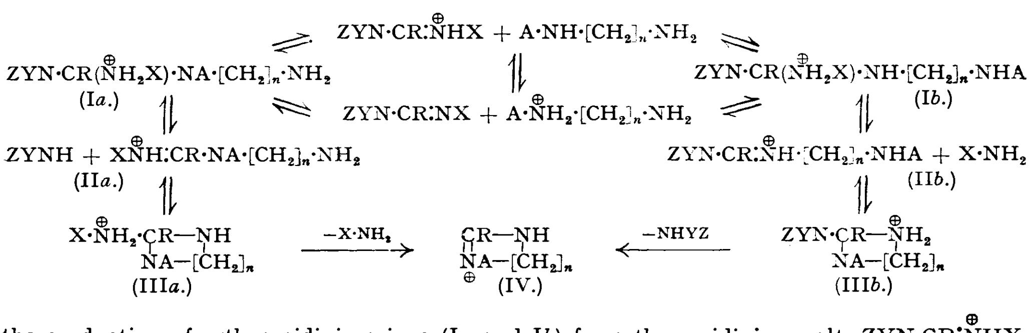
174. *Amidines. Part XIII. Preparation of 2-Substituted 4 : 5-Dihydroglyoxalines and Ring Homologues from Substituted Amidines and Alkylenediamines.*

By P. Oxley and W. F. Short.

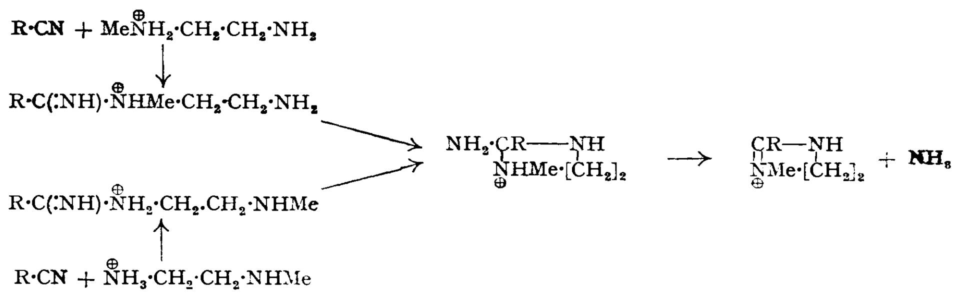
2-Substituted 4 : 5-dihydroglyoxalines and ring homologues are produced in good yield by heating substituted amidinium salts with an alkylenediamine. Ketoxime sulphonates and ethylenediamine also give 2-substituted 4 : 5-dihydroglyoxalines. Reaction mechanisms are proposed.

As a sequel to the investigation of the action of ammonia and monoamines on *N*-substituted amidinium salts and on ketoxime sulphonates (Parts IX and XI, *J.*, 1948, 1514; 1949, 449) we have examined the behaviour of these compounds with alkylenediamines. Miescher, Urech, Klarer, and Ciba (U.S.P., 2,252,721), Klarer and Urech (*Helv. Chim. Acta*, 1944, **27**, 1772), and Djerassi and Scholz (*J. Amer. Chem. Soc.*, 1947, **69**, 1688) have prepared a few 2-arylaminomethyl-, 2-hydroxymethyl-, and 2-aryloxymethyl-4 : 5-dihydroglyoxalines from ethylenediamine and the appropriate unsubstituted amidinium chloride in boiling alcohol, but the reaction of alkylenediamines with *N*-substituted amidines has not been investigated. We find that 2-substituted 4 : 5-dihydroglyoxalines and ring homologues are obtained in good yield by heating *N*-substituted amidinium salts with an alkylenediamine at temperatures within the range 50—180°. It is convenient to use the amidinium sulphonates, but chlorides, benzoates, and picrates have also been used. Aniline, nitrobenzene, and other solvents used in the ammonolysis of *N*-arylamidinium salts (Part XI, *loc. cit.*) could be employed in the reaction but were usually unnecessary. The amidine may have one, two, or three alkyl or aryl substituents on the nitrogen atoms, and the *N*-monoaryl derivatives are especially suitable owing to their ready availability (Part I, *J.*, 1946, 147; Part XI, *J.*, 1949, 449). The scope of the method is illustrated by the twenty-three examples in Table I, and it will be noted that *N*-alkylethylenediamines give 2-substituted 1-alkyl-4 : 5-dihydroglyoxalines. Since there is no reaction between an alkylenediamine and an *N*-substituted amidine at temperatures which yield a cyclic base when the amidinium salt is employed, it is probable that the reaction involves



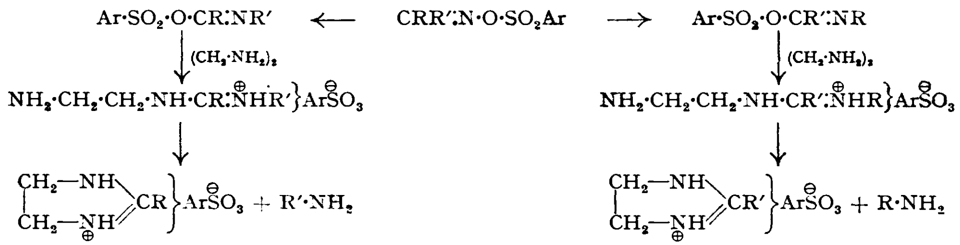
the production of orthoamidinium ions (I*a* and I*b*) from the amidinium salt, ZYN·CR:$\overset{\oplus}{N}$HX, and the alkylenediamine, A·NH·$[CH_2]_n$·NH_2, or from the reciprocal pair. The orthoamidinium ions subsequently lose two molecules of amine (or one of ammonia and one of amine), as shown in the annexed scheme, representative of other routes in which the amines are eliminated in the reverse order and of structures with a different distribution of the positive charge. The intervention of cyclic compounds of the type (III*a* and *b*) is postulated since the dihydroglyoxaline resulting from the direct elimination of an amine from (II*b*) would not necessarily contain the group A, whereas, in fact, 1-methyldihydroglyoxalines (IV; A = Me, *n* = 2), unaccompanied by the corresponding dihydroglyoxalines (IV; A = H, *n* = 2), are obtained from a substituted amidinium salt and *N*-methylethylenediamine.

The 2-arylmethyl-1-alkyl-4 : 5-dihydroglyoxalines enumerated in Table II were prepared by the interaction of the appropriate cyanide with a salt of *N*-methyl- or *N*-ethyl-ethylenediamine (Part VI, *J.*, 1947, 497), and the exclusive formation of dihydroglyoxalines containing a 1-alkyl group suggests the production of a cyclic intermediate which subsequently loses the elements of ammonia:



These *N*-alkyldihydroglyoxalines were examined by Gowdey (*Brit. J. Pharmacol.*, 1948, **3**, 254; 1949, **4**, 45) who found that, regardless of the action of the compounds not containing a *N*-substituent, they all cause a rapid rise of the blood-pressure and an increased heart-rate; moreover, the compounds unsubstituted on nitrogen affect the perivascular system directly whereas the *N*-alkyl derivatives affect the blood-pressure by a more central action, involving stimulation of the sympathetic ganglia, liberation of adrenaline, and direct action on the cardiac muscle.

Rearrangement of ketoxime sulphonates in presence of ethylenediamine gives 2-substituted dihydroglyoxalines, the ester of methyl ethyl ketoxime giving rise to both 2-methyl- and 2-ethyl-4 : 5-dihydroglyoxaline (compare Part IX, *J.*, 1948, 1514).



A number of the 1-methyldihydroglyoxalines were converted into quaternary salts for pharmacological examination, but an attempt to methylate and quaternise 1-benzyldihydroglyoxaline in one stage resulted in fission of the nucleus with formation of *N*-2-dimethylaminoethylphenylacetamide (*picrate*, m. p. 165·5—166°).

EXPERIMENTAL.*

Preparation of Alkylenediamine Salts.—The following salts were prepared by the method described in Part VI (*J.*, 1947, 502).

N-*Methylethylenediammonium ditoluene*-p-*sulphonate*, which separated from ethanol in colourless needles, m. p. 176° (Found: N, 6·6. $C_{17}H_{26}O_6N_2S_2$ requires N, 6·7%), was obtained from *N*-methylethylenediamine, prepared in 42% yield from ethylenediamine by modification of Aspinall's method (*J. Amer. Chem. Soc.*, 1939, **61**, 822). Direct methylation of ethylenediamine was not a practical method for the preparation of the *N*-monomethyl derivative (cf. Linsker and Evans, *J. Amer. Chem. Soc.*, 1945, **67**, 1581). Attempts to prepare a crystalline monotoluene-*p*-sulphonate of the *N*-methyl base were unsuccessful.

* See also B.P. 614,032/1946.

N-*Ethylethylenediammonium ditoluene*-p-*sulphonate*, m. p. 158—159° (Found: N, 6·55. $C_{18}H_{28}O_6N_2S_2$ requires N, 6·5%) was prepared from *N*-ethylethylenediamine, obtained in 35% yield by Aspinall's method (*loc. cit.*).

Dihydroglyoxalines and Ring Homologues from N-*Substituted Amidinium Salts and Alkylenediamines.*—All the amidinium salts used in the experiments have been described in previous parts of the series. An equimolecular mixture of the *N*-substituted amidine, alkylenediamine, and acid (the last being introduced as free acid or as the amidinium, alkylenediammonium, or ammonium salt) was heated under the conditions recorded in Table I. Often no solvent was necessary, but reactions involving compounds of relatively high m. p. were facilitated by the addition of a small excess of alkylenediamine, or of a solvent such as aniline, dimethylaniline, or nitrobenzene. The salt of the heterocyclic base usually crystallised directly from the reaction mixture, but dilution with acetone or ether was occasionally necessary. One recrystallisation from methanol, *iso*propanol, or acetone was sufficient to give a product of constant m. p. The experiments recorded in Table I were conducted with 0·005—0·01 g.-mol. of the amidinium salt, and the yields are calculated on the amidine.

Preparation of 2-*Substituted* 1-*Alkyl*-4 : 5-*dihydroglyoxalines.*—Since dihydroglyoxalines and their 1-alkyl derivatives are of comparable basic strength, direct alkylation gives a mixture of dihydroglyoxaline, 1-alkyldihydroglyoxaline, and quaternary salt. The separation of this mixture is often laborious and yields are poor. Thus when 2-benzyl-4 : 5-dihydroglyoxaline (36 g.), methyl toluene-*p*-sulphonate (42 g., 1 mol.), and benzene (100 c.c.) were boiled for an hour, a heavy oil was obtained from which a mixture of 2-benzyl-4 : 5-dihydroglyoxaline and its 1-methyl derivative were liberated by 5N-sodium hydroxide. This mixture could not be satisfactorily separated into its constituents by distillation, but fractional crystallisation of the mixed picrates from methanol afforded hexagonal plates of 2-benzyl-1-methyl-4 : 5-dihydroglyoxalinium picrate, m. p. 125—125·5° (15·5 g., 17%), identical with that obtained by the alternative method (see Table II).

The 1-alkyldihydroglyoxalines described in Table II were prepared from the appropriate cyanide, *N*-alkylethylenediamine (1 mol.), and ammonium toluene-*p*-sulphonate (1 mol.), according to the method described in Part VI (*loc. cit.*). No unsubstituted dihydroglyoxalines were formed in this reaction, and the 1-alkyldihydroglyoxalines were very easily purified and obtained in good yield.

1 : 8-*Di*-(1-*methyl*-4 : 5-*dihydro*-2-*glyoxalinyl*)*octane*. A mixture of octamethylene dicyanide (8·2 g.), *N*-methylethylenediammonium ditoluene-*p*-sulphonate (20·9 g., 0·5 mol.), and *N*-methylethylenediamine (3·7 g., 0·5 mol.) was heated at 190° for 2 hours. Crystallisation of the crude product from *iso*propanol afforded 1 : 8-di-(1-methyl-4 : 5-dihydro-2-glyoxalinyl)octane ditoluene-*p*-sulphonate (16·6 g., 53%). The properties of this salt and of the dipicrate are recorded in Table II.

1 : 2-*Di*-(2-*benzyl*-4 : 5-*dihydro*-1-*glyoxalinyl*)*ethane*. Benzyl cyanide (11·7 g.), 3 : 6-diazaoctane-1 : 8-diamine ("triethylenetetramine") (7·3 g., 0·5 mol.), and ammonium toluene-*p*-sulphonate (18·9 g.; 1 mol.) were heated at 190° for 90 minutes. The resulting yellow gum was dissolved in water, made alkaline with 5N-sodium hydroxide, and extracted with chloroform. The light-brown residue (15 g.) obtained by evaporating the solvent was crystallised from benzene (15 c.c.) giving 1 : 2-*di*-(2-*benzyl*-4 : 5-*dihydro*-1-*glyoxalinyl*)*ethane*, m. p. 131—132° (Found: N, 16·0. $C_{22}H_{26}N_4$ requires N, 16·2%) (7·5 g., 43%). The *dipicrate* had m. p. 235° (decomp.) (Found: N, 17·5. $C_{34}H_{32}O_{14}N_{10}$ requires N, 17·4%), and the *dihydrochloride*, obtained from the base and hydrogen chloride in *iso*propanol, separated as a crystalline powder, m. p. 275° (decomp.) (Found: N, 13·3. $C_{22}H_{28}N_4Cl_2$ requires N, 13·4%).

Dihydroglyoxalines from Ketoxime Sulphonates.—The ketoxime sulphonates were prepared as described in Part IX (*loc. cit.*).

2-*Phenyl*-4 : 5-*dihydroglyoxaline*. Ethylenediammonium dibenzenesulphonate, m. p. >360° (5·8 g., 32%), was deposited when benzophenone oxime benzenesulphonate (16·4 g.), anhydrous ethylenediamine (3 g., 1 mol.), and benzene (100 c.c.) were boiled for 1 hour and then cooled. The filtrate was washed with aqueous sodium hydroxide to remove benzenesulphonic acid, concentrated, and distilled on the steam-bath at 1 mm. to remove aniline (3 g., 64%). The residue consisted of *NN'*-diphenylbenzamidine, resulting from the action of aniline on the imidosulphonate produced by rearrangement of part of the oxime ester (Part IX, *loc. cit.*), and 2-phenyl-4 : 5-dihydroglyoxaline. Neutralisation of the mixture with aqueous benzenesulphonic acid afforded the sparingly soluble *NN'*-diphenylbenzamidinium benzenesulphonate, m. p. and mixed m. p. 218° (4 g., 19%), and 2-phenyl-4 : 5-dihydroglyoxaline, m. p. and mixed m. p. 101° (5·5 g., 77·5%), was isolated from the aqueous solution.

2-*Methyl*-4 : 5-*dihydroglyoxaline*. (i) Acetoxime benzenesulphonate (21·3 g.) ethylenediamine (6·0 g., 1 mol.), and toluene (50 c.c.) were boiled under reflux for ½ hour and the cold solution was extracted with water (25 c.c.). The aqueous layer was made alkaline with 5N-sodium hydroxide (50 c.c.), and the crude methyldihydroglyoxaline (7·9 g.) was collected in chloroform and converted into the picrate, m. p. 202° (24·0 g., 74·5%) with methanolic picric acid. Recrystallisation from water gave flat needles of 2-methyl-4 : 5-dihydroglyoxalinium picrate, m. p. and mixed m. p. 204° (Aspinall, *loc. cit.*; Chitwood and Reid, *J. Amer. Chem. Soc.*, 1935, **57**, 2424).

(ii) 2-Methyl-4 : 5-dihydroglyoxalinium benzenesulphonate was the major product when methyl ethyl ketoxime benzenesulphonate (22·7 g.), ethylenediamine (6 g., 1 mol.), and benzene (50 c.c.) were boiled for 1 hour, but a little 2-ethyl-4 : 5-dihydroglyoxalinium benzenesulphonate was also formed. The bases, b. p. 100—103°/18 mm. (5·9 g.), were obtained by shaking the product with 5N-sodium hydroxide, extracting the aqueous solution with chloroform, and uniting the chloroform and benzene solutions. A solution of the mixed bases and picric acid (15·5 g.) in methanol (80 c.c.) deposited a crude picrate, m. p. 190°, after 1 hour at 0°, and recrystallisation from methanol afforded 2-methyl-4 : 5-dihydroglyoxalinium picrate, m. p. and mixed m. p. 204° (15·2 g., 48·5%). The original filtrate was evaporated to dryness and the residue was recrystallised from *iso*propanol, giving 2-ethyl-4 : 5-dihydroglyoxalinium picrate, m. p. and mixed m. p. 135—136° (2·5 g., 7·5%).

Preparation of Quaternary Salts of Dihydroglyoxalines.—2-*Benzyl*-1 : 3-*dimethyl*-4 : 5-*dihydroglyoxalinium salts*. An aqueous solution of the oily product which separated when 2-benzyl-1-methyl-4 : 5-dihydroglyoxaline (16·2 g.), methyl toluene-*p*-sulphonate (17·5 g., 1 mol), and dry benzene (100 c.c.) were boiled for 15 minutes, was treated with 2N-lithium picrate, and the solid (26 g.; m. p. 115—118°)

TABLE I.

Preparation of 2-substituted 4 : 5-dihydroglyoxalines and ring homologues from substituted amidines.

Heterocyclic compound.	Salt.[a]	M. p.	Yield, %.	Amidine.	Salt of amidine.[a]	Alkylene-diamine (mols.).	Reaction: temp.	Reaction: time (mins.).
4 : 5-Dihydroglyoxalines.								
(1) 2-Methyl-	Picrate	204°	80	*N-cyclo*Hexyl-*N'*-ethylacet-	T	1·0	100°	30
(2) ,,	Picrate	204	88	*NN'*-Diphenylacet-	HCl	1·2	100	120
(3) 2-Ethyl-	Picrate	135—136	79	*NNN'*-Triethylpropion-	T	1·0	100	60
(4) 2-*n*-Butyl-	T	98	87	*N-p*-Tolylvaler-	T	1·33	100	30
(5) 2-Benzyl-	HCl	174	78	*N-cyclo*Hexylphenylacet-	HCl	1·7	*ca.* 180	5
(6) 2-*cyclo*Hexyl-	T *	171	97·5	*N*-Phenyl*cyclo*hexanecarboxy-	T	1·0	80	30
(7) 2-Phenyl-	T	165	73	*NNN'*-Trimethylbenz-	T	1·0	100	30
(8) ,,	Benzoate	115·5	77	*N*-Phenyl-*N'*-benzylbenz-	Benzoate	1·0	100	30
(9) ,,	B	141	92	*NN*-Pentamethylene-*N'*-phenylbenz-	B	1·7	100	60
(10) ,,	B	141	87	*N*-Phenylbenz-	B	1·7	100	120
(11) ,,	T	164	91	*N*-Phenylbenz-	T	1·0	100	120
(12) 2-*p*-Methoxyphenyl-	T	201	86	*N-p*-Tolyl-*p*-methoxybenz-	T	1·7	100	120
(13) ,,	T	201	81	*N-p*-Tolyl-*p*-methoxybenz-	T	1·7	140	60
(14) 2-*o*-Chlorophenyl-	T *	163	88	*N*-Phenyl-*o*-chlorobenz-	T	1·0	140	30
(15) 2-3' : 4'-Dimethoxyphenyl-	B *	192—192·5	88	*N*-Phenyl-3 : 4-dimethoxybenz-	B	1·5	100	60
(16) 2-2'-Naphthyl-	B *	188·5	82	*N-o*-Tolyl-2-naphth-	B	1·7	100	120
1-Methyl-4 : 5-dihydroglyoxalines.								
(17) 2-Benzyl-	HCl	88	74	*N-p*-Tolylphenylacet-	HCl	1·0	100	60
(18) 2-1'-Naphthyl-	Picrate	181·5	88	*N*-Phenyl-1-naphthylacet-	Picrate	1·35	130	5
3 : 4 : 5 : 6-Tetrahydropyrimidines.								
(19) 2-Phenyl-	T	122	91	*N*-Phenyl-*N*-methylbenz-	T	1·0	55	60
(20) 2-(*p*-Methylsulphonylphenyl)-	T	187	96	*N*-Ethyl-*p*-methylsulphonylbenz-	T	1·0	100	60
*2 : 7-Diaza*cyclo*heptenes.*								
(21) 1-Benzyl-	Picrate	131	89	*N-p*-Tolylphenylacet-	T	1·0	100	60
(22) 1-(*p*-Methylsulphonylphenyl)-	Picrate	186	71	*N*-2-Pyridyl-*p*-methylsulphonylbenz-	Picrate	1·25	140	5
(23) 1-3'-Pyridyl-	Dipicrate *	177	86	*N*-Phenylnicotin-	B	1·25	100	30

* New compound. [a] B = Benzenesulphonate. T = Toluene-*p*-sulphonate.

Notes to Table I.

Except where otherwise indicated, the dihydroglyoxalines and ring homologues have been described in Part VI (*J.*, 1947, 497) and the known compounds were identified by comparison with authentic specimens.

(1), (2) Chitwood and Reid (*J. Amer. Chem. Soc.*, 1935, **57**, 2424) state that 2-methyl-4 : 5-dihydroglyoxalinium picrate has m. p. 205°. Aspinall (*ibid.*, 1939, **61**, 822) records m. p. 204°. See also Note (26) of Part IX (*J.*, 1948, 1521). (3) Chitwood and Reid (*loc. cit.*) and Aspinall (*loc. cit.*) state that the picrate has m. p. 137°. (5) The reaction mixture consisted of *N-cyclo*hexylphenylacetamidinium chloride (2·5 g.), ethylenediamine (1 c.c.), and nitrobenzene (5 c.c.). (6) *N*-Phenyl*cyclo*hexanecarboxyamidine (1·01 g.), 2-aminoethylammonium toluene-*p*-sulphonate (1·16 g.), and aniline (1 c.c.) gave 2-cyclo*hexyl*-4 : *5-dihydroglyoxalinium toluene*-p-*sulphonate*, m. p. 171° (Found: N, 8·7. $C_{16}H_{24}O_3N_2S$ requires N, 8·6%). (8) *2-Phenyl*-4 : *5-dihydroglyoxalinium benzoate* consisted of rectangular plates, m. p. 115·5° (Found: N, 10·5. $C_{16}H_{16}O_2N_2$ requires N, 10·54%). (14) 2-o-*Chlorophenyl*-4 : *5-dihydroglyoxalinium toluene*-p-*sulphonate* crystallised in colourless plates, m. p. 163° (Found: N, 8·0. $C_{16}H_{17}O_3N_2ClS$ requires N, 7·9%). (15) 2-(3 : 4-*Dimethoxyphenyl*)-4 : *5-dihydro-*

Notes to Table I (contd.).

glyoxalinium benzenesulphonate had m. p 192—192·5° (Found : N, 7·9. $C_{17}H_{20}O_5N_2S$ requires N, 7·7%). (16) 2-2'-*Naphthyl*-4 : 5-*dihydroglyoxalinium benzenesulphonate* separated from *iso*propanol in slender needles, m. p. 188·5° (Found : N 7·9. $C_{19}H_{18}O_3N_2S$ requires N, 7·9%). (19) The reaction mixture consisted of *N*-phenyl-*N*-methylbenzamidine (1·05 g.), trimethylenediamine (0·37 g.), ammonium toluene-*p*-sulphonate (0·95 g.), and dimethylaniline (0·55 c.c.). (20) The reaction mixture consisted of *N*-ethyl-*p*-methylsulphonylbenzamidinium toluene-*p*-sulphonate (1·99 g.), trimethylenediamine (0·37 g.), and nitrobenzene (5 c.c.). (23) An aqueous solution of the reaction product from *N*-phenylnicotinamidine (0·4 g.), tetramethylenediamine (0·2 g.), and ammonium benzenesulphonate (0·35 g.) was made alkaline with 5N-sodium hydroxide, and the crude solid was purified by sublimation, giving 1-3'-*pyridyl*-2 : 7-*diaza*cyclo*heptene*, m. p. 102° (Found : N, 23·8. $C_{10}H_{13}N_3$ requires N, 24·0%). The *dipicrate* separated from methanol in long needles, m. p. 177° (Found : N, 20·0. $C_{22}H_{19}O_{14}N_9$ requires N, 19·9%).

TABLE II.

Preparation of 2-substituted 1-alkyl-4 : 5-dihydroglyoxalines from cyanides and N-alkylethylenediamines.

	Reaction, temp.	Reaction, time (hrs.).	Yield, %.	Base. B. p. /mm.	Formula.	Found, N, %.	Reqd., N, %.
(1) 2-*Benzyl*-1-*methyl*-4 : 5-*dihydroglyoxaline* [a]	190°	1½	92	107°/1	$C_{11}H_{14}N_2$	15·6	16·1
(2) 2-p-*Methoxybenzyl*-1-*methyl*-4 : 5-*dihydroglyoxaline*	190	1	69	—	—	—	—
(3) 2-1'-*Naphthylmethyl*-1-*methyl*-4 : 5-*dihydroglyoxaline* [b]	190	1	87	—	—	—	—
(4) 1 : 8-*Di*-(1-*methyl*-4 : 5-*dihydro*-2-*glyoxalinyl*)*octane*	190	2	53	—	—	—	—
(5) 2-*Benzyl*-1-*ethyl*-4 : 5-*dihydroglyoxaline*	190	3	83	109—112/1·5	$C_{12}H_{16}N_2$	14·9	14·9

[a] *Hydrochloride*, m. p. 88° (Found : N, 13·2. $C_{11}H_{15}N_2Cl$ requires N, 13·3%). [b] *Hydrochloride*, m. p. 241° (Found : N, 10·9. $C_{15}H_{17}N_2Cl$ requires N, 10·75%).

	Toluene-p-*sulphonate*. M. p.	Formula.	Found, N, %.	Reqd., N, %.	*Picrate*. M. p.	Formula.	Found, N, %.	Reqd., N, %.
(1)	—	—	—	—	125—125·5°	$C_{17}H_{17}O_7N_5$	17·4	17·4
(2)	114°	$C_{19}H_{14}O_4N_2S$	7·55	7·45	172·5	$C_{18}H_{19}O_7N_3$	16·4	16·2
(3)	—	—	—	—	181—181·5	$C_{21}H_{19}O_7N_3$	15·5	15·45
(4)	149·5—150·5	$C_{30}H_{46}O_6N_4S_2$	9·1	9·0	167	$C_{28}H_{36}O_{14}N_{10}$	19·2	19·0
(5)	—	—	—	—	141	$C_{18}H_{19}O_7N_5$	17·1	16·8

Notes to Table II.

The compounds described in the Table are new with the exception of 2-benzyl-1-methyl-4 : 5-dihydroglyoxaline which is mentioned, without physical constants, by Hartmann and Isler (*Arch. exp. Path.*, 1939, **192**, 141).

(1) The base gave erratic results on analysis by the Dumas method. (4) The preparation of this compound is described in detail below. (5) The base gave erratic results on analysis by the Dumas method. The hydrochloride was a gum but 2-*benzyl*-1-*ethyl*-4 : 5-*dihydroglyoxalinium sulphate* was obtained in deliquescent crystals, m. p. 151—152° (Found : N, 12·0. $C_{24}H_{34}O_4N_4S$ requires N, 11·8%).

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was crystallised from alcohol (50 c.c.) giving 25 g. of 2-*benzyl*-1 : 3-*dimethyl*-4 : 5-*dihydroglyoxalinium picrate*, m. p. 120°. This salt gave erratic results on Dumas analysis (Found : N, 17·4, 16·4, 17·4. $C_{18}H_{19}O_7N_5$ requires N, 16·8%). The picrate was treated with 5N-hydrochloric acid and, after removal of picric acid by extraction with benzene, the aqueous solution was evaporated to dryness and the residue crystallised from *iso*propanol giving large deliquescent octahedral crystals of the *chloride*, m. p. 210° (Found : N, 12·7. $C_{12}H_{17}N_2Cl$ requires N, 12·5%).

When 2-benzyl-4 : 5-dihydroglyoxaline (8 g.) was added to a stirred solution of methyl toluene-*p*-sulphonate (20 g., 2·15 mols.) in benzene (25 c.c.), the temperature rose to 33° in 15 minutes and then fell again, the solution remaining homogeneous. On addition of 5N-sodium hydroxide (20 c.c., 2 mols.) the temperature again rose to 30°. After being stirred for an hour, the product was neutralised (brilliant-yellow) with toluene-*p*-sulphonic acid, and the aqueous layer was separated and evaporated to dryness. The residue consisted of sodium toluene-*p*-sulphonate and an acetone-soluble gum (13 g.) which on treatment with 2N-lithium picrate afforded a solid *picrate*, m. p. 165·5—166°, probably the picrate of *N*-2-dimethylaminoethylphenylacetamide (Found : C, 50·0; H, 4·9; N, 16·0. $C_{18}H_{21}O_8N_5$ requires C, 49·7; H, 4·8; N, 16·1%).

The dimethotoluene-p-*sulphonate of* 1 : 2-*di*-(2-*benzyl*-4 : 5-*dihydro*-1-*glyoxalinyl*)*ethane*. This separated as an oil when the dihydroglyoxaline (3·46 g.) and methyl toluene-*p*-sulphonate (3·72 g., 2 mols.) were boiled in benzene solution (20 c.c.). The quaternary *salt*, m. p. 167—169° (6·53 g., 91%), crystallised on trituration with acetone, and the m. p. remained unchanged after crystallisation from *iso*propanol (Found : N, 7·8. $C_{38}H_{46}O_6N_4S_2$ requires N, 7·8%). The corresponding *dimethopicrate*, prepared by double decomposition, separated from ethanol in flat needles, m. p. 175° (Found: N, 17·0. $C_{36}H_{36}O_{14}N_{10}$ requires N, 16·8%).

Methosalts of 1 : 8-*di*-(2-*benzyl*-4 : 5-*dihydro*-1-*glyoxalinyl*)*octane*. The oily base obtained from the dihydroglyoxalinium ditoluene-*p*-sulphonate (15·5 g.) and 2·5N-sodium hydroxide (50 c.c.) reacted exothermally with a solution of methyl toluene-*p*-sulphonate (10·2 g., 2·2 mols.) in benzene (10 c.c.), and the metho-salt separated as an oil which crystallised on manipulation. After recrystallisation from a mixture of methanol and acetone, the *dimethotoluene*-p-*sulphonate* (12 g., 74%) had m. p. 158—160° (Found: N, 8·7. $C_{32}H_{50}O_6N_4S_2$ requires N, 8·6%). The *dimethopicrate* separated from methanol in orange blades, m. p. 134° (Found: N, 18·2. $C_{30}H_{40}O_{14}N_{10}$ requires N, 18·3%).

2-p-*Hydroxy- and* 2-p-*Methoxy-benzyl*-4 : 5-*dihydroglyoxaline*, 2-*Benzylglyoxaline*, *and* 2-*Benzyl*-3 : 4 : 5 : 6-*tetrahydropyrimidine*.—*p*-Hydroxybenzyl cyanide (6·65 g.), prepared in 60% yield from *p*-aminobenzyl cyanide as described by Kossler and Hanke (*J. Biol. Chem.*, 1919, **39**, 585), and 2-aminoethylammonium toluene-*p*-sulphonate (11·6 g., 1 mol.) were heated at 155° for 1½ hours. The solid was crystallised from *iso*propanol (20 c.c.), giving unchanged 2-aminoethylammonium toluene-*p*-sulphonate (3 g.) and then 2-p-*hydroxybenzyl*-4 : 5-*dihydroglyoxalinium toluene*-p-*sulphonate* (11·0 g., 63%), m. p. 146—147°, unchanged after recrystallisation from water or alcohol (Found: N, 8·05. $C_{17}H_{20}O_4N_2S$ requires N, 8·0%). The *picrate* crystallised from water in rhombs, m. p. 161° (Found: N, 17·35. $C_{16}H_{15}O_8N_5$ requires N, 17·3%).

p-Methoxybenzyl cyanide (11·76 g.), b. p. 107—110°/1 mm., obtained in 91% yield by methylating the hydroxy-cyanide with methyl iodide and alcoholic sodium ethoxide, and 2-aminoethylammonium toluene-*p*-sulphonate (18·56 g., 1 mol.) afforded a solid when heated at 190° for 1 hour. After being triturated with acetone and recrystallised from *iso*propanol (60 c.c.) this solid afforded 2-p-*methoxybenzyl*-4 : 5-*dihydroglyoxalinium toluene*-p-*sulphonate* (20 g., 69%), m. p. 138° (Found: N, 7·8. $C_{18}H_{22}O_4N_2S$ requires N, 7·7%). The corresponding *picrate* had m. p. 119° (Found: N, 16·8. $C_{17}H_{17}O_8N_5$ requires N, 16·7%), and 2-p-*methoxybenzyl*-4 : 5-*dihydroglyoxaline* separated from benzene in flat needles, m. p. 121—122° (Found: N, 15·0. $C_{11}H_{14}ON_2$ requires N, 14·7%).

When 2-benzyl-4 : 5-dihydroglyoxaline (8 g.) was heated at 250° with a 40% cobalt–kieselguhr catalyst (1 g.) evolution of hydrogen was complete in 45 minutes. The product was separated from the catalyst by extraction with benzene, and was converted into the hydrochloride by shaking the benzene solution with 2N-hydrochloric acid (50 c.c.). The residue obtained by evaporating the aqueous solution was crystallised from *iso*propanol giving colourless, deliquescent needles of 2-*benzylglyoxalinium chloride* (7·0 g., 72%), m. p. 176° (Found: N, 14·2. $C_{10}H_{11}N_2Cl$ requires N, 14·4%). The picrate had m. p. 172° and the free base m. p. 125°; Sonn and Grief (*Ber.*, 1933, **66**, 1900) record 172° and 125—126°, respectively.

When benzyl cyanide (11·7 g.), trimethylenediammonium ditoluene-*p*-sulphonate (20·9 g.) and tetramethylenediamine (4·0 g.) were heated at 190° for an hour, and the base, liberated with 5N-sodium hydroxide (25 c.c.) and collected in benzene, was distilled, 2-*benzyl*-3 : 4 : 5 : 6-*tetrahydropyrimidine* (15·0 g., 86%) was obtained in colourless needles m. p. 114—114·5°, b. p. 135—136°/0·5 mm. (Found: N, 16·2. $C_{11}H_{14}N_2$ requires N, 16·1%). The *picrate* separated from methanol in prisms m. p. 174·5° (Found: N, 16·3, 16·9. $C_{17}H_{17}O_7N_5$ requires N, 17·4%). 2-*Benzyl*-3 : 4 : 5 : 6-*tetrahydropyrimidinium chloride*, prepared from the base and hydrogen chloride in acetone, had m. p. 210° (Found: N, 13·3. $C_{12}H_{15}N_2Cl$ requires N, 13·3%).

Research Laboratories, Messrs. Boots Pure Drug Co., Ltd.,
Nottingham.
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