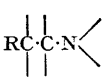
534. *New 5-Aminoglyoxalines as Potential Adrenergic Agents.*

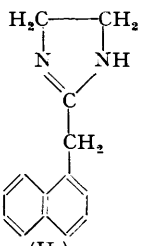
By H. BADER, J. D. DOWNER, and (MRS.) P. DRIVER.

The preparation of a number of 5-aminoglyoxaline hydrochlorides containing part of the 2-substituted ethylamine structure in the hetero-ring is described. A novel application of the Mannich reaction to the glyoxaline ring is also described, and a discussion on ultra-violet absorption spectra of the 5-aminoglyoxalines is given. The compounds are to be tested for sympathomimetic activity.

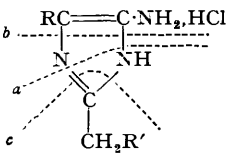
WITH the exception of the carbonic acid derivatives for which "pressor effects" have been claimed (Fastier, *Nature*, 1944, **154**, 429), compounds endowed with a true adrenergic or sympathomimetic action all appear to possess a strongly basic character and the fundamental structure (I) where R is an alkyl, aromatic, or heterocyclic radical.



(I.)



(II.)



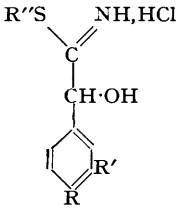
(III.)

The aim of the present work is to find new drugs in this field possessing comparable activity to that of adrenaline and related compounds but without their instability and associated undesirable side activities. It appeared to us that the most promising development might be the introduction of new ring systems in the basic structures, which incorporate the nitrogen atom in the ring. This development has already been successful in the employment of the dihydroglyoxaline ring [*e.g.*, Privine (II), which is now used clinically in peripheral vascular disorders] (Hartmann and Isler, *Arch. Exp. Path. Pharm.*, 1939, **192**, 141; Scholz, *Ind. Eng. Chem.*, 1945, **37**, 120).

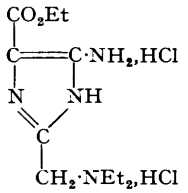
This communication describes the preparation of a number of potential pressor amines of the type (III) with the nitrogen atoms of the basic structure (I) contained in a glyoxaline ring. The 5-aminoglyoxalines have been chosen because, unlike glyoxalines in general, which are conspicuously stable to degradative reagents, they are on the whole easily broken down under acid conditions. Existing information (Fargher and Pyman, *J.*, 1919, **115**, 217; Fargher, *J.*, 1920, **117**, 668; Grant and Pyman, *J.*, 1921, **119**, 1893; Pyman, *J.*, 1922, **121**, 2616; Balaban, *J.*, 1930, 268) suggests that the fission may proceed in three ways (III; *a*, *b*, or *c*). Fission (*a*) is the more usual and is thought to proceed through the ketodihydroglyoxaline. The other degradations (*b*) and (*c*) are more conspicuous where R is electropositive, *e.g.*, Me (Pyman, *loc. cit.*). The fission (*a*) or (*b*) if occurring in glyoxalines of structure (III) would still preserve the basic skeleton (I) of adrenergic drugs. In the main, therefore, 2-substituted 5-amino-4-phenyl(or carbethoxy)glyoxalines (type III) have been prepared. The effect of substituents in the basic structure (I) on the physiological activity is fully reviewed elsewhere (Hartmann and Isler, *loc. cit.*; Hartung, *Chem. Reviews*, 1931, **9**, 389; Rajagopalan, *Current Sci.*, 1945, **14**, 56) and has been used in selecting the substituents R′ in (III). Many of the 5-aminoglyoxalines prepared, such as [III; R = CO_2Et, R′ = Ph; R = Ph, R′ = 3 : 4 : 5-$C_6H_2(OMe)_3$; and R = H, R′ = β-$C_{10}H_7$], will, therefore, be found to contain substituents analogous to the aryl substituents in known effective adrenergic agents.

The 5-aminoglyoxaline hydrochlorides (III; R = CO_2Et or Ph; R′ = phenyl, *m*- or *p*-substituted phenyl, α- or β-$C_{10}H_7$) were prepared by the method of Cook, Davis, Heilbron, and Thomas (*J.*, 1949, 1071) by condensing ethyl α-aminocyanoacetate or α-aminobenzyl cyanide with the appropriate thio-iminoether hydrochloride in boiling chloroform. This reaction proceeded smoothly in most cases to give excellent yields. In a few cases yields were much reduced owing to the reverse condensation taking prominence with the formation of ammonium chloride and presumably the *N*-substituted thio-iminoether (Abraham, Baker, Barltrop, Chain, King, Robinson, and Waley, CPS. 549). This was most noticeable in attempts to condense the thio-iminoethers (IV; R = R′ = H, R = OMe, R′ = H) with ethyl α-aminocyanoacetate

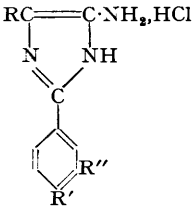
and the thio-iminoether (IV; RR′ = OCH_2O) with α-aminobenzyl cyanide, in which the required glyoxalines could not be isolated.



(IV; R″ = Et or CH_2Ph)



(V.)



(VI.)

In many cases, occurring only when α-aminobenzyl cyanide was used as one of the reactants, an abnormally long period of refluxing was necessary for a good yield of glyoxaline (see Table III). When only the usual time of refluxing was given, besides a poor yield of glyoxaline, α-aminobenzyl cyanide hydrochloride was isolated. In this connection it was shown that α-aminobenzyl cyanide hydrochloride reacts slowly with *p*-nitrophenylacetimino benzyl thioether base to give the required glyoxaline. When, however, the reaction between α-aminobenzyl cyanide and thio-iminoether hydrochlorides was performed in the presence of an excess of hydrogen chloride, no glyoxalines could be isolated.

Condensation of α-aminopropionitrile with thio-iminoether hydrochlorides from substituted benzyl cyanides invariably proceeded in the reverse direction. With benzimino benzyl thioether hydrochloride, however, the expected 5-amino-2-phenyl-4-methylglyoxaline hydrochloride was obtained. When aminoacetonitrile reacted with thio-iminoether hydrochlorides under the usual conditions, its hydrochloride was precipitated and failed to react further. This was overcome by performing the reaction at room temperature in the presence of one equivalent of pyridine, the glyoxalines (*e.g.*, III; R = H, R′ = β-$C_{10}H_7$) then being obtained. These last two α-amino-nitriles have not previously been employed in the thio-iminoether–α-amino-nitrile synthesis of glyoxalines.

Reduction of the glyoxalines (III; R = CO_2Et or Ph, R′ = *p*- or *m*-$NO_2{\cdot}C_6H_4$) with stannous chloride in hydrochloric acid readily gave the corresponding amino-derivatives.

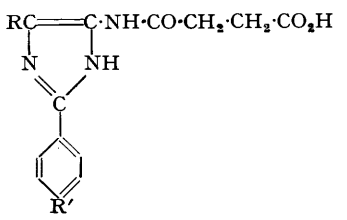
Refluxing of 5-amino-4-carbethoxyglyoxaline, trioxymethylene, and diethylamine in ethanol gave a good yield of 5-amino-4-carbethoxy-2-diethylaminomethylglyoxaline dihydrochloride (V). Only in a few isolated cases has the Mannich reaction been applied to azole rings, and in particular the thiazole ring (Albertson, *J. Amer. Chem. Soc.*, 1948, **70**, 669). Reactions are known, however, where 1-alkyl- and 1-aralkyl-glyoxalines have been condensed with formaldehyde to give 2-hydroxymethylglyoxalines (*e.g.*, Sarisin, *Helv. Chim. Acta*, 1923, **6**, 377; Sonn *et al.*, *Ber.*, 1924, **57**, 953; Grindley and Pyman, *J.*, 1927, 3128; Jones, *J. Amer. Chem. Soc.*, 1949, **71**, 383). In the present case, the 4- and 5-positions being occupied, condensation has occurred in the 2-position, as proved by an alternative synthesis of (V) from diethylaminoacetonitrile by the general method.

Since glyoxaline itself has pressor activity (Fastier, *Brit. J. Pharmacol.*, 1948, **3**, 198; Fastier and Reid, *ibid.*, p. 205), and moreover the 5-amino-group introduces an additional amidino-grouping, it was considered possible that the 5-aminoglyoxaline moiety itself might possess pressor activity, especially in the case of the 4-phenyl derivatives which contain a hidden 2-phenylethylamine structure. This possibility was examined by preparing a number of glyoxalines of the type (VI; R = Me, Ph, or CO_2Et; R′ = H, Cl, NO_2, or NH_2; R″ = H; R′ = R″ = OMe). These were found to possess little or no activity but were surprisingly non-toxic. They were all strongly fluorescent in solution. Succinyl derivatives (VII) in place of the more insoluble glyoxaline hydrochlorides were prepared.

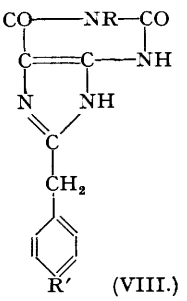
In order to investigate the effect of the introduction of a pyrimidine ring on physiological activity, the purines (VIII; R = Me, R′ = NO_2 or NH_2,HCl; R = Ph, R′ = H) have been prepared by ring closure of the appropriate 5-ureido-4-carbethoxyglyoxalines according to the method of Cook, Heilbron, Macdonald, and Mahadevan (*J.*, 1949, 1064).

In the aliphatic amines effective pressor activity is found in members with a chain of 6—8 carbon atoms (Rohrmann and Shonle, *J. Amer. Chem. Soc.*, 1944, **66**, 1516). This prompted the preparation of 5-amino-4-phenyl-2-*n*-heptylglyoxaline hydrochloride from *n*-amyl cyanide and the bisiminazole (IX) from sebaconitrile *via* the bisthio-iminoether hydrochloride. The latter might also be expected to exhibit trypanocidal activity (see King, Lourie, and Yorke, *Lancet*, 1937, **233**, 1360; *Ann. Trop. Med. Parasit.*, 1938, **32**, 177).

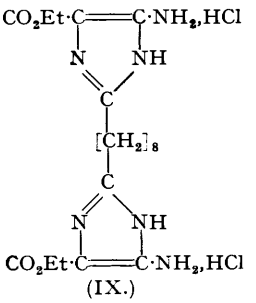
The biological results will be published elsewhere.



(VII.)

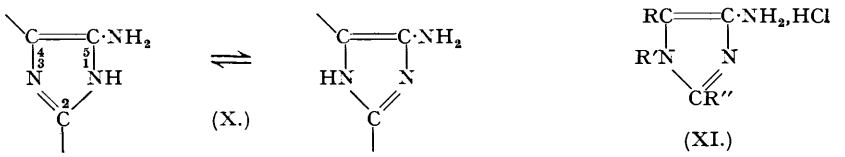


(VIII.)



(IX.)

Light-absorption Properties of 5-Aminoglyoxalines.—With a view to assess the influence of substitution in the glyoxaline ring, the ultra-violet light absorption of many of the compounds described in this paper has been determined. The results are collected in Table I. They will be seen to agree with the generally accepted basic structure (X) deduced from chemical evidence (Cook, Heilbron, *et al.*, Studies in the Azole Series, *J.*, 1948—1949). The glyoxaline hydro-



(X.) (XI.)

chlorides (XI; R = H, CO_2Et, or Ph; R′ = H or Me; R″ = H, Me, or aralkyl) exhibit a wide absorption band, in general of high intensity and with a maximum in the 2650—2850-A. region. With regard to the effect of substitution in the 4-position in the unsubstituted glyoxaline (XI; R = R′ = H; R″ = *p*-NO_2·C_6H_4·CH_2), the absorption curves (Fig. 1) of the corresponding 4-carbethoxy- or 4-phenyl- compounds are essentially similar but are shifted by some 100 and

FIG. 1.
Absorption curves showing effect of 4-substituent.

FIG. 2.
Absorption curves showing effect of acidification.

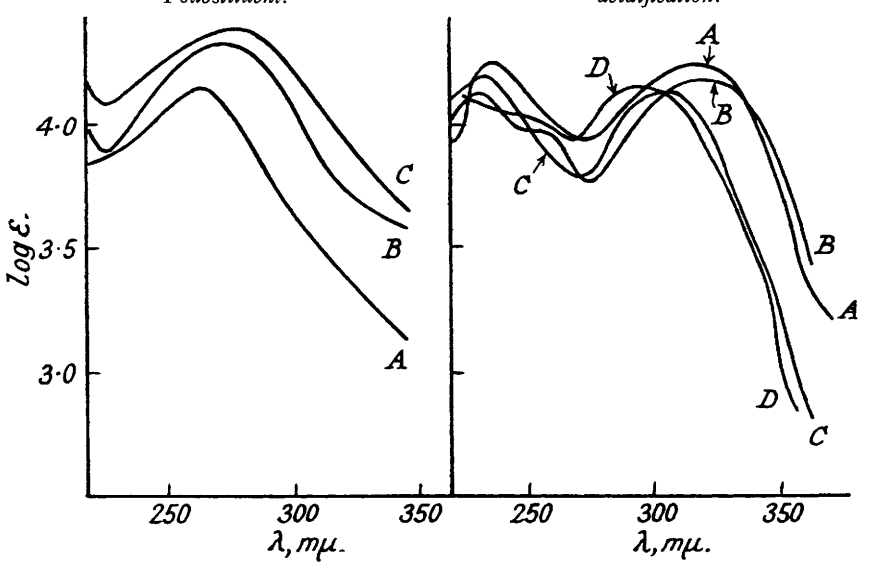
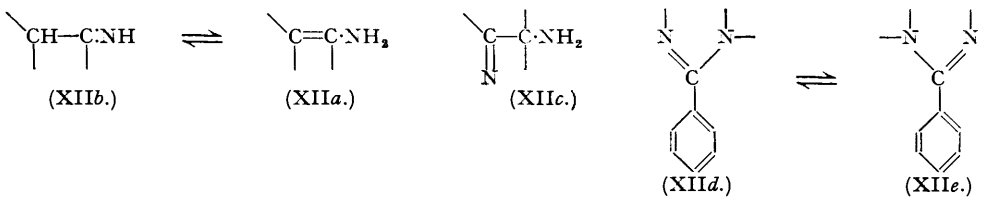


FIG. 1.—*A.* 5-*Amino*-2-p-*nitrobenzylglyoxaline hydrochloride. B.* 5-*Amino*-2-p-*nitrobenzyl*-4-*carbethoxy glyoxaline hydrochloride. C.* 5-*Amino*-2-p-*nitrobenzyl*-4-*phenylglyoxaline hydrochloride.*

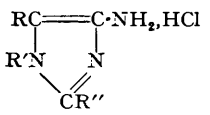
FIG. 2.—*A.* 5-*Amino*-4-*carbethoxy*-2-*phenylglyoxaline. B.* 5-*Amino*-4-*carbethoxy*-2-*phenylglyoxaline hydrochloride. C.* 5-*Amino*-4-*carbethoxy*-2-*phenyl*-3-*methylglyoxaline. D.* 5-*Amino*-4-*carbethoxy*-2-*phenyl*-3-*methylglyoxaline hydrochloride.*

130 A. respectively to longer wave-lengths and possess higher maximum intensity. This is in accordance with the basic structure (X), both bathochromic and hyperchromic shifts resulting from the extra conjugation of a CO_2Et or Ph group attached directly to the heterocyclic ring. It implies the presence in the ring of a double bond on the 4-carbon atom as existing in the partial tautomeric forms (XII*a*) and XII*c*). The existence of (XII*a*) is confirmed by the ready methylation of (XI; R = CO_2Et, R′ = H, R″ = Ph) with diazomethane, the methyl group attaching itself to the 3-nitrogen atom (Cook and Thomas, *J.*, 1950, 1884).



(XII*b*.) (XII*a*.) (XII*c*.) (XII*d*.) (XII*e*.)

TABLE I.



No.	R.	R′.	R″.	Hydrochloride. $\lambda_{max.}$, A.[c]	Hydrochloride. ε.	Base. $\lambda_{max.}$, A.[c]	Base. ε.
1	CO_2Et [b, c]	H	H	2740	14,450	—	—
2	CO_2Et [c]	H	Me	2730	17,200	—	—
3	CO_2Et [b]	Me	Me	2705	12,750	2810	13,650
4	H	H	*p*-NO_2·C_6H_4·CH_2	2640	14,000	—	—
5	H	H	β-$C_{10}H_7$·CH_2	2660	6,600	—	—
6	Ph	H	α-$C_{10}H_7$·CH_2	2875	21,150	—	—
7	Ph	H	β-$C_{10}H_7$·CH_2	2800	21,150	—	—
8	Ph	H	*p*-NO_2·C_6H_4·CH_2	2770	23,450	—	—
9	Ph	H	*p*-Cl·C_6H_4·CH_2	2810	12,600	—	—
10	Ph	H	CH_2·C_6H_4·NH_2,HCl (*p*)	2800	15,150	—	—
11	Ph	H	*p*-OH·C_6H_4·CH_2	2835	19,500	—	—
12	Ph	H	*m*-NO_2·C_6H_4·CH_2	2700	15,400	—	—
13	Ph	H	CH_2·C_6H_4·NH_2,HCl(*m*)	2835	10,550	—	—
14	Ph	H	*m*-OH·C_6H_4·CH_2	2810	17,000	—	—
15	Ph	H	3 : 4-$(OMe)_2C_6H_3$·CH_2	2830	20,150	—	—
16	Ph	H	3 : 4 : 5-$(OMe)_3C_6H_2$·CH_2	2810	15,900	—	—
17	Ph	H	3 : 4-$(O_2CH_2)C_6H_3$·CH_2	2870	14,650	—	—
18	CO_2Et	H	Ph·CH_2	2730	14,900	—	—
19	CO_2Et	H	*p*-NO_2·C_6H_4·CH_2	2745	21,150	—	—
20	CO_2Et	H	CH_2·NEt_2,HCl	2795; 2395	11,100; 6,100	—	—
21	Ph	H	Ph	2760; 3380	10,400; 17,400	2330; 3370	9,000; 13,900
22	Ph	H	*p*-Cl·C_6H_4	2345; 3460	13,500; 18,050	—	—
23	Ph	H	3 : 4-$(OMe)_2C_6H_3$	2790 [a]; 3360	10,550; 23,600	—	—
24	CO_2Et	H	*p*-NO_2·C_6H_4	2700; 3900	12,450; 13,150	—	—
25	CO_2Et	H	Ph	2310; 3170	13,050; 14,150	2365; 3175	17,400; 16,400
26	CO_2Et [b, d]	Me	Ph	2960	13,500	2325; 3050	15,150; 12,900
27	CO_2Et	H	3 : 4-$(OMe)_2C_6H_3$	2555; 3250	12,400; 20,400	—	—

[a] Inflexion. [b] The preparation of these compounds is described in a later paper. [c] For preparation, see Cook, Davis, Heilbron, and Thomas, *loc. cit.* [d] For preparation, see Cook and Thomas, *loc. cit.* [e] Ethanol was used as solvent.

Structure (XII*b*) can exist only in the free bases and should be eliminated by acidification. If it does exist in the free base a hypsochromic shift should be detectable on acidification. In the case of glyoxalines unsubstituted in position 3 (compounds 21 and 25, Table I) the spectra are not appreciably shifted on acidification, suggesting that the equilibrium is not in favour of the form (XII*b*) (Fig. 2). On the other hand, comparison of the 3-methylglyoxaline bases with their hydrochlorides (compounds 3 and 26, Table I) reveals the existence of a hypsochromic effect of *ca.* 100 A. in each case showing a definite contribution of the (XII*b*) form to their resonance equilibrium (Fig. 2).

Introduction of a methyl or aralkyl group in the 2-position of (XI; R = CO_2Et, R′ = R″ =

H) does not alter sensibly the position or intensity of the light-absorption maximum. With aryl substituents in the 2-position, however (compounds 25 and 27, Table I), the maximum is shifted some 600 A. to longer wave-lengths (Fig. 3). This again agrees with the basic structure resulting from the extra conjugating of an aryl group (attached directly to the heterocyclic ring) right through to the 4-carbethoxy-group. In addition the absorption curves of the 2 arylglyoxalines exhibit a fine structure in the 2350—2550 A. region. Again with 2-aryl-4-phenylglyoxaline hydrochlorides (compounds 21 to 23, Table I) the same effect is noticed and the bathochromic shift is even greater. This effect, therefore, agrees with the presence in the ring of a double bond on the 2-carbon atom as in the partial structures (XII*d*) and (XII*e*).

FIG. 3.

Absorption curves showing effect of 2-substituent.

FIG. 4.

Absorption curves showing effect of 3-methyl substitution.

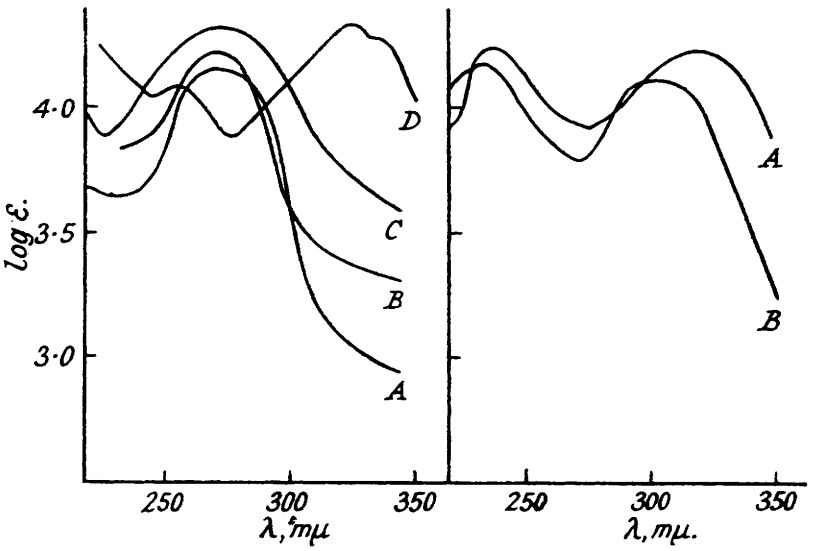


FIG. 3.—*A. 5-Amino-4-carbethoxyglyoxaline hydrochloride. B. 5-Amino-4-carbethoxy-2-methylglyoxaline hydrochloride. C. 5-Amino-4-carbethoxy-2-*p*-nitrobenzylglyoxaline hydrochloride. D. 5-Amino-4-carbethoxy-2-(3′ : 4′-dimethoxyphenyl)glyoxaline hydrochloride.*

FIG. 4.—*A. 5-Amino-4-carbethoxy-2-phenylglyoxaline. B. 5-Amino-4-carbethoxy-2-phenyl-3-methylglyoxaline.*

Methylation of the nitrogen in the 3-position (*e.g.*, compound 26) eliminates the partial structures (XII*c*) and (XII*d*) which account for the hypsochromic shift (Fig. 4) of 120 A.

EXPERIMENTAL.

(M. p.s are uncorrected. Analyses are by Drs. Weiler and Strauss.)

Nitriles.—The preparation of the required nitriles according to methods described in the literature, in the main, presented no difficulty. The following observations are made. Purification of the crude *p*-nitrobenzonitrile–copper salt complex, prepared by Sandmeyer reaction on *p*-nitroaniline (Bogert and Kohnstamm, *J. Amer. Chem. Soc.*, 1903, **25**, 479), was facilitated by Soxhlet extraction with carbon tetrachloride, giving a yield of 75%; m. p. 146°.

m-Nitrobenzyl alcohol (required for the *m*-substituted benzyl cyanides) was prepared in improved yield (83%) [b. p. 166—169°/0·3—1·5 mm., n_D^{22} 1·5760 (see Ferrier, *Compt. rend.*, 1945, **220**, 460)] by reduction of *m*-nitrobenzaldehyde (500 g.) with aluminium *iso*propoxide (116 g.) and dry *iso*propyl alcohol (7 l.) with distillation of the acetone as it is formed through a Dufton column at *ca.* 60 drops/minutes for 24 hours. Concentration *in vacuo* to 1 l., acidification with a mixture of concentrated hydrochloric acid (320 c.c.) and water (2·4 l.), and extraction with ether gave the alcohol on distillation.

m-Nitrobenzyl cyanide is not adequately described nor is its b. p. given in the literature. It was prepared as follows: Potassium cyanide (121·6 g.) in ethanol (130 c.c.) and water (250 c.c.) was added to a boiling solution of *m*-nitrobenzyl chloride (321 g.) (from the alcohol by the method of Norris and Taylor, *J. Amer. Chem. Soc.*, 1924, **46**, 755) in ethanol (1·5 l.). The resulting mixture was refluxed for 3 hours and concentrated to 500 c.c. *in vacuo*. Addition of water (1 l.), extraction with ether (700 c.c.), and distillation *in vacuo* gave yellow needles of *m*-nitrobenzyl cyanide (256 g., 84·5%), b. p. 180°/1·5 mm.

Thio-iminoether Hydrochlorides.—The following general method, essentially that of Pinner ("Die Imido Ether"), was employed for their preparation: Dry hydrogen chloride was passed into a mixture of the nitrile (1 mol.) and the thiol (1—2 mols.) at 0—5° until 1·1 mols. of hydrogen chloride had been absorbed. (In most cases a diluent, chloroform or ether, was employed to effect dissolution of the nitrile or aid subsequent filtration.) The resultant product was then kept for 1—10 days at 0° until the thio-iminoether hydrochloride separated. Most of these hydrochlorides are new, and where possible they have been titrated against standard alkali and in nearly all cases characterised by their m. p. In some cases, however, the thio-iminoether hydrochloride failed to crystallise (usually when chloroform was employed) or separated as a gum. In these cases either the excess of hydrochloric acid was removed *in vacuo* and the chloroform solution used as such, or the diluent was completely removed, leaving a somewhat crude product which was employed in the condensation. The data, therefore, for the thio-iminoether hydrochlorides prepared as summarised in Table II are not complete.

TABLE II.

Thio-iminoether hydrochlorides, R'S·CR:NH,HCl.

R.	R'	Solvent.	Yield, %.	M. p.†	Formula.	HCl: Found, %.	HCl: Req., %.
Ph	CH_2Ph	(Nil)	94	172—174° †	$C_{14}H_{14}NSCl$	12·55	13·85
p-NO_2·C_6H_4	CH_2Ph	Et_2O	60	166—170 †	—	—	—
p-Cl·C_6H_4	CH_2Ph	,,	64	180—181	—	—	—
3 : 4-$(OMe)_2C_6H_3$	CH_2Ph	,,	5 *	191—193	—	—	—
3 : 4-$(OMe)_2C_6H_3$	Et	Excess EtSH	94	190 †	—	—	—
p-OAc·C_6H_4	CH_2Ph	$CHCl_3$	63·8	215	$C_{16}H_{16}O_2NSCl$	11·4	11·35
CH_2Ph	CH_2Ph	(Nil)	69	141 †	$C_{15}H_{16}NSCl$	13·25	13·15
CH_2Ph	Et	Et_2O	63	117	$C_{10}H_{14}NSCl$	16·1	16·9
p-NO_2·C_6H_4·CH_2	CH_2Ph	$CHCl_3$	100	174 †	$C_{15}H_{15}O_2N_2SCl$	11·35	11·30
p-Cl·C_6H_4·CH_2	CH_2Ph	Et_2O	62	155—156	$C_{15}H_{15}NSCl_2$	11·35	11·70
p-OH·C_6H_4·CH_2	Et	,,	96	171	$C_{10}H_{14}ONSCl$	15·75	15·75
p-OMe·C_6H_4·CH_2	CH_2Ph	Et_2O–$CHCl_3$	100	—	$C_{16}H_{18}ONSCl$	12·3	11·9
m-NO_2·C_6H_4·CH_2	Et	,,	81·8	142	$C_{10}H_{13}O_2N_2SCl$	14·05	14·0
m-OH·C_6H_4·CH_2	Et	,,	76·2	152—153	$C_{10}H_{14}ONSCl$	15·3	16·3
3 : 4-$(OMe)_2C_6H_3$·CH_2	Et	$CHCl_3$	49	163	$C_{12}H_{18}O_2NSCl$	13·9	13·2
3 : 4 : 5-$(OMe)_3C_6H_2$·CH_2	CH_2Ph	,,	61	140—145	$C_{18}H_{22}O_3NSCl$	9·6	9·9
3 : 4-(O_2CH_2)·C_6H_3·CH_2	CH_2Ph	Et_2O	64	123—125	$C_{16}H_{16}O_2NSCl$	11·35	11·35
α-$C_{10}H_7$·CH_2	Et	$CHCl_3$	90	—	—	—	—
β-$C_{10}H_7$·CH_2	Et	Et_2O	66	—	$C_{14}H_{16}NSCl$	14·05	13·8
Ph·CH(OH)	CH_2Ph	,,	58	—	$C_{15}H_{16}ONSCl$	13·15	12·4
Bis-compound –$[CH_2]_8$–	Et	$CHCl_3$ or Et_2O	90	*ca.* 80	—	—	—

* After 36 hours. † With decomposition.

The *glyoxaline hydrochlorides* summarised in Table III were prepared by the following general method, essentially that of Cook, Davis, Heilbron, and Thomas (*loc. cit.*). The thio-iminoether hydrochloride (1 mol.), the α-amino-nitrile (1 mol.), and chloroform (10 mols.) were mixed, usually giving a clear solution, and refluxed for 1—2 hours (unless otherwise stated), and the glyoxaline hydrochloride which separated was collected. They could all be diazotised, the diazonium solutions giving red dyes with sodium β-naphthoxide. With aldehydes they produced coloured Schiff's bases. They were soluble to difficultly soluble in water according to substituents, the addition of alkalis precipitating the bases. They were soluble to difficultly soluble in hot methanol and ethanol but usually insoluble in other organic solvents.

A mixture of *p*-nitrophenylacetimino benzyl thioether hydrochloride (1·5 g.) and anhydrous potassium carbonate (0·41 g., 1 mol.) was mixed into a paste with chloroform. The volume was adjusted to 20 c.c. with chloroform, α-aminobenzyl cyanide hydrochloride (0·75 g.) added, and the mixture refluxed for several hours. The cold crude product was filtered off, ground with water, filtered off, and washed with water. The dried crude solid (0·4 g.), m. p. 220—222° (decomp.), was crystallised from methanol, giving pale lemon-coloured needles of 5-amino-2-*p*-nitrobenzyl-4-phenylglyoxaline hydrochloride, m. p. and mixed m. p. 232° (decomp.).

Glyoxaline Bases.—5-Amino-2 : 4-diphenylglyoxaline hydrochloride (12 g.) was triturated with 3N-sodium carbonate (excess), diluted with water, warmed to 50°, and filtered to give the crude base (9 g.) which crystallised from benzene in prismatic needles of *5-amino-2 : 4-diphenylglyoxaline*, m. p. 165° (Found: C, 76·3; H, 5·5; N, 17·6. $C_{15}H_{13}N_3$ requires C, 76·55; H, 5·55; N, 17·9%). It was very soluble in methanol, ethanol, and ethyl acetate. The crude *base* (4·5 g.) was precipitated when a lukewarm solution of 5-amino-4-carbethoxy-2-(3 : 4-dimethoxyphenyl)glyoxaline hydrochloride (6 g.) in water (250 c.c.) was neutralised with 3N-sodium carbonate; it crystallised from ethyl acetate in colourless prisms, m. p. 198° (Found: C, 57·5; H, 5·4; N, 14·4. $C_{14}H_{17}O_4N_3$ required C, 57·7; H, 5·9; N, 14·4%).

Neutralisation of a solution of 5-amino-4-phenyl-2-*p*-chlorophenylglyoxaline hydrochloride (10 g.) in boiling water (2 l.) with 3N-sodium carbonate gave the crude *base*, which crystallised from aqueous methanol in greenish-yellow prisms (6·5 g.), m. p. 286—290° (decomp.) (Found: C, 66·5; H, 4·7; N, 15·7. $C_{15}H_{12}N_3Cl$ requires C, 66·8; H, 4·5; N, 15·6%). Its solution in methanol, ethanol, or ethyl acetate had a green fluorescence. Similarly, the crude *base* (4 g.) from 5-amino-4-carbethoxy-2-phenyl-

glyoxaline hydrochloride crystallised from aqueous ethanol in colourless prisms, m. p. 219° (decomp.) (Found: C, 62·2; H, 5·8. $C_{12}H_{13}O_2N_3$ requires C, 62·3; H, 5·7%).

Refluxing of 5-amino-4-carbethoxy-2-*p*-nitrophenylglyoxaline hydrochloride (7 g.) with methyl *iso*thiocyanate (4·5 c.c.) in pyridine (60 c.c.) for 1 hour failed to give the methylthioureido-derivative. Instead, the unaltered *base* (4·4 g.), m. p. >280° (decomp.) (Found: C, 52·7; H, 4·55; N, 20·5. $C_{12}H_{12}O_4N_4$ requires C, 52·2; H, 4·4; N, 20·3%), crystallised from the pyridine liquor in colourless small prisms. It was insoluble in water and common organic solvents.

Succinyl Derivatives.—5-Amino-4-phenyl-2-*p*-nitrophenylglyoxaline hydrochloride (6 g.) was refluxed in pyridine (40 c.c.) with succinic anhydride (3·3 g.) for 1 hour. The thick syrup obtained on evaporation *in vacuo* was crystallised from aqueous ethanol give golden-yellow hair-like needles of 5-(*β-carboxypropionamido*)-4-*phenyl*-2-p-*nitrophenylglyoxaline* (3·5 g.), m. p. >300° (Found: N, 15·0. $C_{19}H_{16}O_5N_4$ requires N, 14·75%). It was soluble in dilute aqueous sodium hydrogen carbonate.

Refluxing of a suspension of 5-amino-4-phenyl-2-*p*-chlorophenylglyoxaline (4 g.) in benzene (70 c.c.) with succinic anhydride (2 g.) for 30 minutes and crystallisation of the crude product (5·5 g.) from aqueous ethanol gave pale greenish-yellow needles of 5-(*β-carboxypropionamido*)-4-*phenyl*-2-p-*chlorophenylglyoxaline*, m. p. 223° (decomp.) (Found: C, 61·5; H, 4·6; N, 11·2. $C_{19}H_{16}O_3N_3Cl$ requires C, 61·7; H, 4·4; N, 11·4%).

Stannous Chloride Reductions.—5-Amino-4-phenyl-2-*p*-nitrobenzylglyoxaline hydrochloride (15 g.) was added in small portions during 2 hours to a solution of hydrated stannous chloride (36 g.) in concentrated hydrochloric acid (90 c.c.) with stirring at 0—5°. A further 50 c.c. of the acid was then added, and stirring continued for 1 hour at 0°. After 12 hours at 0°, the mixture was evaporated to dryness *in vacuo* (at 60—70°), the residue dissolved in water (300 c.c.), and the tin precipitated with hydrogen sulphide. Filtration, and evaporation of the filtrate *in vacuo* at 60—70°, gave a crude solid (8 g.) which crystallised from methanol–ethyl acetate in colourless needles of 5-*amino*-4-*phenyl*-2-p-*aminobenzylglyoxaline dihydrochloride* (7·6 g.), decomp. above 260° (Found: C, 56·8; H, 5·35; N, 16·3; Cl, 20·95. $C_{16}H_{18}N_4Cl_2$ requires C, 56·95; H, 5·35; N, 16·6; Cl, 21·05%). It was soluble in water and ethanol but insoluble in ether and ethyl acetate. It could be diazotised. Under similar reduction conditions, the analogous 2-*p*-nitrophenyl hydrochloride (10 g.) gave a crude product (8 g.) which crystallised from aqueous ethanol, giving colourless prisms of 5-*amino*-4-*phenyl*-2-p-*aminophenylglyoxaline dihydrochloride dihydrate*, m. p. 258° (decomp.) (Found: N, 15·4. $C_{15}H_{16}N_4Cl_2,2H_2O$ requires N, 15·6%), and 5-amino-4-phenyl-2-*m*-nitrobenzylglyoxaline hydrochloride (15 g.) gave a crude product which, after charcoal treatment in methanol, crystallised from ethanol–ethyl acetate to give colourless micro-crystals of 5-*amino*-4-*phenyl*-2-m-*aminobenzylglyoxaline dihydrochloride* (6·7 g.), m. p. 233° (Found: C, 56·95; H, 5·45; N, 16·3. $C_{16}H_{18}N_4Cl_2$ requires C, 56·95; H, 5·4; N, 16·65%). All were soluble in water, their bases being precipitated with alkali. They could all be diazotised.

Xanthines.—5-Amino-4-carbethoxy-2-*p*-nitrobenzylglyoxaline hydrochloride (52 g.), suspended in pyridine (200 c.c.) containing methyl *iso*cyanate (20 c.c.), was slowly heated, and finally refluxed for 1 hour. Two further portions (20 c.c. each) of methyl *iso*cyanate were added at hourly intervals to the mixture at 0°, and refluxing continued for 3 hours in all. About 70 c.c. of pyridine were removed *in vacuo* at 60—80°, methanol (500 c.c.) was added, and the crude solid (37·4 g.) crystallised from pyridine–methanol to give colourless needles of 5-*methylureido*-4-*carbethoxy*-2-p-*nitrobenzylglyoxaline*, m. p. 242° (decomp.) (Found: C, 52·0; H, 5·05; N, 20·2. $C_{15}H_{17}O_5N_5$ requires C, 51·85; H, 4·95; N, 20·2%). The preceding ureido-compound (2 g.) was boiled for 1 minute in a mixture of 10% aqueous sodium hydroxide (15 c.c.) and water (45 c.c.). On acidification the crude purine was precipitated. Repeated precipitation with acid from its solution in dilute ammonia gave 8-p-*nitrobenzyl*-1-*methylxanthine* (1·4 g.), m. p. >300° (decomp.), as a yellow solid (Found: C, 51·5; H, 4·0. $C_{13}H_{11}O_4N_5$ requires C, 51·8; H, 3·7%).

5-Methylureido-4-carbethoxy-2-*p*-nitrobenzylglyoxaline (4·5 g.) was reduced with stannous chloride and concentrated hydrochloric acid, as above. The crude reduction product (2·5 g.), m. p. 194° (decomp.), was boiled for 1 minute in 5% aqueous sodium hydroxide solution (100 c.c.), acidified with acetic acid, and the precipitate converted into the hydrochloride by boiling with 8% ethanolic hydrochloric acid (35 c.c.) and ethanol (20 c.c.). Crystallisation from water gave lustrous needles of 8-p-*aminobenzyl*-1-*methylxanthine hydrochloride* (2 g.), m. p. 349—350° (decomp.) (Found: C, 51·3; H, 4·95; N, 22·8; Cl, 11·3. $C_{13}H_{14}O_2N_5Cl$ requires C, 50·7; H, 4·6; N, 22·8; Cl, 11·5%). It was very sparingly soluble in hot ethanol and cold water.

5-Amino-4-carbethoxy-2-benzylglyoxaline hydrochloride (3 g.), pyridine (10 c.c.), and phenyl *iso*cyanate (1·5 c.c.) were refluxed for 1 hour. Treatment with ethanol (10 c.c.) and water (20 c.c.) gave a crude solid (3 g.) which crystallised from methanol (20 c.c.) to give colourless hair-like needles of 5-*phenylureido*-4-*carbethoxy*-2-*benzylglyoxaline*, m. p. 186—187° (Found: C, 65·9; H, 5·5; N, 15·4. $C_{20}H_{20}O_3N_4$ requires C, 66·1; H, 5·9; N, 15·1%). It was moderately soluble in methanol, ethanol, and ethyl acetate. The phenylureido-compound (1·77 g.) was converted with alkali, as above, into 1-*phenyl*-8-*benzylxanthine* (0·68 g.), m. p. 316—318° (decomp.) (Found: N, 17·6. $C_{18}H_{14}O_2N_4$ requires N, 17·5%). It gave a positive murexide test.

Mannich Reaction.—5-Amino-4-carbethoxyglyoxaline (3·1 g.) (Cook, David, Heilbron, and Thomas, *loc. cit.*), trioxymethylene (0·66 g.), diethylamine (1·68 g.), and ethanol (15 c.c.) were refluxed for 2 hours and then concentrated *in vacuo*. The red gummy residue was dissolved in 7·8% ethanolic hydrochloric acid (30 c.c.), kept for 3 days at 0°, and the jelly-like product was poured into ether and filtered off. Crystallisation of the crude product (4·4 g.) from ethanolic hydrochloric acid gave colourless micro-crystals of 5-*amino*-4-*carbethoxy*-2-*diethylaminomethylglyoxaline dihydrochloride*, m. p. 192—193° (Found: C, 42·0; H, 7·2; N, 17·8. $C_{11}H_{22}O_2N_4Cl_2$ requires C, 42·2; H, 7·1; N, 17·9%). The reaction can also be performed in ethanolic hydrochloric acid (2 mols. of HCl). The compound could be diazotised.

TABLE III.

5-Aminoglyoxaline hydrochlorides.

Substituents: 4.	2.	Yield, %.	Crystalline form[f] and solvent.	M. p.*	Formula.	Analyses.	Found, %.	Req., %.
Me	Ph[a]	76	Prisms; MeOH–Et_2O	264—265° *	$C_{10}H_{21}N_3Cl$	C	57·05	57·3
						H	5·65	5·75
						N	20·1	20·05
						Cl	17·1	16·95
CO_2Et	Ph[a]	82[g]	Microcrystals; EtOH	218—220 *	—		—	
Ph	Ph[a]	95	Very pale lemon needles; MeOH	261 *	$C_{15}H_{14}N_3Cl$	Cl	13·0	13·0
CO_2Et	*p*-NO_2·C_6H_4[a]	98	Yellow silky needles; MeOH	277 *	$C_{12}H_{13}O_4N_4Cl,1H_2O$	C	44·2	43·6
						H	4·8	4·6
						N	17·0	17·0
						Cl	11·0	10·75
						H_2O	5·7	5·4
Ph	*p*-NO_2·C_6H_4[a]	67[e]	Orange-yellow microcrystals; EtOH–Et_2O	268—269 *	$C_{15}H_{13}O_2N_4Cl$	C	56·5	56·85
						H	4·2	4·1
						N	17·3	17·7
Ph	*p*-C_6H_4Cl[a]	90	Yellow microcrystals; MeOH–Et_2O	Decomp. above 260°	$C_{15}H_{13}N_3Cl_2$ $C_{15}H_{13}N_3Cl_2$	C	58·8	58·8
						H	4·35	4·3
						N	13·8	13·7
						Cl	23·2	23·2
CO_2Et	3 : 4-$(OMe)_2C_6H_3$[b]	66	Needles; EtOH	233 *	$C_{14}H_{18}O_4N_3Cl$	N	12·5	12·8
						Cl	10·5	10·8
Ph	3 : 4-$(OMe)_2C_6H_3$[a, b]	60—70	Pale lemon-yellow rods; MeOH	253—254 *	$C_{17}H_{18}O_2N_3Cl$	N	12·5	12·7
						Cl	10·45	10·7
CO_2Et	CH_2Ph[b]	94[f]	Prismatic needles; MeOH–Et_2O	195—196 *	$C_{13}H_{16}O_2N_3Cl$	N	14·8	14·9
Ph	CH_2Ph[a]	80[e]	EtOH	183—183·5 *	$C_{16}H_{16}N_3Cl$	C	67·2	67·2
						H	5·6	5·65
						N	14·8	14·7
						Cl	12·5	12·4
CO_2Et	*p*-NO_2·C_6H_4·CH_2[a]	90	Microcrystals; EtOH–CH_3·CO_2Et	226 *	$C_{13}H_{15}O_4N_4Cl$	N	17·1	17·15
Ph	*p*-NO_2·C_6H_4·CH_2[a]	80[e]	Pale lemon needles; MeOH	232 *	$C_{16}H_{15}O_2N_4Cl$	C	58·2	58·1
						H	4·65	4·6
						N	17·3	16·95
						Cl	11·0	10·7
Ph	*p*-Cl·C_6H_4·CH_2[a]	85	Microcrystals; EtOH–CH_3·CO_2Et	225 *	$C_{16}H_{15}N_3Cl_2$	C	59·7	60·0
						N	4·85	4·7
						N	12·9	13·1
						Cl	22·5	22·3
Ph	*p*-OH·C_6H_4·CH_2[b]	83	Needles; H_2O	255 *	$C_{16}H_{16}ON_3Cl$	C	63·8	63·7
						H	5·35	5·35
						N	13·6	13·9
						Cl	11·95	11·8

Ph	*m*-NO_2·C_6H_4·CH_2 [b]	79 [e]	Pale yellow needles; EtOH	249 *	$C_{16}H_{15}O_2N_4Cl$	C	57·8	58·1
						H	4·85	4·6
						N	17·1	16·95
						Cl	10·7	10·7
Ph	*m*-OH·C_6H_4·CH_2 [b]	78 [e]	Cream prisms; EtOH	245 *	$C_{16}H_{16}ON_3Cl$	C	63·7	63·7
						H	5·65	5·35
						N	13·5	13·9
Ph	3 : 4-$(OMe)_2C_6H_3$·CH_2 [b]	61 [d]	Prisms; EtOH	208—209	$C_{18}H_{20}O_2N_3Cl$	C	62·45	62·5
						H	5·55	5·85
						N	11·9	12·15
						Cl	9·9	10·25
CO_2Et	3 : 4-$(OMe)_2C_6H_3$·CH_2 [b]	67	Prisms; MeOH–Et_2O	193—194 *	$C_{15}H_{20}O_4N_3Cl$	C	53·0	52·65
						H	6·2	5·9
						N	12·55	12·3
Ph	3 : 4-(OCH_2O)·C_6H_3·CH_2	24	Prisms; EtOH–Et_2O	141—143	$C_{17}H_{16}O_2N_3Cl$	N	12·9	12·75
						Cl	11·1	10·75
Ph	3 : 4 : 5-$(OMe)_3C_6H_2$·CH_2 [a]	71	Needles; EtOH	218 *	$C_{19}H_{22}O_3N_3Cl$	C	60·85	60·7
						H	5·6	5·9
						N	11·0	11·2
						Cl	9·05	9·45
CO_2Et	α-$C_{10}H_7$·CH_2 [b]	35	Prisms; EtOH–CH_3·CO_2Et	203 *	$C_{17}H_{18}O_2N_3Cl$	C	61·85	61·5
						H	5·45	5·45
						N	12·7	12·7
						Cl	11·05	10·7
Ph	α-$C_{10}H_7$·CH_2 [c]	82 [e]	Cream microcrystals; MeOH–CH_3·CO_2Et	250 *	$C_{20}H_{16}N_3Cl$	C	71·7	71·5
						H	5·4	5·4
						N	12·4	12·5
						Cl	10·75	10·6
Ph	β-$C_{10}H_7$·CH_2 [b]	81 [c]	Buff prisms; EtOH	246 *	$C_{20}H_{16}N_3Cl$	C	71·4	71·5
						H	5·6	5·4
						N	12·5	12·5
Ph	*n*-C_7H_{15} [b, h]	44 [g]	Needles; $CHCl_3$	123	$C_{10}H_{24}N_3Cl$	C	65·35	65·4
						H	8·25	8·25
						N	14·3	14·3
						Cl	12·1	12·1
CO_2Et	–$[CH_2]_8$– Bis-compound [b]	44	Prisms; EtOH–CH_3·CO_2Et	Efflorescence at at 120—132°, resolidifying, and m. p. 187°	$C_{20}H_{34}O_4N_6Cl_2,C_2H_5$·OH	C	48·65	48·9
						H	7·1	7·45
						N	15·9	15·6
						Cl	13·3	13·2
						C_2H_5·OH	8·1	8·5

[a] From the iminobenzyl thioether hydrochloride. [b] From the iminoethyl thioether hydrochloride. [c] 6—7 Hours' refluxing. [d] 10 Hours' refluxing. [e] 20 Hours' refluxing. [f] Colourless unless stated. [g] Cook, Davis, Heilbron, and Thomas, *loc. cit.* [h] Iminoethyl thioether hydrochloride not isolated; yield based on nitrile. [i] Robinson *et al.*, CPS, 549. * With decomposition.

Dry hydrogen chloride was passed into a solution of diethylaminoacetonitrile (15 g.), chloroform (250 c.c.), and ethanethiol (30 c.c.) at 0° for 2 hours. The hydrochloride of the nitrile was first precipitated and then further reacted, forming an upper oily layer. After being left for 2 days at 0°, the oily layer solidified, giving colourless prisms of diethylaminoacetimino ethyl thioether dihydrochloride (22 g.). It was very hygroscopic. The preceding thioiminoether dihydrochloride (10·5 g.), ethyl α-aminocyanoacetate (6·6 g.), and pyridine (4 g.) in chloroform (20 c.c.) were refluxed for 17 hours, then filtered from ammonium chloride (0·95 g.); the filtrate was evaporated to dryness *in vacuo*, and the black oily residue purified by crystallisation from 7·8% ethanolic hydrochloric acid (45 c.c.) to give the above glyoxaline (4 g.), m. p. and mixed m. p. 192—193°.

Aminoacetonitrile Condensations.—Aminoacetonitrile (1·75 g.) was added to a partial solution of *p*-nitrophenylacetimino benzyl thioether hydrochloride (10 g.) in chloroform (25 c.c.) containing pyridine (2·5 c.c.), shaken in an atmosphere of nitrogen for 7 hours, and left overnight at 0°; 8% ethanolic hydrochloric acid (20 c.c.) was added, and the crude solid (2·8 g.) filtered off. Crystallisation from methanol (120 c.c.) gave yellow needles of 5-*amino*-2-p-*nitrophenylglyoxaline hydrochloride*, m. p. >250° (decomp.) (Found: N, 22·4; Cl, 13·7. $C_{10}H_{11}O_2N_4Cl$ requires N, 22·0; Cl, 13·9%). It was moderately soluble in water; after diazotisation it coupled with sodium β-naphthoxide to give a red dye. Similarly, β-naphthylacetimino ethyl thioether hydrochloride (9·4 g.) gave a crude solid (7·8 g.) which crystallised from methanol to give small colourless needles of 5-*amino*-2-*β-naphthylmethylglyoxaline hydrochloride*, m. p. 154—155° (decomp.) (Found: C, 64·9; H, 5·45; Cl, 14·2. $C_{14}H_{14}N_3Cl$ requires C, 64·7; H, 5·45; Cl, 13·7%).

We thank the Directors of Beecham Research Laboratories Limited for permission to publish this paper, and Mr. L. J. Edwards for the determination of the absorption spectra.

BEECHAM RESEARCH LABORATORIES, LTD.,
BROCKHAM PARK, BETCHWORTH, SURREY.

[*Received, May 3rd*, 1950.]