstituted amido-chlorides of aromatic acids (*Ber.*, 1904, **37**, 2812, 2915, 3210).



$$\mathrm{Ar{\cdot}CO{\cdot}NR_2 \longrightarrow Ar{\cdot}CCl{-}NR{-}R \longrightarrow RCl + Ar{\cdot}C{=}N{-}R \longrightarrow RCl + Ar{\cdot}CN}$$

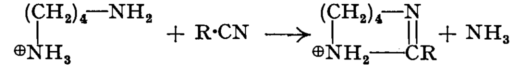
$$\begin{array}{l} \mathrm{CH_2{-}NBz{\cdot}SO_2{\cdot}T} \\ | \\ \mathrm{CH_2{-}NBz{\cdot}SO_2{\cdot}T} \end{array} \longrightarrow \begin{array}{l} \mathrm{CH_2{-}N{=}CPh{\cdot}O{\cdot}SO_2T} \\ | \\ \mathrm{CH_2{-}N{=}CPh{-}O{\cdot}SO_2T} \end{array} \longrightarrow \begin{array}{l} \mathrm{CH_2{-}N{=}CPh{\cdot}O{\cdot}SO_2T} \\ | \\ \mathrm{CH_2{\cdot}O{\cdot}SO_2T + Ph{\cdot}CN} \end{array}$$

$$\big\downarrow \overset{\oplus}{\mathrm{N}}\mathrm{H_4}$$

$$= p\text{-}\mathrm{Me{\cdot}C_6H_4)} \qquad \mathrm{T{\cdot}SO_3H} + \begin{array}{l} \mathrm{CH_2{-}\overset{\oplus}{N}H} \\ | \qquad\qquad \rangle \mathrm{CPh} \\ \mathrm{CH_2{-}NH} \end{array} \longleftarrow \begin{array}{l} \mathrm{CH_2{-}N{=}CPh{\cdot}O{\cdot}SO_2T} \\ | \\ \mathrm{CH_2{\cdot}\overset{\oplus}{N}H_3 + T{\cdot}SO_3H} \end{array}$$

So little is known of the ring homologues of dihydroglyoxaline that it seemed desirable to ascertain whether they could be prepared from cyanides and salts of aliphatic diamines. Derivatives of 3 : 4 : 5 : 6-tetrahydropyrimidine substituted in position 2 have been prepared (*a*) from trimethylene dibromide and amidines (Pinner, *Ber.*, 1893, **26**, 2122; Branch and Titherley, *J.*, 1912, **101**, 2342), (*b*) by heating diacyltrimethylenediamides in a stream of hydrogen chloride (Hofmann, *Ber.*, 1888, **21**, 2336), (*c*) by fusing trimethylenediammonium dichloride with sodium acetate (Harries and Haga, *Ber.*, 1899, **32**, 1191; Haga and Majima, *Ber.*, 1903, **36**, 333), and (*d*) by heating a mixture of monoacyltrimethylenediamines and calcium oxide under pressure at 250° (Aspinall, *J. Amer. Chem. Soc.*, 1940, **62**, 2160). Methods (*a*)—(*c*) afford low yields (usually a few per cent.) and, although much better yields are obtained by method (*d*), it is somewhat laborious, and only three members of the group have been prepared. Tetrahydropyrimidines can be conveniently prepared from cyanides and trimethylenediamine or its salts and a number of examples are collected in the Table (Nos. 26—31). It will be noted that the method gives compounds containing two tetrahydropyrimidine nuclei when applied to dicyanides.

1-*Phenyl*-2 : 7-*diaza*cyclo*heptene* is obtained in 88% yield from an equimolecular mixture of phenyl cyanide, tetramethylenediamine, and *tetramethylenediammonium bistoluene*-p-*sulphonate* at 200°; a number of other members of this group have been prepared, including a compound (No. 36) containing two diaza*cyclo*heptene nuclei (see Table Nos. 32—36).



$$\begin{array}{l} \mathrm{(CH_2)_4{-}NH_2} \\ | \\ \mathrm{{}^{\oplus}NH_3} \end{array} + \mathrm{R{\cdot}CN} \longrightarrow \begin{array}{l} \mathrm{(CH_2)_4{-}N} \\ | \qquad\quad \| \\ \mathrm{{}^{\oplus}NH_2{-}CR} \end{array} + \mathrm{NH_3}$$

The only representative of this type hitherto described is 1-methyl-2 : 7-diaza*cyclo*heptene which was obtained in very low yield from tetramethylenediammonium dichloride and sodium acetate at 250° (Haga and Majima, *Ber.*, 1903, **36**, 337).

The practical limit of the method appears to be reached with the formation of diaza*cyclo*heptenes, since attempts to produce 8- and 9-membered ring compounds by condensing penta- and hexa-methylenediamines or their salts with cyanides result in the production of mixtures from which no homogeneous solid derivatives can be isolated. The results do not preclude the possibility that in each case 8- and 9-membered ring compounds are formed, but indicate simultaneous formation of condensation products of higher molecular weight, including, for example, substances of the type $\mathrm{NH{:}CR{\cdot}NH{\cdot}[CH_2]_n{\cdot}\{N{:}CR{\cdot}NH{\cdot}[CH_2]_n\}_x{\cdot}N{:}CR{\cdot}NH_2}$.

Notes to Table.—Except where otherwise indicated, the experiments were conducted with 0·02—0·1 g.-mol. of cyanide, using one mol. of the monotoluene-*p*-sulphonate of the alkylenediamine (or 0·5 mol. of the base and 0·5 mol. of the bistoluene-*p*-sulphonate) per mol. of cyanide or per 0·5 mol. of dicyanide. Yields are expressed in terms of the cyanide employed. Some of the dihydroglyoxalines described in the patent literature have not been indexed in abstract journals since no analyses were recorded in the patents cited below. Methods for isolating the products are illustrated by typical examples in the experimental section.

(1) Chitwood and Reid (*loc. cit.*) state that the base and its picrate have m. p. 41° and 125·8° respectively.

(2) Other methods of preparation are recorded in the experimental section. The hydrochloride had m. p. 175° (Found: C, 61·3; H, 6·8; N, 14·3. Calc. for $\mathrm{C_{10}H_{13}N_2Cl}$: C, 61·1; H, 6·7; N, 14·3%). Ciba (B.P.P., 460,528; 514,411) state that the base and the hydrochloride have m. p. 61—62° and 168—170° respectively. Aspinall (*J. Amer. Chem. Soc.*, 1939, **61**, 3195) records m. p. 68°, 174°, and 149° for the base, the hydrochloride, and the picrate respectively.

(3) A *dipicrate*, m. p. 195° (decomp.), was also prepared (Found: N, 19·8. $\mathrm{C_{22}H_{19}O_{14}N_9}$ requires N, 19·9%). The bistoluene-*p*-sulphonate was a yellow gum considerably more soluble than the mono-acid salt. Sonn and Ciba (B.P. 460,528) state that the dihydrochloride has m. p. 280—285°.

Compound.	Reaction.		Yield (%).	Base.			
	Temp.	Time (hrs.).		M. p.	Formula.	Found, N (%).	Req., N (%).
(1) 2-*n*-Butyldihydroglyoxaline	160°	5	96	41·4°	—	—	—
(2) 2-Benzyldihydroglyoxaline	200	1	91	66—68	—	—	—
(3) 2-(4′-*Aminobenzyl*)*dihydroglyoxaline*	140	6	74	124	$C_{10}H_{13}N_3$	24·0	24·0
(4) 2-(4′-Sulphamidobenzyl)dihydroglyoxaline	180	2¼	100	—	—	—	—
(5) 2-(1′-*Naphthylmethyl*)*dihydroglyoxaline*	175—200	1	99	119·5	$C_{14}H_{14}N_2$	13·4	13·3
(6) 2-Phenyldihydroglyoxaline	100	112	44	101	$C_9H_{10}N_2$	18·9	19·2
(7) 2-(4′-*Chlorophenyl*)*dihydroglyoxaline*	160	1	90	187	$C_9H_9N_2Cl$	15·5	15·5
(8) 2-p-*Anisyldihydroglyoxaline*	200	1½	72	140	$C_{10}H_{12}ON_2$	16·0	15·9
(9) 2-(3′ : 4′-*Dimethoxyphenyl*)*dihydroglyoxaline*	200	1	34	158·5	$C_{11}H_{14}O_2N_2$	13·6	13·6
(10) 2-(2′-*Nitrophenyl*)*dihydroglyoxaline*	160	1	74	98	$C_9H_9O_2N_3$	22·1	22·0
(11) 2-(4′-*Sulphophenyl*)*dihydroglyoxaline*	160	¼	97	>360	$C_9H_{10}O_3N_2S$	12·0	12·4
(12) 2-(4′-*Sulphonamidophenyl*)*dihydroglyoxaline*	160—225	½	81	245 (decomp.)	$C_9H_{11}O_2N_3S$	18·5	18·6
(13) 2-(4′-*Methylsulphonylphenyl*)*dihydroglyoxaline*	200	½	89	213·5	$C_{10}H_{12}O_2N_2S$	12·5	12·5
(14) 2-α-*Naphthyldihydroglyoxaline*	200	3	66	133·5—134	$C_{13}H_{12}N_2$	14·3	14·3
(15) 2-β-*Naphthyldihydroglyoxaline*	160	2	75·5	118	$C_{13}H_{12}N_2$	14·4	14·3
(16) 2-α-*Pyridyldihydroglyoxaline*	200	⅓	95	98·5—99	$C_8H_9N_3$	28·8	28·6
(17) 2-β-*Pyridyldihydroglyoxaline*	200	⅓	96	111—111·5	$C_8H_9N_3$	28·6	28·6
(18) 1 : 2-*Bis*-(2′-*dihydroglyoxalinyl*)*ethane*	150—200	⅓	99	235 (decomp.)	$C_8H_{14}N_4$	33·6	33·7
(19) 1 : 3-Bis-(2′-dihydroglyoxalinyl)propane	170—200	1	84	—	—	—	—
(20) 1 : 4-Bis-(2′-dihydroglyoxalinyl)butane	170—200	1	93	218·5—219	$C_{10}H_{18}N_4$	28·6	28·9
(21) 1 : 5-Bis-(2′-dihydroglyoxalinyl)pentane	170—200	1	96	—	—	—	—
(22) 1 : 8-Bis-(2′-dihydroglyoxalinyl)octane	175—225	1½	93	187·5	$C_{14}H_{26}N_4$	22·4	22·4
(23) 1 : 11-*Bis*-(2′-*dihydroglyoxalinyl*)*undecane*	175—225	1½	91	162·5	$C_{17}H_{32}N_4$	19·2	19·2
(24) 4 : 4′-Bis-(2-dihydroglyoxalinyl)diphenyl	225	½	100	—	—	—	—
(25) 4 : 4′-Bis-(2-dihydroglyoxalinyl)stilbene	200—245	¾	65	—	—	—	—
(26) 2-Phenyl-3 : 4 : 5 : 6-tetrahydropyrimidine	140	½	94·5	86—87	—	—	—
(27) 2-(4′-*Sulphophenyl*)-3 : 4 : 5 : 6-*tetrahydropyrimidine*	160	¼	98	>360	$C_{10}H_{12}O_3N_2S$	11·6	11·7
(28) 2-(4′-*Methylsulphonylphenyl*)-3 : 4 : 5 : 6-*tetrahydropyrimidine*	255	1½	71	173·5	$C_{11}H_{14}O_2N_2S$	11·8	11·8
(29) 2-(1′-*Naphthylmethyl*)-3 : 4 : 5 : 6-*tetrahydropyrimidine*	165—225	2	95	124	$C_{15}H_{16}N_2$	12·65	12·5
(30) 2-α-Pyridyl-3 : 4 : 5 : 6-tetrahydropyrimidine	200	1½	96	*ca.* 15	—	—	—
(31) 1 : 2-Bis-(2′-tetrahydropyrimidyl)ethane	140	½	94·5	—	—	—	—
(32) 1-Benzyl-2 : 7-diaza*cyclo*heptene	200	2	99	—	—	—	—
(33) 1-*Phenyl*-2 : 7-*diaza*cyclo*heptene*	200	1	88	105	$C_{11}H_{14}N_2$	16·0	16·1
(34) 1-(4′-*Sulphophenyl*)-2 : 7-*diaza*cyclo*heptene*	160	¼	83	>360	$C_{11}H_{14}O_3N_2S$	10·6	11·0
(35) 1-(4′-*Methylsulphonylphenyl*)-2 : 7-*diaza*cyclo*heptene*	200	1	83	175	$C_{12}H_{16}O_2N_2S$	10·9	11·1
(36) 1 : 4-Bis-(2′ : 7′-diaza*cyclo*heptenyl)butane	200	1	30	—	—	—	—

	Picrate.				Toluene-*p*-sulphonate.			
	M. p.	Formula.	Found, N (%).	Req., N (%).	M. p.	Formula.	Found, N (%).	Req., N (%).
(1)	126°	$C_{13}H_{17}O_7N_5$	19·75	19·7	98°	$C_{14}H_{22}O_3N_2S$	9·45	9·4
(2)	148·5	$C_{16}H_{15}O_7N_5$	17·8	17·9	91	$C_{17}H_{20}O_3N_2S$	8·3	8·4
(3)	138·5	$C_{16}H_{16}O_7N_6$	21·0	20·8	190	$C_{17}H_{21}O_3N_3S$	12·3	12·1
(4)	168·5	$C_{16}H_{16}O_9N_6S$	18·1	17·95	213—213·5	$C_{17}H_{21}O_5N_3S_2$	10·2	10·2
(5)	197	$C_{20}H_{17}O_7N_5$	16·2	15·9	143·5	$C_{21}H_{22}O_3N_2S$	7·5	7·3
(6)	242	$C_{15}H_{13}O_7N_5$	18·8	18·7	165	$C_{16}H_{18}O_3N_2S$	9·0	8·8
(7)	206—206·5	$C_{15}H_{12}O_7N_5Cl$	17·0	17·1	218	$C_{16}H_{17}O_3N_2ClS$	7·9	7·95
(8)	209	$C_{16}H_{15}O_8N_5$	17·3	17·3	201	$C_{17}H_{20}O_4N_2S$	8·15	8·05
(9)	206	$C_{17}H_{17}O_9N_5$	16·2	16·1	—	—	—	—
(10)	185	$C_{15}H_{12}O_9N_6$	20·1	20·0	—	—	—	—
(11)	—	—	—	—	—	—	—	—
(12)	—	—	—	—	253·5	$C_{16}H_{19}O_5N_3S_2$	10·4	10·6
(13)	—	—	—	—	265	$C_{17}H_{20}O_5N_2S_2$	7·1	7·1
(14)	246	$C_{19}H_{15}O_7N_5$	16·5	16·5	—	—	—	—
(15)	205	$C_{19}H_{15}O_7N_5$	16·3	16·5	190	$C_{20}H_{20}O_3N_2S$	7·5	7·6
(16)	235	$C_{14}H_{12}O_7N_6$	22·3	22·3	145—146	$C_{15}H_{17}O_3N_3S$	12·7	13·2
(17)	216·5	$C_{20}H_{15}O_{14}N_9$	20·8	20·8	172	$C_{15}H_{17}O_3N_3S$	12·9	13·2
(18)	—	—	—	—	245	$C_{22}H_{30}O_6N_4S_2$	11·1	11·0
(19)	—	—	—	—	148	$C_{23}H_{32}O_6N_4S_2$	10·8	10·7
(20)	—	—	—	—	176	$C_{24}H_{34}O_6N_4S_2$	10·4	10·4
(21)	—	—	—	—	157	$C_{25}H_{36}O_6N_4S_2$	10·1	10·15
(22)	—	—	—	—	161—161·5	$C_{28}H_{42}O_6N_4S_2$	9·4	9·4
(23)	—	—	—	—	161·5—162	$C_{31}H_{48}O_6N_4S_2$	8·7	8·8
(24)	—	—	—	—	*ca.* 375 (decomp.)	$C_{32}H_{34}O_6N_4S_2$	8·9	8·8
(25)	—	—	—	—	347	$C_{34}H_{36}O_6N_4S_2$	8·5	8·5
(26)	180·5	$C_{16}H_{15}O_7N_5$	18·2	18·0	122·5	$C_{17}H_{20}O_3N_2S$	8·5	8·4
(27)	—	—	—	—	—	—	—	—
(28)	—	—	—	—	187	$C_{18}H_{22}O_5N_2S_2$	6·8	6·8
(29)	258 (decomp.)	$C_{21}H_{19}O_7N_5$	15·5	15·45	183·5	$C_{22}H_{24}O_3N_2S$	7·1	7·1
(30)	186·5	$C_{15}H_{14}O_7N_6$	21·6	21·5	—	—	—	—
(31)	—	—	—	—	285	$C_{24}H_{34}O_6N_4S_2$	10·5	10·45
(32)	131	$C_{18}H_{19}O_7N_5$	16·8	16·8	—	—	—	—
(33)	184	$C_{17}H_{17}O_7N_5$	17·2	17·4	153—153·5	$C_{18}H_{22}O_3N_2S$	8·2	8·1
(34)	—	—	—	—	—	—	—	—
(35)	186	$C_{18}H_{19}O_9N_5S$	14·65	14·55	184	$C_{19}H_{24}O_5N_2S$	6·8	6·6
(36)	—	—	—	—	85	$C_{28}H_{42}O_6N_4S_2$	9·0	9·2

(4) The toluene-*p*-sulphonate crystallised unchanged from 2N-sodium carbonate, and the dihydroglyoxaline was not extracted by chloroform from a solution of the salt in one equivalent of N-sodium hydroxide.

(5) The temperature was 175—180° during the first ½ hour and 200° during the second ½ hour. 1-Naphthylmethyl cyanide and the monohydrochloride of ethylenediamine (1 mol.) afforded a 71% yield of the dihydroglyoxaline after 1¼ hours at 180—185°, and unchanged cyanide (24%) was recovered. 2-(1′-*Naphthylmethyl*)*dihydroglyoxalinium chloride* had m. p. 258—259° (Found: N, 11·3; Cl, 14·3. $C_{14}H_{15}N_2Cl$ requires N, 11·4; Cl, 14·4%). Ciba (B.PP. 460,528; 514,411) record 119—120° and 252—253° as the m. p. of the base and the hydrochloride respectively.

(6) The low temperature was employed in an unsuccessful attempt to isolate the intermediate amidine. This dihydroglyoxaline was also prepared from ethylenediammonium dichloride and the bistoluene-*p*-sulphonate (see Experimental section). 2-*Phenyldihydroglyoxalinium benzenesulphonate* had m. p. 141° (Found: N, 9·3. $C_{15}H_{16}O_3N_2S$ requires N, 9·2%). The m. p. of the base is given as 101° by Hofmann (*loc. cit.*), Forssel (*Ber.*, 1892, **25**, 2135), and Hill and Aspinall (*J. Amer. Chem. Soc.*, 1939, **61**, 822), and as 100—102° by the I.G. (B.P. 492,812). Hill and Aspinall (*loc. cit.*) state that the picrate has m. p. 244°.

(11) This compound was soluble in aqueous sodium hydroxide and formed no salts with acids.

(12) This compound was soluble in aqueous sodium hydroxide.

(13) Other methods of preparation are described in the Experimental section. 2-(4′-*Methylsulphonylphenyl*)*dihydroglyoxalinium chloride* had m. p. 337° (decomp.) (Found: N, 10·8. $C_{10}H_{13}O_2N_2ClS$ requires N, 10·75%).

(14) 2-α-*Naphthyldihydroglyoxalinium chloride* had m. p. 305—306° (Found: N, 12·1. $C_{13}H_{13}N_2Cl$ requires N, 12·05%). The I.G. (B.P. 492,812) give the m. p. of the base as 136°.

(15) The base is stated to have m. p. 124° by the I.G. (*loc. cit.*). 2-β-*Naphthyldihydroglyoxalinium benzenesulphonate* had m. p. 188·5° (Found: N, 7·9. $C_{19}H_{18}O_3N_2S$ requires N, 7·9%).

(17) The dipicrate separated from a solution containing equimolecular proportions of the base and picric acid. Ciba (B.PP., 460,528; 514,411) state that the base has m. p. 104—105°.

(18) The temperature was 150° for the first 10 minutes and 200° during the final 10 minutes. There is a marked alternation in the m. ps. of the toluene-*p*-sulphonates of the αω-bis(dihydroglyoxalinyl)-alkanes, the odd members having lower m. ps. and much higher solubility in water.

(19) The temperature was kept at 170° for ½ hour and then at 200° for ½ hour. The base was readily soluble in water.

(20) The temperature was kept at 170° for ½ hour and then at 200° for ½ hour. Lehr and Erlenmeyer (*Helv. Chim. Acta*, 1944, **27**, 491) record m. p. 209—210° and 207° for the base and the dipicrate respectively.

(21) After ½ hour at 170°, the temperature was kept at 200° for ½ hour. The base was readily soluble in water.

(22) The temperature was kept at 175° for ½ hour and then at 225° for 1 hour. According to B.P. 501,522 the base has m. p. 185—187°.

(25) The temperature was 200° during the first ¼ hour and 245° during the final ½ hour. There was no unchanged cyanide and the crude yield was *ca.* 100%.

(26) Aspinall (*J. Amer. Chem. Soc.*, 1940, **62**, 2160) records m. p. 87° for the base and 181° for the picrate.

(28) Trimethylenediammonium bistoluene-*p*-sulphonate (1 mol.) was used. There was no reaction after an hour at 205°.

(29) The temperature was 165° during 1 hour and 225° during the remaining hour. 2-(1′-*Naphthylmethyl*)-3 : 4 : 5 : 6-*tetrahydropyrimidinium chloride* had m. p. 214° and was dried at 100° before analysis (Found: N, 10·8. $C_{15}H_{17}N_2Cl$ requires N, 10·75%).

(30) Trimethylenediamine was used in this experiment. The free base gave unsatisfactory results on analysis by the Dumas method. The *bistoluene*-p-*sulphonate*, m. p. 65°, afforded a strongly acid solution and was very deliquescent (Found: N, 8·85. $C_{23}H_{27}O_6N_3S_2$ requires N, 8·3%).

(31) The free *base*, obtained from the bistoluene-*p*-sulphonate and sodium hydroxide at 0° and recrystallised from benzene, had m. p. *ca.* 200° (decomp.) (Found: N, 27·9, 28·0. $C_{10}H_{18}N_4$ requires N, 28·9%). This compound was rapidly hydrolysed by cold water or by cold aqueous alkali.

(32) A 16% yield of this compound, b. p. 125—130°/0·7 mm., was obtained by heating the cyanide and tetramethylenediamine (1 mol.) under reflux for 6 hours (bath at 200°) but there was considerable decomposition during distillation.

(35) The picrate first separated from methanol in orange prisms m. p. 155° but changed to yellow needles, m. p. 186°, on crystallisation from ethanol and the low-melting form could not be obtained subsequently.

(36) The bistoluene-*p*-sulphonate crystallised very slowly, the yield quoted being obtained after keeping for a week.

EXPERIMENTAL.*

Preparation of Alkylenediamine Salts.

2-*Aminoethylammonium Toluene*-p-*sulphonate*—Toluene-*p*-sulphonic acid monohydrate (190 g.) in water (100 c.c.) was neutralised to Congo-red with hydrated ethylenediamine (40 c.c.); more diamine (40 c.c.) was then added and the solution evaporated to dryness on the steam-bath at 5 mm. The residue, recrystallised from *iso*propanol (250 c.c.), afforded 206—218 g. (89—94%) of 2-*aminoethylammonium toluene*-p-*sulphonate*, m. p. 123° (Found: N, 11·8. $C_9H_{16}O_3N_2S$ requires N, 12·1%). This salt is not deliquescent and did not lose an appreciable amount of diamine when heated at 200° in an open vessel. An attempt to prepare the monobenzenesulphonate in the same way resulted in the separation of the neutral salt.

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* See also B.P. Applns. 11,156/2·5·1945 and 34,294/18·12·1945.

*Ethylenediammonium Bistoluene-*p*-sulphonate.*—Neutralisation of toluene-*p*-sulphonic acid to Congo-red with ethylenediamine and crystallisation from 50% aqueous alcohol gave the *diammonium bistoluene-*p*-sulphonate,* m. p. 360° (decomp.) (Found: N, 6·9. $C_{16}H_{24}O_6N_2S_2$ requires N, 6·9%).

*Trimethylenediammonium bistoluene-*p*-sulphonate* was prepared in the same way as the lower homologue; it crystallised from *iso*propanol in colourless plates, m. p. 251° (Found: N, 6·9. $C_{17}H_{26}O_6N_2S_2$ requires N, 6·7%). Heat was evolved when this salt was added to an equivalent of the diamine, but attempts to crystallise the product from *iso*propanol and other solvents resulted in the isolation of the crystalline bis-sulphonate only.

*Tetramethylenediamine and Tetramethylenediammonium Bistoluene-*p*-sulphonate.*—The diamine was prepared by the application of the Hofmann reaction to adipodiamide (v. Braun and Lemke, *Ber.*, 1922, **55**, 3529), using a method similar to that employed by Aspinall (*J. Amer. Chem. Soc.*, 1941, **63**, 2843) for the preparation of trimethylenediamine. Adipodiamide (72 g.) was added at 10° to a stirred solution of potassium hypobromite, prepared from bromine (160 g.; 2 mols.), potassium hydroxide (330 g.; 10 mols.), and water (1·5 l.) The temperature rose rapidly to 15° and then to 20° during the next 20 minutes. The clear solution was heated on the steam-bath for 2 hours, then neutralised with concentrated hydrochloric acid (250 c.c.) and evaporated to a small volume. The solution was cooled and filtered, and the salts were washed with 80% aqueous acetone. The filtrate and washings were evaporated almost to dryness, potassium hydroxide (100 g.) and water (25 c.c.) were added, and the mixture was distilled to dryness at 20 mm. The distillate was saturated with potassium hydroxide (60 g.), the layer of oil was separated and diluted with benzene (50 c.c.), and the solution was dried (KOH; 10 g.). The liquid was decanted and distilled from sodium (1 g.), using a short column. A forerunning, b. p. 77—78°, was collected, and tetramethylenediamine then distilled at 158—159° and solidified on cooling to plates, m. p. 27—27·2° (29·8 g.; 67·7%). The forerunning and distillation residue were neutralised to Congo-red with aqueous toluene-*p*-sulphonic acid, the solution was evaporated to dryness, and the residue, crystallised from methanol, gave colourless prisms of *tetramethylenediammonium bistoluene-*p*-sulphonate,* m. p. 224° (Found: N, 6·6. $C_{18}H_{28}O_6N_2S_2$ requires N, 6·5%). The yield was 17·4 g., so that the total yield was equivalent to 75·8% of diamine.

*Hexamethylenediammonium bistoluene-*p*-sulphonate* crystallised from alcohol in slender needles, m. p. 183° (Found: N, 6·2. $C_{20}H_{32}O_6N_2S_2$ requires N, 6·1%). The heat evolution on mixing this salt with the base indicated the production of a mono-acid salt but this could not be isolated.

Dihydroglyoxalines and Ring Homologues from Cyanides.

The cyanide and alkylenediamine or alkylenediamine salt were heated under reflux until ammonia was no longer evolved, the temperature being regulated so that a steady evolution of gas was maintained. Ammonia was often not evolved until the mixture had been maintained at the reaction temperature for a few minutes. Free diamines and their monotoluene-*p*-sulphonates afforded homogeneous mixtures with cyanides but other salts sometimes afforded heterogeneous mixtures and stirring was necessary to promote rapid reaction. Ethylenediamine gave a monotoluene-*p*-sulphonate which could be isolated, but other mono-salts were not obtained crystalline. When mono-salts could not be isolated, the cyanide was heated with an equivalent mixture of the diamine with either the neutral salt of the diamine or an ammonium salt. When an ammonium salt was employed, the cyanide was usually added after heating the mixture until ammonia was no longer evolved; a slight excess of diamine reduced frothing. When a sulphonate was employed, the corresponding salt of the heterocyclic base was usually isolated from the reaction product by crystallisation from water, or, if too soluble, from ethanol or *iso*propanol. Acetic acid was a suitable solvent in cases (*e.g.*, No. 25) where the sulphonate was too sparingly soluble in water. The hydrochlorides of the heterocyclic bases were usually less tractable than the sulphonates, many being deliquescent, and, when the hydrochloride of a diamine was employed, it was usually preferable to liberate the base from the reaction product by means of 2—3N-sodium hydroxide, collect it in chloroform or benzene, and purify it by distillation, sublimation, or crystallisation. The hydrochloride can then be prepared from the purified base and ethanolic hydrogen chloride.

2-*Benzyldihydroglyoxaline.*—(1) A mixture of benzyl cyanide (5·85 g.) and 2-aminoethylammonium toluene-*p*-sulphonate (11·6 g.; 1 mol.) was maintained at 200° for 1 hour, during which ammonia was evolved. The product was dissolved in water (20 c.c.), made alkaline with 5N-sodium hydroxide, and extracted with chloroform. The residue obtained by evaporating the dried chloroform solution was distilled; the fraction, b. p. 125°/2 mm., afforded 2-benzyldihydroglyoxaline, m. p. 66—68° after recrystallisation from light petroleum (7·3 g.; 91%). The product was characterised by preparing the derivatives recorded in the Table (No. 2). (2) Benzyl cyanide (58·5 g.), ethylenediammonium dichloride (33·25 g.; 0·5 mol.), and ethylenediamine (15 g.; 0·5 mol.) were heated at 200° for 1 hour and then treated as described in (1). The crude base (yield 80%) was distilled and converted into the hydrochloride, m. p. 175°, by means of hydrogen chloride in *iso*propanol. Yield, 66%. (3) A mixture of benzyl cyanide (5·85 g.) and ethylenediamine (3·0 g.; 1·0 mol.) was heated under reflux for 36 hours in a bath at 200° and then distilled under diminished pressure. The first fraction (2 g.), b. p. 79—81°/2 mm., consisted of crude benzyl cyanide; 2-benzyldihydroglyoxaline distilled at 125°/2 mm. and solidified to crystals, m. p. 64—66° (4 g.; 50%). The distillation residue was crystallised from acetic acid and afforded *s*-*bisphenylacetoethylenediamide* (15%), m. p. 204° (Found: C, 72·8; H, 6·7; N, 9·6. $C_{18}H_{20}O_2N_2$ requires C, 72·9; H, 6·8; N, 9·5%). The production of this amide was probably due to the presence of water in the ethylenediamine.

2-*Phenyldihydroglyoxaline.*—(1) A mixture of phenyl cyanide (10·3 g.) and ethylenediammonium bistoluene-*p*-sulphonate (20·2 g.; 0·5 mol.) was heated in a sealed tube for 60 hours at 270°. The product was dissolved in hot water and the crystals (6·0 g.; 20%) which separated on cooling were identified as benzamidinium toluene-*p*-sulphonate, m. p. and mixed m. p. 195° (Found: N, 9·8. Calc. for $C_{14}H_{16}O_3N_2S$: N, 9·6%). The filtrate was extracted with benzene to remove a little phenyl cyanide, and the aqueous solution was then made alkaline with sodium hydroxide. The oil which separated was collected in chloroform and afforded on distillation a fraction, b. p. 162°/5 mm., which solidified to crystals of 2-phenyldihydroglyoxaline, m. p. 101° (6·1 g.; 42%). The product was characterised by preparing the derivatives mentioned in the Table (No. 6). (2) Ammonia was evolved when phenyl cyanide (5·15 g.), ethylenediammonium dichloride (3·35 g.; 0·5 mol.), and ethylenediamine (1·5 g.; 0·5 mol.) were heated under reflux for 2·5 hours in a bath at 200°. The product was shaken with water, unchanged phenyl cyanide (3·3 g.; 64%) was collected in benzene, and the amidine, liberated by adding 5N-sodium hydroxide, was purified by distillation, and had m. p. and mixed m. p. 101°. Yield, 2·7 g.; 36%.

2-(4'-*Methylsulphonylphenyl*)*dihydroglyoxaline*.—(1) *p*-Cyanophenyl methyl sulphone (9·05 g.) and 2-aminoethylammonium toluene-*p*-sulphonate (11·6 g.; 1 mol.) were heated at 200° for ½ hour, ammonia being evolved. The product was crystallised from water (100 c.c.) giving 17·7 g. (89%) of 2-(4'-*methylsulphonylphenyl*)*dihydroglyoxalinium toluene*-p-*sulphonate*, m. p. 265°, which afforded 2-(4'-*methylsulphonylphenyl*)*dihydroglyoxaline*, m. p. 213·5°, with aqueous alkali (see No. 13 in Table). When the reaction mixture was heated at 125° for an hour the product consisted of unchanged cyanide (26%) and the dihydroglyoxalinium toluene-*p*-sulphonate (74%), which were separated by extracting the cyanide with acetone. (2) The product obtained by heating the cyanide (9·05 g.) and ethylenediammonium bistoluene-*p*-sulphonate (20·2 g.; 1 mol.) at 270° for 1½ hours was recrystallised from water and afforded 17·1 g. (86%) of 2-(4'-methylsulphonylphenyl)dihydroglyoxalinium toluene-*p*-sulphonate, m. p. 265°. (3) A mixture of *p*-cyanophenyl methyl sulphone (9·05 g.), ethylenediammonium dichloride (3·35 g.; 0·5 mol.), and ethylenediamine (1·5 g.; 0·5 mol.) was heated at 200° for ½ hour and the product crystallised from aqueous 80% *iso*propanol or from methanol giving 12·0 g. (92%) of 2-(4'-*methylsulphonylphenyl*)*dihydroglyoxalinium chloride*, m. p. 337° (decomp.) (see Note 13). (4) The cyanide (4·5 g.) and ethylenediamine (1·75 g.; 1·2 mols.) were heated at 205—210° for 1¾ hour under reflux and the product crystallised from *iso*propanol. The yield of 2-(4'-methylsulphonylphenyl)dihydroglyoxaline, m. p. 213·5°, was 5 g. (90%).

Dihydroglyoxalines from Mixed Imides.

2-*Phenyldihydroglyoxaline from* N-*Benzoylbenzenesulphonmethylamide*.—A mixture of *N*-benzoylbenzenesulphonmethylamide (13·75 g.) and ethylenediammonium dichloride (3·35 g.; 0·5 mol.) was heated to *ca.* 225°, then cooled to 210° during the vigorous evolution of hydrogen chloride, and finally maintained at 225° for 15 minutes. The product was made strongly alkaline with aqueous sodium hydroxide and the basic oil (7·1 g.) was collected in chloroform. Sulphamic acid was added to a solution of this oil in methanol until the solution was just acid to Congo-red; the colourless rhombic plates (5·0 g.) which separated on keeping proved to be 2-*phenyldihydroglyoxalinium sulphamate*, m. p. 220° (decomp.) (Found: N, 17·1. $C_9H_{13}O_3N_3S$ requires N, 17·3%). 2-Phenyldihydroglyoxaline, m. p. and mixed m. p. 101°, was liberated from this salt and was converted into the picrate, benzenesulphonate, and toluene-*p*-sulphonate (see Table No. 6). When the filtrate from the first crop of sulphamate was diluted with a little ether it afforded 1·1 g. of sulphamate, m. p. 210—212° raised to 220° (decomp.) on recrystallisation from methanol. The yield of pure sulphamate was 5·6 g. (46%). The crystals (5·15 g.; 42%), m. p. 157—158°, which separated when the mother-liquor from the sulphamate was diluted with ether and kept for 12 hours were recrystallised from *iso*propanol and gave NN'-*dimethylbenzamidinium sulphamate*, m. p. 159° (Found: N, 17·1. $C_9H_{15}O_3N_3S$ requires N, 17·1%). This salt was converted successively into *NN'*-dimethylbenzamidine, m. p. and mixed m. p. 80—81°, and its picrate, m. p. and mixed m. p. 172·5°.

NN'-*Dibenzoyl*-1 : 2-*bistoluene*-p-*sulphonamidoethane*.—1 : 2-Bistoluene-*p*-sulphonamidoethane, m. p. 163°, was prepared from ethylenediamine, toluene-*p*-sulphonyl chloride (2 mols.), and aqueous sodium hydroxide (2 mols.) as described by Howard and Marckwald (*loc. cit.*), who record m. p. 159·5—160·5°. When a solution of potassium hydroxide (9 g.; 1 mol.) in methanol (50 c.c.) was added to a clear solution of potassium hydroxide (9 g.) and the bis-sulphonamide (53 g.) in methanol (150 c.c.), the dipotassium salt began to separate. After addition of *iso*propanol (100 c.c.), the salt (65 g.) was collected, dried, and suspended in benzene (250 c.c.). When benzoyl chloride (40·5 g.; 2 mols.) was added there was a vigorous reaction and, after 15 minutes' boiling, the solid was collected, washed with methanol and then with water to remove potassium chloride. The crude product (58 g.; 70%), m. p. 192—194°, was recrystallised from 2-ethoxyethanol giving colourless needles of NN'-*dibenzoyl*-1 : 2-*bistoluene*-p-*sulphonamidoethane*, m. p. 195° (Found: N, 4·9. $C_{30}H_{28}O_6N_2S$ requires N, 4·9%). A mixture of this compound (14·4 g.) with ammonium toluene-*p*-sulphonate (9·45 g.; 2 mols.) was heated at 200—205° for 1 hour, a liquid refluxing during the final stages. The mixture was shaken with water (100 c.c.) and benzene, which collected phenyl cyanide, b. p. 76—77°/14 mm. (1·5 g.; 58·5%). The aqueous solution was mixed with 5N-sodium hydroxide (50 c.c.) and extracted with chloroform giving 3·4 g. (93%) of 2-phenyldihydroglyoxaline, which had m. p. 101° after crystallisation from benzene–light petroleum. The product did not depress the m. p. of an authentic specimen of 2-phenyldihydroglyoxaline and its identity was confirmed by preparing the picrate, m. p. and mixed m. p. 242°.

Demethylation of 2-p-*Anisyldihydroglyoxaline*.—A mixture of 2-*p*-anisyldihydroglyoxaline (5·9 g.) and 45% aqueous hydrobromic acid (60 g.; 10 mols.) was boiled for 7 hours, distilled to remove most of the acid, and an aqueous solution of the residue was made alkaline with sodium carbonate. The solid was collected, washed, dried (5·1 g.; 94·5%), and recrystallised from methanol or water, giving colourless needles which slowly became yellow on exposure to air. 2-p-*Hydroxyphenyldihydroglyoxaline* begins to char at 290° and has m. p. *ca.* 300° (Found: N, 17·1. $C_9H_{10}ON_2$ requires N, 17·3%). The *picrate* crystallised from methanol in large rhombs, m. p. 223° (Found: N, 18·0. $C_{15}H_{13}O_8N_5$ requires N, 17·9%), and the *hydrochloride* separated from *iso*propanol in prisms, m. p. 246—247° (Found: N, 13·8, 14·0. $C_9H_{11}ON_2Cl$ requires N, 14·1%).

Amidines from 2-*Diethylaminoethylamine.*

N-2-*Diethylaminoethylbenzamidine*.*—Ammonium toluene-*p*-sulphonate (8·75 g.; 1 mol.) and 2-diethylaminoethylamine (5·8 g.) (Bloom, Breslow, and Hauser, *J. Amer. Chem. Soc.*, 1945, **67**, 539)

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* Experiments by Mr. J. Miller.

were kept at 100° until ammonia ceased to be evolved; phenyl cyanide (5·2 g.; 1 mol.) was then added and the mixture heated at 200° for an hour. The product was shaken with water and unchanged phenyl cyanide removed in chloroform. The aqueous solution was made strongly alkaline, and the oil which separated was collected in chloroform. Distillation of the extract afforded a fraction (4·4 g.; 40%) of crude N-2-*diethylaminoethylbenzamidine*, b. p. 152—156°/0·5 mm. (Found: equiv., by titration, 115. $C_{13}H_{21}N_3$ requires equiv., 109·5). The *dipicrate* had m. p. 134—135° (Found: N, 18·8. $C_{25}H_{27}O_{14}N_9$ requires N, 18·6%), and the *dihydrochloride trihydrate* consisted of deliquescent crystals with no definite m. p. (Found: N, 12·0, 12·1; Cl, 20·8. $C_{13}H_{23}N_3Cl_2,3H_2O$ requires N, 12·1; Cl, 20·5%).

N-2-*Diethylaminoethyl*-p-*amidinophenyl Methyl Sulphone*.*—Equimolecular proportions of ammonium toluene-*p*-sulphonate, 2-diethylaminoethylamine, and *p*-cyanophenyl methyl sulphone, brought into reaction as described in the preceding section, afforded 55% of recovered cyanide and 20% of crude *N*-2-diethylaminoethyl-*p*-amidinophenyl methyl sulphone as a light brown oil. The *dipicrate* had m. p. 202° (Found: N, 16·5, 16·4. $C_{26}H_{29}O_{16}N_9S$ requires N, 16·7%), and the *dihydrochloride dihydrate* decomposed at 100° (Found: N, 10·4. $C_{14}H_{25}O_2N_3Cl_2S,2H_2O$ requires N, 10·35%).

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