429. N^1-*Sulphanilamides derived from Aminoquinoxalines and Aminomethylquinoxalines.*

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The three possible aminoquinoxalines, nine of the fifteen possible aminomethylquinoxalines, and nine of the corresponding N^1-sulphanilamides have been synthesised.

The identity of the product obtained from 2 : 3-diaminotoluene hydrochloride and mesoxalic ester has been established as 2-hydroxy-3-carbethoxy-5-methylquinoxaline.

A convenient method for the preparation of 3 : 5-dinitro-*o*-toluidine is described, and attention is drawn to a neglected method for the preparation of 3 : 5-dinitro-*p*-toluidine (Ullmann and Gross, *Ber.*, 1910, **43**, 2697).

It has been reported (Schmith, *Dansk Tids. Farm.*, 1940, **14**, 215) that the seven isomeric sulphanilamidoquinolines have bacteriostatic activity against pneumococcus type I *in vitro* equal to that of sulphapyridine. It was thought that the isomeric sulphanilamidoquinoxalines—which stand in the same structural relationship to sulphanilamidopyrazine as do the sulphanilamidoquinolines to sulphapyridine—might be of chemotherapeutic interest, since favourable clinical reports of the use of sulphapyrazine have been published (*e.g.*, Ruegsegger, Hamburger, junr., Turk, Spies, and Blankenhorn, *Amer. J. Med. Sci.*, 1941, **202**, 432; Broh-Kahn and Erdman, *ibid.*, 1946, **212**, 170).

The effect of the introduction of a methyl group into the quinoxaline nucleus of sulphanilamidoquinoxalines has also been examined, since the presence and position of such an apparently inert group are known to cause profound changes in the biological activity of many types of compound, although at present no completely satisfactory explanations of these changes have been suggested. For example, 1 : 4-naphthaquinone has a slight vitamin-*K* activity which is increased 500-fold by the introduction of a methyl group into the 2-position (Dam, Glavind, and Karrer, *Helv. Chim. Acta*, 1940, **23**, 229), while a second methyl group in the 6-position results in an inactive compound (Fieser, Bowen, Campbell, Fry, and Gates, *J. Amer. Chem. Soc.*, 1939, **61**, 1927). The substitution of two methyl groups in the 1 : 9-positions of 2 : 8-diaminoacridine (proflavine) gives a compound with greatly enhanced antibacterial action (Albert, Rubbo, Goldacre, Davey, and Stone, *Brit. J. Exp. Path.*, 1945, **26**, 160). The effect of a change in position of the methyl groups is very marked in the riboflavin series. A shift of the methyl groups from the 6 : 7- to either the 5 : 7- or the 6 : 8-positions gives rise to inactive compounds (Kuhn, *Ber.*, 1937, **70**, 1293), but a shift to the 5 : 6-positions produces a compound which is an antagonist to the growth effect of riboflavin on rats (Emerson and Tishler, *Proc. Soc. Exp. Biol. Med.*, 1944, **55**, 184). In the sulphonamide field, Läuger and Martin (*Schweiz. Med. Woch.*, 1943, **73**, 402) have shown that the 4-monomethyl derivative of N^1-benzoylsulphanilamide has a slight activity against experimental pneumococcal infections in mice, but the 3 : 4-dimethyl derivative (" Irgafen ") has a very high activity. Change of position of one of the methyl groups or the introduction of more methyl groups give rise to inactive compounds.

An instance of the enhancing effect of a methyl group on chemotherapeutic activity is provided in the present series of sulphanilamidoquinoxalines. It has been found by

Dr. G. Brownlee, of the Wellcome Physiological Research Laboratories, that N¹-(3′-*methyl*-2′-*quinoxalyl*)*sulphanilamide* is much more active against *Hæmophilus pertussis* infections of mice than N^1-(2′-quinoxalyl)sulphanilamide. It is also only about one-sixth as toxic.

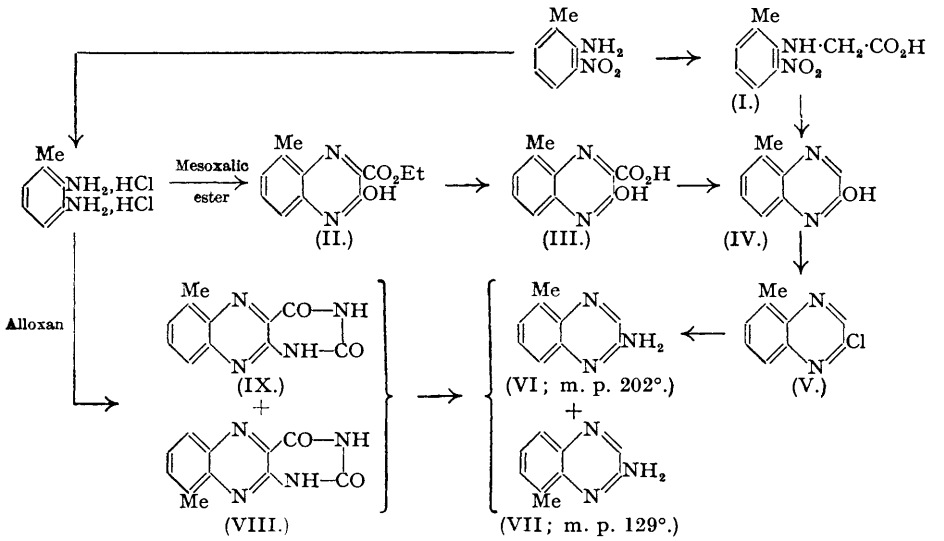
The sulphanilamidoquinoxalines were made either from the amine and acetylsulphanilyl chloride followed by hydrolysis of the N^4-acetyl group, or from the chloro-derivative and sulphanilamide. All were sparingly soluble in water.

The preparation of N^1-(2′-quinoxalyl)sulphanilamide was announced during the course of the present work by Weijlard, Tishler, and Erickson (*J. Amer. Chem. Soc.*, 1944, **66**, 1957), who obtained it from 2-aminoquinoxaline and acetylsulphanilyl chloride followed by deacetylation; it has now been found that this sulphonamide can be conveniently made in good yield by the interaction of 2-chloroquinoxaline (Gowenlock, Newbold, and Spring, *J.*, 1945, 622) with sulphanilamide in the presence of potassium carbonate and potassium iodide. The product diazotises and couples with alkaline β-naphthol; it is therefore N^1-(2′-quinoxalyl)sulphanilamide and not the isomeric N^4-(2′-quinoxalyl)sulphanilamide.

Similarly, interaction of 2-*chloro*-3-*methylquinoxaline* with sulphanilamide in the presence of potassium carbonate has given N^1-(3′-methyl-2′-quinoxalyl)sulphanilamide and not the isomeric N^4-(3′-methyl-2′-quinoxalyl)sulphanilamide. This was proved by the ability of the product to diazotise and couple and by its synthesis from 2-*amino*-3-*methylquinoxaline* and acetylsulphanilyl chloride, followed by deacetylation with alcoholic hydrochloric acid.

N¹-(5′-*Methyl*-2′-*quinoxalyl*)*sulphanilamide* has been prepared by two similar routes starting from 2-*amino*-5-*methylquinoxaline* (VI) and 2-*chloro*-5-*methylquinoxaline* (V). The latter was prepared from 2-*hydroxy*-5-*methylquinoxaline* (IV) which was obtained both from 2-*hydroxy*-3-*carbethoxy*-5-*methylquinoxaline* (II) and from N-(3-*nitro*-o-*tolyl*)*glycine* (I).

Although the reaction between 2 : 3-diaminotoluene hydrochloride and mesoxalic ester might have led to two isomeric hydroxy-carbethoxymethylquinoxalines, it did in fact give only one isomeride. This failure to give both isomeric products is of interest since 2 : 3-diaminotoluene hydrochloride gives the two isomeric products (VIII and IX) with alloxan; further, it has been shown that 3 : 4-diaminotoluene hydrochloride gives two isomerides with mesoxalic ester, alloxan (Platt, this vol., p. 1310) or ω-bromoacetophenone (Hinsberg, *Annalen*, 1887, **237**, 370; Lellmann and Donner, *Ber.*, 1890, **23**, 166). On the other hand, only one isomeride is formed from 3 : 4-diaminotoluene and monochloroacetone (Hinsberg, *loc. cit.*), oximinoacetone or methylglyoxal (von Pechmann, *Ber.* 1887, **20**, 2544). Moreover, only one isomeride is reported in each case from the interaction of 4 : 5-diamino-*m*-xylene or 3 : 4-diamino-*o*-xylene with alloxan (Stern and Holiday, *Ber.*, 1934, **67**, 1450).



The identity of the 2-hydroxy-5-methylquinoxaline (IV) has been established by its unambiguous synthesis from *N*-(3-nitro-*o*-tolyl)glycine (I). Pollak (*J. pr. Chem.*, 1915, **91**, 285), who investigated a series of reactions of chloro- and bromo-acetic acids with nitroamino-

toluenes, was unable to prepare this substituted glycine; it has now been obtained in 15% yield by heating 3-nitro-*o*-toluidine and bromoacetic acid at 125—140° with zinc chloride (absence of zinc chloride halves the yield).

2-Hydroxy-5-methylquinoxaline (IV) was converted *via* the 2-chloro-derivative (V) into 2-amino-5-methylquinoxaline (VI), m. p. 202°. This was identical with one of the two isomeric aminomethylquinoxalines obtained by treating a mixture of 5- and 8-methylalloxazines (IX and VIII) with concentrated sulphuric acid; the second isomeride (m. p. 129°) is most probably 2-*amino*-8-*methylquinoxaline* (VII). The possibility exists that this product may be an inseparable mixture of 2-amino-8- and -5-methylquinoxaline since no independent synthesis of the former has been carried out.

It has not been found possible to synthesise N^4-acetyl-N^1-(8′-methyl-2′-quinoxalyl)-sulphanilamide from 2-amino-8-methylquinoxaline and acetylsulphanilyl chloride.

There are five possible monomethyl 5-aminoquinoxalines, of which only one, *viz.*, 5-*amino*-7-*methylquinoxaline*, has been prepared. This exists as the monohydrate, as does also 5-*aminoquinoxaline*; all the other amino- or aminomethyl-quinoxalines are anhydrous. 5-Amino-7-methylquinoxaline was synthesised from 3 : 5-dinitro-*p*-toluidine as starting material; this was readily obtained in quantity by the apparently neglected method of Ullmann and Gross (*Ber., loc. cit.*) by heating **p*-tosyl-*p*-toluidide with nitric acid under reflux. The more usual route of nitrating aceto-*p*-toluidide is unsatisfactory owing to the ease of removal of the acetyl group; tar formation follows from the presence of the then unprotected amino-group.

The only satisfactory method for the preparation of 3 : 5-dinitro-*o*-toluidine (required for the synthesis of 7-*amino*-5-*methylquinoxaline*) described in the literature appeared to be that of McGookin (*J. Soc. Chem. Ind.*, 1941, **60**, 297) who commenced with *o*-cresol and obtained an overall yield of 85%, but a repetition of this method gave an overall yield of only 16%. It was found that 3 : 5-dinitro-*o*-toluidine could be conveniently prepared in good yield and in quantity by simply refluxing *p*-tosyl-*o*-toluidide successively with 25% and 35% nitric acid, followed by hydrolysis of the crude nitration product. This gave 3 : 5-dinitro-*o*-toluidine in 68—91% overall yields from *p*-toluidine. It is to be noted that no nitro-group entered the "*p*-tosyl ring" under these conditions.

TABLE I.

Preparation of N^1-*quinoxalylsulphanilamides from aminoquinoxalines and acetylsulphanilyl chloride.*

	N^4-Acetylsulphonamides.†							Sulphonamides.					
Amino-quin-oxalines.	M. p.	Solvent for recryst.	Analysis. Found, %. C.	H.	N.	S.	Method of hydro-lysis.	M. p.	Solvent for recryst.	Analysis. Found, %. C.	H.	N.	S.
5-Amino-	228—230°	Aq. EtOH	56·2	4·3	16·3	9·4	2·5% Aq. NaOH	163—165°	EtOH	—	—	18·6	10·7
6-Amino-	277 (dec.)	Aq. EtOH	56·2	4·1	16·6	9·6	5% Aq. NaOH	227—229	Aq. acetone	—	—	18·8	10·5
$C_{16}H_{14}O_3N_4S$ requires			56·1	4·1	16·4	9·4		$C_{14}H_{12}O_2N_4S$ requires				18·7	10·7
2-Amino-3-methyl-	—	—	—	—	—	—	Alc. HCl	207	HOAc	57·7	4·7	17·7	9·8
2-Amino-5-methyl-	—	—	—	—	—	—	Alc. HCl	202—204	C_6H_6	—	—	17·7	9·9
5-Amino-7-methyl-	209	$CHCl_3$	—	—	15·6	8·7	Alc. HCl	214—216	EtOH	57·4	4·7	18·1	10·9
6-Amino-2 (or 3)-methyl-	283—285	—	—	—	—	—	Alc. HCl	258	EtOH	57·7	4·6	17·8	10·7
7-Amino-6-methyl-	262—265	—	—	—	—	—	Alc. HCl	219—220	EtOH	57·4	4·5	18·2	10·2
7-Amino-5-methyl-	262	Aq. EtOH	—	—	15·6	—	Alc. HCl	225—227	PrOH	57·5	4·4	18·2	10·2
$C_{17}H_{16}O_3N_4S$ requires					15·7	9·0		$C_{15}H_{14}O_2N_4S$ requires		57·3	4·5	17·8	10·2

† The N^4-acetylsulphonamides were prepared from the corresponding amine and acetylsulphanilyl chloride in dry pyridine.

* *p*-Tosyl is used throughout for toluene-*p*-sulphonyl, except that new compounds are named systematically.

TABLE II.

Preparation of N^1-*quinoxalylsulphanilamides from 2-chloroquinoxalines and sulphanilamide.*

Chloro-quin-oxalines.	Conditions for prep.	Yield, %.	M. p.	Solvent for recryst.	Found, %. C.	H.	N.	S.	Calc., %. C.	H.	N.	S.
2-Chloro- *	5 Hrs. at 165—175° + KI (0·1M) + K_2CO_3 (1M) + Cu in autoclave	82	250—252°†	Aq. dioxan	56·2	4·1	19·0	10·6	56·0	4·03	18·7	10·7
2-Chloro-3-methyl	12 Hrs. at 160—180° + K_2CO_3 (1M) + Cu in autoclave	63	207—209	$COMe_2$	57·7	4·7	17·7	9·8	57·3	4·5	17·8	10·2
2-Chloro-5-methyl	2½ Hrs. at 160—190° + KI (1M) + K_2CO_3 (1M) + Cu in autoclave	—	202—204	C_6H_6	—	—	17·7	9·9	57·3	4·5	17·8	10·2

* Gowenlock, Newbold, and Spring, *loc. cit.*

† Weijlard, Tishler, and Erickson, *loc. cit.*, obtained this compound by hydrolysis of the N^4-acetyl derivative and give m. p. 247—248°.

EXPERIMENTAL.*

2 : 3-, 3 : 4-, *and* 2 : 5-*Dinitroacetanilides.*—These were obtained by nitration of *m*-nitroacetanilide by modifications of the methods of Macciotta (*Ann. Chim. appl.*, 1939, **29**, 81) and Welsh (*J. Amer. Chem. Soc.*, 1941, **63**, 3276). A solution of *m*-nitroacetanilide (10 g.) in fuming nitric acid freed from nitrous acid (25 c.c.) was run into a well-stirred mixture of concentrated sulphuric acid (125 c.c.) and glacial acetic acid (25 c.c.), the temperature being kept between −10° and 0°. While the *m*-nitroacetanilide solution was being run in, a second similar solution was prepared and kept in the freezing mixture until required : this was repeated 5 times until a total of 50 g. of *m*-nitroacetanilide had been added. This procedure was necessary to prevent the latter from reacting with the nitric acid before its addition to the acetic–sulphuric acids (cf. Welsh, *loc. cit.*). After all the nitric acid solution had been added (50 mins.), stirring in the freezing mixture was continued for a further hour. The solution was *slowly* poured into stirred ice-water to give a pale yellow precipitate which was washed free from acid. If the addition to ice-water is carried out too quickly, a sticky mass is obtained which can be dealt with only by dissolution in acetic acid and repouring into water.

2 : 3-Dinitroacetanilide was obtained from this precipitate by crystallisation from benzene–acetone (2 : 1) in 31% yield (19·6 g.), m. p. 187°. 3 : 4-Dinitroacetanilide could be isolated from the more soluble fractions most conveniently by recrystallisation from chloroform, but this was unnecessary since the mixture of 3 : 4- and 2 : 5-dinitroacetanilides (34·4 g., 55%) was converted on hydrolysis and reduction into 1 : 2 : 4-triaminobenzene (used for 6-aminoquinoxaline preparation).

2 : 3-*Dinitroaniline.*—2 : 3-Dinitroacetanilide was hydrolysed with concentrated sulphuric acid at 110° (method of Wender, *Atti Reale Accad. Lincei*, 1889, **5**, I, 540; *Gazzetta*, 1889, **19**, 226).

1 : 2 : 3-*Triaminobenzene.*—2 : 3-Dinitroaniline (45 g.) was added in portions to a solution of stannous chloride (560 g.) in concentrated hydrochloric acid (750 c.c.). After the vigorous reaction had subsided, the solution was heated for 1½ hours on the water-bath, then cooled overnight in the refrigerator. The precipitate was freed from tin with hydrogen sulphide in weakly acid solution to give, on concentration, 1 : 2 : 3-triaminobenzene dihydrochloride (does not melt below 300°; 77—92% yields). The *dipicrate* was obtained as yellow crystals from water (decomp. 183°) (Found : C, 37·4; H, 2·78; N, 21·9. $C_6H_9N_3,2C_6H_3O_7N_3$ requires C, 37·2; H, 2·60; N, 21·7%).

5-*Aminoquinoxaline.*—Glyoxal "sulphate" (42 g.; K. Ott, D.R.-P. 362,743; 1922) was added in portions to a solution of 1 : 2 : 3-triaminobenzene dihydrochloride (25 g.) in aqueous sodium carbonate (800 c.c. of 10%) and the solution was refluxed for 1½ hours. After cooling, it was continuously extracted with ether; removal of the ether after drying (Na_2SO_4) gave the required base, m. p. 85—86° (16·8 g., 81%). Recrystallisation from light petroleum (b. p. 40—60°) gave pale yellow plates, m. p. 87—88°, of the *monohydrate* (Found : C, 59·1; H, 5·54; N, 26·2. $C_8H_7N_3,H_2O$ requires C, 58·9; H, 5·56; N, 25·7%). On drying at 75° in a vacuum it lost 11·5% of its weight ($C_8H_7N_3,H_2O$ requires loss, 11·0%) to give the pale orange anhydrous *base*, m. p. 93—95° (Found : C, 66·3; H, 5·1; N, 28·5. $C_8H_7N_3$ requires C, 66·2; H, 4·86; N, 28·9%), which reverts to the paler monohydrate on exposure to air.

Note on Preparation of 5- *and* 6-*Aminoquinoxalines.*—Instead of separating the isomerides obtained in the nitration of *m*-nitroacetanilide (above) and acting on them separately with glyoxal, the mixture of 2 : 3-, 3 : 4-, and 2 : 5-dinitroanilines can be reduced to the mixed triaminobenzenes and treated with glyoxal. The resulting 5- and 6-aminoquinoxalines were readily separated by extraction with light petroleum, in which the 6-isomeride is insoluble.

6-Aminoquinoxaline was obtained in 79% yield, m. p. 157° (Hinsberg, *Ber.*, 1886, **19**, 1253, gives m. p. 158—159°).

2-Hydroxy-3-methylquinoxaline (Hinsberg, *Annalen*, 1896, **292**, 249), m. p. 245°, was obtained in 77% yield from *o*-phenylenediamine and pyruvic acid in alcoholic solution (Found : C, 67·3; H, 5·1. Calc. for $C_9H_8ON_2$: C, 67·4; H, 5·0%).

2-*Chloro-3-methylquinoxaline.*—Phosphorus oxychloride (600 c.c.) was heated under reflux with 2-hydroxy-3-methylquinoxaline (60 g.) for ¾ hour. The solution was poured cautiously into stirred

* *Added in Proof.*—A paper by Wolf, Bentel, and Stevens (submitted February 24th, 1948) has just appeared (*J. Amer. Chem. Soc.*, 1948, **70**, 2572) in which eight of the compounds recorded here as new are also described.

ice-water and made alkaline with sodium hydroxide solution. The precipitated *2-chloro-3-methylquinoxaline* (m. p. 83—87°; 57 g., 85%) after recrystallisation from light petroleum or sublimation in a vacuum gave colourless needles, m. p. 87° (Found: Cl, 19·9. $C_9H_7N_2Cl$ requires Cl, 19·9%). It is readily soluble in organic solvents.

2-Amino-3-methylquinoxaline.—A solution (300 c.c.) of dry ammonia in absolute alcohol, saturated at 0°, and 2-chloro-3-methylquinoxaline (13·4 g.) were heated in an autoclave for 7 hours at 160—175°. After removal of the alcohol, the solid was washed with cold water and extracted with hot water to give, on cooling, very pale yellow needle clusters of *2-amino-3-methylquinoxaline*, m. p. 163—165° (6·4 g., 54%) (Found: C, 68·2; H, 6·1; N, 25·9. $C_9H_9N_3$ requires C, 67·9; H, 5·7; N, 26·4%). The base can be sublimed in a vacuum and is moderately soluble in organic solvents, but sparingly soluble in hot carbon tetrachloride and in light petroleum.

3-Nitro-*o*-toluidine was prepared by nitration of aceto-*o*-toluidide by Cohen and Dakin's method (*J.*, 1901, **79**, 1127), but the hydrolysis of the resulting mixed nitroacetotoluidides and separation of the 3-nitro- and 5-nitro-*o*-toluidines was carried out according to Gabriel and Thieme (*Ber.*, 1919, **52**, 1080). This gave yields of 45—66% of 3-nitro- and 27—15% of 5-nitro-base.

5- and 8-Methylalloxazines.—Concentrated hydrochloric acid (730 c.c.) was cautiously added during 1 hour to a suspension of 3-nitro-*o*-toluidine (66 g.) and iron filings (110 g.) in water (440 c.c.). The mixture was heated on the water-bath for ½ hour and filtered hot from unreacted iron, and a hot solution of alloxan (70 g.) and boric acid (58 g.) in water (580 c.c.) was added to the filtrate. Within a few minutes a yellow precipitate separated; after 1 hour's heating on the water-bath, water (4 l.) was added, and the yellowish-green mixture of 5- and 8-methylalloxazines (decomp. 315—325°; 50 g., 50%) filtered off. These were separated by fractional crystallisation from acetic acid; the less soluble fractions yielded 8-methylalloxazine, m. p. 298° (Found: C, 57·1; H, 3·78; N, 23·5. Calc. for $C_{11}H_8O_2N_4$: C, 57·8; H, 3·53; N, 24·5%) (cf. Karrer and Musante, *Helv. Chim. Acta*, 1935, **18**, 1140), and from the more soluble fractions there was obtained *5-methylalloxazine*, decomp. 332° (Found: C, 57·7; H, 3·73; N, 23·7%). The latter is contaminated with a small proportion of its 8-isomeride, since on treatment with concentrated sulphuric acid (see below) it gave a small amount of 2-amino-8-methylquinoxaline together with the main product, 2-amino-5-methylquinoxaline.

2-Amino-8-methylquinoxaline.—8-Methylalloxazine (2 g.) was treated with concentrated sulphuric acid (14 c.c.) at 230—240° for 10 mins.; the solution was poured into water, made alkaline with sodium hydroxide, and the product isolated by continous extraction with ether. After recrystallisation from light petroleum (b. p. 60—80°) *2-amino-8-methylquinoxaline* was obtained in very pale yellow crystals, m. p. 129° (Found: C, 67·2; H, 5·9; N, 25·9. $C_9H_9N_3$ requires C, 67·9; H, 5·7; N, 26·4%). The base is soluble in organic solvents and can be sublimed.

2-Amino-5-methylquinoxaline.—(*a*) The mixed crude 5- and 8-methylalloxazines (37 g.) were treated as above with concentrated sulphuric acid. The residue from the ethereal extracts was recrystallised from benzene to yield very pale yellow crystals of *2-amino-5-methylquinoxaline*, m. p. 201—202°, identical with that obtained in (*b*) (Found: C, 67·9; H, 5·9; N, 25·7%). 2-Amino-8-methylquinoxaline was obtained from the more soluble benzene fractions and purified by recrystallisation from light petroleum. The total yield of 2-amino-5- and -8-methylquinoxalines was 4·0 g. (16%).

(*b*) A solution (50 c.c.) of dry ammonia in absolute alcohol, saturated at 0°, and 2-chloro-5-methylquinoxaline (see below; 3 g.) were heated in an autoclave at 145—160° for 15 hours. After evaporation, the residue was extracted with hot light petroleum, and the insoluble portion recrystallised from benzene to yield 2-amino-5-methylquinoxaline, m. p. 202° (1·0 g.), identical with that from (*a*) above.

2-Chloro-5-methylquinoxaline.—2-Hydroxy-5-methylquinoxaline (see below; 5 g.) was heated under reflux with phosphorus oxychloride (50 c.c.) for ¾ hour. The cooled red solution was cautiously poured on ice and finally made alkaline to precipitate a solid, which was crystallised from light petroleum or sublimed in a vacuum to give colourless needles of *2-chloro-5-methylquinoxaline*, m. p. 95° (3·1 g., 56%) (Found: C, 60·2; H, 3·78; N, 16·0; Cl, 19·9. $C_9H_7N_2Cl$ requires C, 60·5; H, 3·95; N, 15·7; Cl, 19·9%).

2-Hydroxy-5-methylquinoxaline.—(*a*) *N*-(3-Nitro-*o*-tolyl)glycine (see below; 5 g.) was treated with concentrated hydrochloric acid (25 c.c.) and tin (5 g.). After completion of the reaction on the water-bath (1 hr.), the solution was diluted, freed from tin, and finally concentrated, whereupon it became pink and deposited a precipitate. Sublimation in a vacuum gave colourless needles of *2-hydroxy-5-methylquinoxaline*, m. p. 286° (Found: C, 67·6; H, 5·1. $C_9H_8ON_2$ requires C, 67·5; H, 5·0%).

(*b*) 2-Hydroxy-5-methylquinoxaline-3-carboxylic acid (5 g.; see below) was heated at 230—245° for ½ hr. The crude product (3·7 g., 95%) on recrystallising from benzene gave 2-hydroxy-5-methylquinoxaline, m. p. 286° (Found: C, 67·6; H, 4·9; N, 17·1%), identical with that in (*a*). This quinoxaline is insoluble in water, slightly soluble in acetone and carbon tetrachloride, more soluble in alcohol, ether, and ethyl acetate and crystallises well from benzene.

N-(3-Nitro-o-tolyl)glycine.—Monobromoacetic acid (47·7 g.; 1 mol.), 3-nitro-*o*-toluidine (101·7 g.; 2 mols.), and zinc chloride (9 g.) were heated together at 125—140° for 3 hours. The red mass, obtained after pouring into water, was extracted several times with hot sodium carbonate solution (leaving a residue of recovered 3-nitro-*o*-toluidine); the combined extracts were acidified, and the precipitate recrystallised from carbon tetrachloride to give scarlet needles of *N-(3-nitro-o-tolyl)glycine*, m. p. 135° (gas evolution at 175°) (10·5 g.; 15% yield calc. from bromoacetic acid) (Found: C, 51·9; H, 4·79; N, 13·1. $C_9H_{10}O_4N_2$ requires C, 51·4; H, 4·79; N, 13·3%).

2-Hydroxy-3-carbethoxy-5-methylquinoxaline.—Iron filings (180 g.) were added in portions to a suspension of 3-nitro-*o*-toluidine (100 g.) in concentrated hydrochloric acid (600 c.c.); after completion of the reaction on the water-bath (½ hr.), water (600 c.c.) was added, unreacted iron removed, and a solution of diethyl mesoxalate monohydrate (100 g.; *Org. Synth.*, Coll. Vol. I, 1941, p. 266) in water (800 c.c.) was added. A precipitate formed at once and after one hour on the water-bath it was filtered off, washed with water, and dried (101 g., 66%). After recrystallisation from carbon tetrachloride, *2-hydroxy-3-carbethoxy-5-methylquinoxaline* formed pale yellow needles, m. p. 225° (Found: C, 62·1; H, 5·50; N, 12·1. $C_{12}H_{12}O_3N_2$ requires C, 62·1; H, 5·21; N, 12·1%). The ester is soluble in most organic solvents, but is insoluble in light petroleum and in cold water.

2-*Hydroxy*-5-*methylquinoxaline*-3-*carboxylic Acid.*—The foregoing ester (105·5 g.) was hydrolysed by heating with sodium hydroxide solution (900 c.c. of 10%) on the water-bath for 1 hr. Acidification yielded the *methyl acid* (93 g., 100%), m. p. 230° (with loss of carbon dioxide) (Found : C, 58·8; H, 4·3; N, 14·0. $C_{10}H_8O_3N_2$ requires C, 58·8; H, 4·0; N, 13·7%). The acid is insoluble or sparingly soluble in most organic solvents and crystallises from 50% acetic acid in yellow prisms.

3 : 5-*Dinitro*-p-*toluidine.*—The method of Ullmann and Gross (*loc. cit.*) was found to be very convenient, giving overall yields from *p*-toluidine of 51% on large batches. It has been confirmed that the more usual nitration of aceto-*p*-toluidide cannot be effected on larger than 20—25 g. batches (Niementowski, *Ber.*, 1886, **19**, 717; Brady, Day, and Rolt, *J.*, 1922, **121**, 527).

5-*Amino*-7-*methylquinoxaline.*—3 : 5-Dinitro-*p*-toluidine (30 g.) and iron filings (90 g.) were suspended in hot alcohol (500 c.c.) and concentrated hydrochloric acid (90 c.c.) was added in small portions. After the vigorous reaction had subsided, the mixture was refluxed for one hour, and the alcohol distilled off. Addition of sodium carbonate solution and filtration gave an aqueous solution of 3 : 4 : 5-triaminotoluene. Glyoxal bisulphite (40 g.) was added, and the solution heated for one hour on the water-bath; yellow-brown crystals separated within a few minutes and later redissolved. After cooling, the crude base was filtered off and extracted with benzene to give 5-*amino*-7-*methylquinoxaline monohydrate* (10 g., 37% overall yield from 3 : 5-dinitro-*p*-toluidine), yellow needles, m. p. 122° (with steam evolution), which after cooling remelt at 103° (Found : C, 61·2; H, 6·22; N, 23·8. $C_9H_9N_3,H_2O$ requires C, 61·0; H, 6·26; N, 23·7%. Found : loss at 60°/25 mm., 10·0. $C_9H_9N_3,H_2O$ requires loss, 10·2%). The anhydrous *base* melts at 103° (Found : C, 67·3; H, 5·9. $C_9H_9N_3$ requires C, 67·9; H, 5·7%); on exposure to air it readily reverts to the monohydrate. It is soluble in the common warm organic solvents and crystallises in yellow needles from light petroleum or water; it can be sublimed in a vacuum.

2(or 3)-*Methyl*-6-*aminoquinoxaline.*—A solution of methylglyoxal (18·4 g.; Riley, Morley, and Friend, *J.*, 1932, 1875) in water (70 c.c.) was added to a solution of 1 : 2 : 4-triaminobenzene dihydrochloride (50 g.) in aqueous sodium carbonate solution (10%; 500 c.c.) and heated for ½ hour on the water-bath; a yellow-green solid was precipitated. This was recrystallised from carbon tetrachloride to give the *base* (19·7 g., 49%) as yellow crystals, m. p. 172°, raised to 173° by passing its benzene solution through alumina (Found : C, 68·5; H, 5·90; N, 26·0. $C_9H_9N_3$ requires C, 67·9; H, 5·70; N, 26·4%). This base can be sublimed in a vacuum; it is readily soluble in acetone and alcohol, moderately soluble in hot benzene and hot water, readily soluble in hot chloroform and ethyl acetate, and very sparingly soluble in hot ether.

5-*Nitro*-2 : 4-*diaminotoluene.*—5-Nitro-2 : 4-bisacetamidotoluene (102 g.; Maron and Salsberg, *Ber.*, 1911, **44**, 3004) was heated with concentrated sulphuric acid (204 c.c.) on the water-bath until a clear solution resulted (1—2 hours). This was poured on ice-water, made alkaline, and the precipitated 5-nitro-2 : 4-diaminotoluene, m. p. 152° (41·3 g., 61%), filtered off.

7-*Amino*-6-*methylquinoxaline.*—Sodium hydrosulphite (dithionite) (100 g.) was added to a suspension of 5-nitro-2 : 4-diaminotoluene (34·2 g.) in warm 50% alcohol (960 c.c.). After completion of the reduction, a solution of glyoxal bisulphite (46·5 g.) in water (700 c.c.) was added, and the whole heated on the water-bath for 2 hours. Addition of alkali precipitated 7-*amino*-6-*methylquinoxaline*, pale orange crystals from benzene, m. p. 194—195° (24·7 g., 76%) (Found : C, 68·1; H, 6·1; N, 25·8. $C_9H_9N_3$ requires C, 67·9; H, 5·7; N, 26·4%). The base is readily soluble in cold acetone, alcohol, chloroform, and ethyl acetate, soluble in hot benzene, carbon tetrachloride, ether, and water, and insoluble in light petroleum.

3 : 5-*Dinitro*-o-*toluidine.*—*p*-Tosyl-*o*-toluidide (85·6 g.) was heated under reflux with nitric acid (240 c.c., 25% w/v) until the solid melted to a red oil and resolidified (12 mins.); concentrated nitric acid (38 c.c.; to give a 35%w/v solution) was added, and heating continued for 1½ hours. After cooling, the supernatant liquid was decanted, the residue was ground under water, filtered off, washed free from acid (this is essential), and dried to give the crude 3 : 5-*dinitro*-2-*toluene*-p-*sulphontoluidide* (97 g., m. p. 145—150°). Recrystallisation from alcohol or benzene gave buff-coloured crystals, m. p. 161—163° (Found : C, 48·0; H, 4·3; N, 12·0; S, 9·2. $C_{14}H_{13}O_6N_3S$ requires C, 47·9; H, 3·7; N, 12·0; S, 9·1%).

Direct reaction of *p*-tosyl-*o*-toluidide with 36% w/v nitric acid gave only a poor yield, while the use of 25% nitric acid alone gave mainly 5-nitro-2-*p*-tosyltoluidide, m. p. 174—175° (lit. m. p. 174°) (Found C, 54·6; H, 4·80; N, 9·4; S, 10·3. Calc. for $C_{14}H_{14}O_4N_2S$: C, 54·9; H, 4·61; N, 9·2; S, 10·5%).

Hydrolysis of the 3 : 5-dinitro-compound (97 g.) with concentrated sulphuric acid (265 c.c.) at 110° for 10 mins. gave 3 : 5-dinitro-*o*-toluidine (52 g., 81% overall yield) (Found : N, 21·2. Calc. for $C_7H_7O_4N_3$: N, 21·3%), m. p. 211—213°, identical with a sample made by McGookin's method (*loc. cit.*).

7-*Amino*-5-*methylquinoxaline.*—3 : 5-Dinitro-*o*-toluidine (5 g.) was suspended in water (60 c.c.) and sodium hydrosulphite (dithionite) (38 g.) added; a vigorous reaction ensued which was finally completed on the water-bath. After the mixture had been made just alkaline, glyoxal bisulphite (6·7 g.) in water (50 c.c.) was added, and the whole heated for 1 hr. on the water-bath. Addition of sodium hydroxide solution to the cooled solution precipitated a yellow solid, m. p. 157—160° (1·2 g., 30%). After purification of its benzene solution through alumina, 7-*amino*-5-*methylquinoxaline* was obtained in yellow crystals, m. p. 158—160° (Found : C, 68·2; H, 5·77; N, 25·7. $C_9H_9N_3$ requires C, 67·9; H, 5·69; N, 26·4%). It is very soluble in cold acetone and glacial acetic acid, moderately soluble in cold ether and ethyl acetate, sparingly soluble in cold benzene and chloroform, and soluble in hot carbon tetrachloride or water.

The authors thank Messrs. D. Latham and C. J. Keattch for assistance with the experimental work. Microanalyses were carried out by Mr. J. McMurray of the Wellcome Chemical Works, Dartford, and by Drs. Weiler and Strauss, Oxford.

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[*Received, January 14th*, 1948.]