744. *The Constitution of Products Formed from* o-*Phenylenediamines and Alloxan in Neutral Solution.*

By F. E. King and J. W. Clark-Lewis.

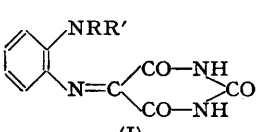
Compounds obtained by the condensation of alloxan with *o*-phenylenediamine and with *N*-methyl- and *N*-phenyl-*o*-phenylenediamine have been shown by methylation studies and the synthesis of degradation products to be quinoxalone-3-carboxyureides and not alloxan-anils (Kühling, *Ber.*, 1893, **26**, 540; Kühling and Kaselitz, *ibid.*, 1906, **39**, 1314; Rudy and Cramer, *ibid.*, 1938, **71**, 1234), thus confirming the structures assigned originally to products of this type by Hinsberg (*ibid.*, 1885, **18**, 1228; *Annalen*, 1896, **292**, 245).

It is well known from the chemistry of riboflavine that the hydrochlorides of diprimary and primary-secondary *o*-phenylenediamines react with alloxan forming respectively alloxazines (Kühling, *Ber.*, 1891, **24**, 2363) and *iso*alloxazines, *e.g.*, 9-methyl*iso*alloxazine (Kuhn and Weygand, *Ber.*, 1934, **67**, 1409). The condensation of alloxan with the free *o*-diamines, on the other hand, follows a different course and gives products which have generally been formulated as alloxan-anils (I). The first thus represented was obtained from 2-amino-5 : 4′-dimethyldiphenylamine (Kühling, *Ber.*, 1893, **26**, 540), and others prepared from *N*-methyl- and *N*-phenyl-*o*-phenylenediamine and *o*-aminodi-*p*-tolylamine were described by Kühling and Kaselitz (*ibid.*, 1906, **39**, 1314). Later, during the researches on riboflavine, similar compounds were obtained from the condensation of alloxan in various mineral acid-free solvents with 4 : 5-dimethyl-2-methylaminoaniline (Kuhn and Reinemund, *Ber.*, 1934, **67**, 1932), 2-L-arabitylamino-4 : 5-dimethylaniline (Kuhn, Weygand, and Rudy, *ibid.*, 1935, **68**, 633), and 4 : 5-dimethyl-2-D-ribitylaminoaniline (Tishler, Wellman, and Ladenburg, *J. Amer. Chem. Soc.*, 1945, **67**, 2165), and they were likewise designated alloxan-anils. Nevertheless, there is little evidence to support the accepted structures of these products of the acid-free condensation of alloxan and *o*-phenylenediamines. Unlike the authentic Schiff's bases, *e.g.* alloxan-5-*p*-dimethylaminoanil (Piloty and Finckh, *Annalen*, 1904, **333**, 37; see King and Clark-Lewis, *J.*, 1951, 3080), they do not undergo hydrolysis to their original components when treated with mineral acids, nor are they cyclised in acid media to alloxazines or *iso*alloxazines. In contrast, alkaline hydrolysis readily yields derivatives of 3-hydroxyquinoxaline-2-carboxylic acid (III; R = H) or the corresponding keto-compound (II; R = alkyl or aryl), so that Hinsberg (*Ber.*, 1885, **18**, 1228; *Annalen*, 1896, **292**, 245), who in a study of quinoxaline formation first examined the action of *o*-phenylenediamine and of its 4-methyl derivative on alloxan, in fact, formulated these products as 3-hydroxyquinoxaline-2-carboxyureides (IV; R = H). Rudy and Cramer (*Ber.*, 1938, **71**, 1234) sought to differentiate between the alternative structures by comparing the products formed, respectively, from *o*-phenylenediamine or *N*-methyl-*o*-phenylenediamine with that obtained from alloxan and *NN*-dimethyl-*o*-phenylenediamine for which an anil formula (I; R = R′ = Me) alone seemed possible. In view of the observed similarity of all three derivatives, Hinsberg's quinoxaline structure was rejected, each compound being represented as an alloxan-anil. However, it has recently been established (King and Clark-Lewis, *loc. cit.*) that through the participation of one of the *N*-methyl substituents of the tertiary amino-group, the condensation of the primary-tertiary *o*-diamines with alloxan actually affords a spiro-compound (V), thus invalidating the argument used by Rudy and Cramer (*loc. cit.*) and necessitating a re-examination of the problem. A further study of these products, including that derived from *N*-phenyl-*o*-phenylenediamine, has shown that in neutral solution the condensation invariably affords 3-hydroxyquinoxaline-2-carboxyureides or its keto-equivalent (cf. IV or VI) as supposed originally by Hinsberg (*loc. cit.*).

The compound prepared from alloxan and *o*-phenylenediamine in aqueous solution was methylated by diazomethane to a colourless product shown by a Zeisel estimation to be an *O*-methyl derivative. Hydrolysis of this ether with cold aqueous sodium hydroxide resulted in the formation of 3-methoxyquinoxaline-2-carboxylic acid (III; R = Me), identified by comparison with an authentic specimen. The latter was obtained from synthetic 3-hydroxyquinoxaline-2-carboxylic acid by treatment with diazomethane, the resulting methyl 3-methoxyquinoxaline-2-carboxylate then being subjected to gentle hydrolysis. It follows that the original compound is a 3-hydroxyquinoxaline, *i.e.* (IV; R = H), the condensation having been accompanied by fracture of the alloxan ring leaving a carboxyureide residue at position 2. The formation of a

methyl ether, *i.e.* (III; R = Me), from 3-hydroxyquinoxaline-2-carboxylic acid is contrary to the experience of Ohle and Gross (*Ber.*, 1935, **68**, 2262) with ethyl 3-hydroxyquinoxaline-2-carboxylate which when treated with diazomethane yields the *N*-methyl derivative.

From *N*-methyl-*o*-phenylenediamine and alloxan in aqueous solution 3 : 4-dihydro-3-keto-4-methylquinoxaline-2-carboxyureide (VI; R = Me) is obtained, the constitution of the product following from its hydrolysis with boiling 2N-hydrochloric acid to 3 : 4-dihydro-3-keto-4-methylquinoxaline-2-carboxylic acid (II; R = Me). This was also synthesised from *N*-methyl-*o*-phenylenediamine and ethyl mesoxalate in the presence of dilute hydrochloric acid (cf. Ohle and Gross, *loc. cit.*), the two specimens being characterised by conversion with diazomethane into the same methyl ester. Methylation of the compounds obtained from both *o*-phenylenediamine and *N*-methyl-*o*-phenylenediamine and alloxan with methyl iodide–potassium carbonate in acetone resulted in the same trimethyl derivative of 3 : 4-dihydro-3-ketoquinoxaline-2-carboxyureide. Obviously one methyl group is attached to the position-4 nitrogen atom, the others being present in the ureido-side-chain, but their precise location has not been ascertained.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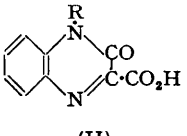
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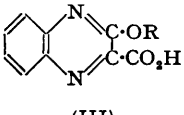
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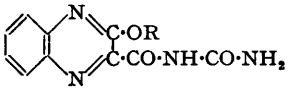

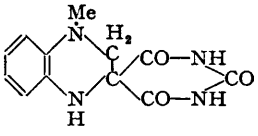
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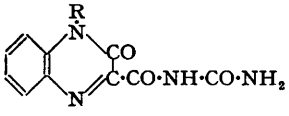

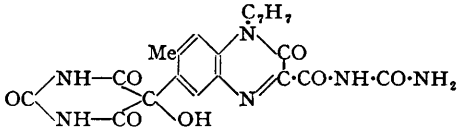
(VII)

Hydrolysis of the trimethyl derivative with aqueous alkali led once more to the formation of 3 : 4-dihydro-3-keto-4-methylquinoxaline-2-carboxylic acid.

The condensation of alloxan with *o*-aminodiphenylamine, described by Kühling and Kaselitz (*loc. cit.*), gave an improved yield of product when aqueous ethanol was used as solvent in place of anhydrous alcohol. Its constitution as 3 : 4-dihydro-3-keto-4-phenylquinoxaline-2-carboxyureide (VI; R = Ph) follows from the resemblance of its ultra-violet spectrum to that of the quinoxalones similarly prepared from *o*-phenylenediamine and the corresponding *N*-methyl base, the curves of all three compounds showing the characteristic quinoxaline maxima and minima recorded by Kuhn and Bär (*Ber.*, 1934, **67**, 898). It is less stable than the latter and when it is dissolved in cold N-alkali, some *o*-aminodiphenylamine is slowly deposited, as well as the 3 : 4-dihydro-3-keto-4-phenylquinoxaline-2-carboxylic acid which is precipitated on acidification of the remaining solution. The dihydroketophenylquinoxalinecarboxyureide is, as expected, unaffected by diazomethane, but gives a dimethyl derivative on methylation by the methyl iodide–potassium carbonate method. With hot aqueous alkali this derivative is very largely degraded to *o*-aminodiphenylamine, isolated as the toluene-*p*-sulphonyl derivative.

These observations may be taken generally to exclude the alloxan-anil formulation in favour of the quinoxalone structure. For example, the compound formed in neutral solution from 5 : 6-diaminoquinoline and alloxan, and represented as an alloxan Schiff's base (Rudy, *Ber.*, 1938, **71**, 847), is doubtless 2-hydroxypyridino(3′ : 2′-5 : 6)quinoxaline-2-carboxyureide or the isomeric pyridino(3′ : 2′-7 : 8)quinoxaline. From the 2-alkylamino-3-aminopyridines, however, Rudy and Majer (*ibid.*, p. 1323) have obtained two series of products, one yellow and unstable, which the authors represent as alloxan-anils, and the other colourless and formed by the ready isomerisation of the former, to which they have assigned the keto-triazanaphthalenecarboxyureide structure. As the dihydroketoquinoxaline-carboxylic acids and -carboxyureides are invariably yellow further data are necessary to determine the precise constitution of these derivatives of 2 : 3-diaminopyridine.

The revision of structure clarifies several previously anomalous features in the chemistry of these products of the neutral condensation of alloxan with *o*-diamines. It is obvious, for

example, why they do not show the properties of a free 2-amino-group expected from their representation as alloxan-anils, and their failure to yield alloxazines (or *iso*alloxazines) when treated with acid is seen to be a natural consequence of the inability of all but the most drastic reagents to effect a ring-closure requiring the interaction of two amido-groups. A compound obtained from alloxan and 2-amino-5 : 4'-dimethyldiphenylamine in hot ethanolic hydrochloric acid, and shown by Kühling (*loc. cit.*) to contain two alloxanyl residues (see also Rudy, *Oest. Chem.-Zeit.*, 1939, **42**, 329), is almost certainly the quinoxalyldialuric acid (VII).

Experimental.

3-*Hydroxyquinoxaline*-2-*carboxyureide* (IV; R = H).—The quinoxalinecarboxyureide was obtained in 90% yield by mixing cold aqueous solutions of equimolecular quantities of alloxan hydrate and *o*-phenylenediamine (Hinsberg, *Ann.*, 1896, **292**, 245). Recrystallisation from acetic acid gave yellow needles, m. p. 250° (decomp.) (Found : C, 52·1; H, 3·8; N, 24·3. Calc. for $C_{10}H_8O_3N_4$: C, 51·7; H, 3·5; N, 24·1%). Ultra-violet light absorption in 95% ethanol : maxima at 234 mμ (ε = 22,900), 312 mμ (ε = 9300), and 393 mμ (ε = 5840); and minima at 218 mμ (ε = 17,500), 270 mμ (ε = 3530), and 350 mμ (ε = 3670).

3-*Methoxyquinoxaline*-2-*carboxyureide* (IV; R = Me).—The ureide (IV; R = H) (3 g.) was treated with excess of ethereal diazomethane, and the suspension filtered after 96 hours. Evaporation of the filtrate gave 3-*methoxyquinoxaline*-2-*carboxyureide*, colourless needles (0·3 g.) (from methanol), m. p. 225°, a further quantity (0·9 g.) of somewhat impure material being obtained from the ether-insoluble residue (Found : C, 54·1; H, 3·9; N, 22·7; OMe, 12·2. $C_{11}H_{10}O_3N_4$ requires C, 53·7; H, 4·1; N, 22·8; OMe, 12·6%).

3-*Methoxyquinoxaline*-2-*carboxylic Acid* (III; R = Me).—(*a*) 3-Methoxyquinoxaline-2-carboxyureide (0·22 g.) dissolved rapidly in cold aqueous sodium hydroxide (10 c.c.; N); after 72 hours at room temperature the solution was acidified with hydrochloric acid (10N), and the precipitated acid (0·143 g., 84%), m. p. 130° (decomp.), collected and recrystallised from hot water (14 c.c.). 3-*Methoxyquinoxaline*-2-*carboxylic acid* was obtained in colourless needles, m. p. 132° (decomp.) (Found : N, 14·3; OMe, 14·8. $C_{10}H_8O_3N_2$ requires N, 13·7; OMe, 15·2%).

(*b*) 3-Hydroxyquinoxaline-2-carboxylic acid (III; R = H), prepared from *o*-phenylenediamine and ethyl mesoxalate in dilute hydrochloric acid solution (Ohle and Gross, *loc. cit.*; Gowenlock, Newbold, and Spring, *J.*, 1945, 622), dissolved rapidly in ethereal diazomethane; after removal of the ether the residue was crystallised from methanol, yielding *methyl* 3-*methoxyquinoxaline*-2-*carboxylate* as colourless needles, m. p. 107° alone or mixed with the methyl ester of the acid derived from (IV; R = Me) (Found : C, 60·6; H, 4·6; N, 12·4. $C_{11}H_{10}O_3N_2$ requires C, 60·5; H, 4·6; N, 12·8%). The methyl ester (0·2 g.) dissolved readily in aqueous sodium hydroxide (12 c.c.; N), and when the solution was acidified with 2N-hydrochloric acid, and the precipitated solid crystallised from hot water, 3-methoxyquinoxaline-2-carboxylic acid (0·15 g., 80%) was obtained; it had m. p. 132° (decomp.), not depressed by the acid obtained from (IV; R = Me).

3-Hydroxyquinoxaline-2-carboxyureide is not only easily hydrolysed by cold 2N-sodium hydroxide, but 3-hydroxyquinoxaline-2-carboxylic acid (0·5 g., 61%), m. p. 268° (decomp.), was obtained when the ureide (1 g.) was boiled with 2N-hydrochloric acid (50 c.c.); the dimethyl derivative obtained with diazomethane had m. p. and mixed m. p. 107°.

3 : 4-*Dihydro*-3-*keto*-4-*methylquinoxaline*-2-*carboxyureide* (VI; R = Me).—A solution of alloxan hydrate (11 g.) in water (50 c.c.) was added to *N*-methyl-*o*-phenylenediamine (7 g.) in ethanol (100 c.c.). Precipitation of a yellow solid (13·4 g., 78%), m. p. 248° (decomp.), began instantly and this was collected after 1 hour. Recrystallisation of the product from acetic acid gave 3 : 4-*dihydro*-3-*keto*-4-*methylquinoxaline*-2-*carboxyureide* (VI; R = Me) in yellow plates, m. p. 247° (decomp.) (Kühling and Kaselitz, *loc. cit.*, give m. p. 224°, and Rudy and Cramer, *loc cit.*, m. p. 250°) (Found : C, 54·1; H, 4·1; N, 23·6. $C_{11}H_{10}O_3N_4$ requires C, 53·7; H, 4·1; N, 22·8%). Ultra-violet light absorption in 95% ethanol : maxima at 236 mμ (ε = 26,100), 317 mμ (ε = 9000), and 387 mμ (ε = 5880); and minima at 219 mμ (ε = 16,900), 268 mμ (ε = 3240), and 348 mμ (ε = 4170).

Methyl 3 : 4-*Dihydro*-3-*keto*-4-*methylquinoxaline*-2-*carboxylate*.—(*a*) The ureide (VI; R = Me) (1 g.) was boiled with 2N-hydrochloric acid (50 c.c.) until dissolution was complete (*ca.* 15 minutes) and thereafter for 10 minutes. 3 : 4-Dihydro-3-keto-4-methylquinoxaline-2-carboxylic acid (II; R = Me) (0·75 g., 90%) crystallised from the cold solution in yellow needles, m. p. 166° raised to 173—174° (decomp.) by recrystallisation from water. Methylation of the acid with ethereal diazomethane gave *methyl* 3 : 4-*dihydro*-3-*keto*-4-*methylquinoxaline*-2-*carboxylate*, which separated from methanol in pale yellow needles, m. p. 126° (Found : C, 60·0; H, 4·4; N, 12·9. $C_{11}H_{10}O_3N_2$ requires C, 60·5; H, 4·6; N, 12·8%).

(*b*) 3 : 4-Dihydro-3-keto-4-methylquinoxaline-2-carboxylic acid m. p. 173—174° (decomp.), was prepared from *N*-methyl-*o*-phenylenediamine and ethyl mesoxalate in N-hydrochloric acid (cf. Ohle and Gross, *loc. cit.*). With diazomethane this yielded the methyl ester as pale yellow needles, m. p. 126° alone or mixed with the product derived from (VI; R = Me).

3 : 4-*Dihydro*-3-*keto*-4-*methylquinoxaline*-2-*carboxydimethylureide*.—(*a*) 3 : 4-Dihydro-3-keto-4-methylquinoxaline-2-carboxyureide (2 g.), anhydrous potassium carbonate (10 g.), methyl iodide (10 g.), and acetone (30 c.c.) were heated under reflux for 24 hours. The mixture was then shaken with water, and the solution extracted with chloroform; the extract when washed, dried, and evaporated yielded an oil which solidified to hard yellow prisms (2·15 g.), m. p. 192°. Recrystallisation from ethanol (50 c.c.) gave 3 : 4-*dihydro*-3-*keto*-4-*methylquinoxaline*-2-*carboxydimethylureide* (1·25 g.), as colourless prisms,

m. p. 194° (Found: C, 57·4; H, 5·3; N, 20·1; OMe, 0; NMe, 23·9. $C_{13}H_{14}O_3N_4$ requires C, 56·9; H, 5·2; N, 20·4; NMe, 31·8%. *M*, determined by Dr. S. C. Wallwork from *X*-ray diffraction, 275; theory, 274). Light absorption in 95% ethanol: maxima at 225 mμ (ε = 30,400) and 302 mμ (ε = 4350); and minimum at 278 mμ (ε = 1950).

(*b*) The methylation of 3-hydroxyquinoxaline-2-carboxyureide (3 g.) with methyl iodide–potassium carbonate for 14 hours gave colourless prisms (1·9 g., 54%), m. p. 194°, identical with the product described above. The methylated ureide was hydrolysed with boiling 2N-sodium hydroxide and, after the solution had been cleared with chloroform, it was acidified and the product extracted with chloroform. The residue left on evaporation of the solvent was crystallised from hot water, which gave 3 : 4-dihydro-3-keto-4-methylquinoxaline-2-carboxylic acid (30%), m. p. 173—174° (decomp.) alone or mixed with an authentic specimen, the methyl ester having m. p. and mixed m. p. 126°.

3 : 4-*Dihydro*-3-*keto*-4-*phenylquinoxaline*-2-*carboxyureide* (VI; R = Ph).—*N*-Phenyl-*o*-phenylenediamine, prepared by shaking *o*-nitrodiphenylamine for 3 hours in hydrogen at 75 lbs./sq. in. over Raney nickel (yield 90%) (cf. Elderfield and McCarthy, *J. Amer. Chem. Soc.*, 1951, **73**, 975), was characterised as 2-(*toluene*-p-*sulphonamido*)*diphenylamine* which crystallised from aqueous ethanol in needles, m. p. 132° (Found: C, 67·7; H, 5·0. $C_{19}H_{18}O_2N_2S$ requires C, 67·4; H, 5·3%). The toluene-*p*-sulphonyl derivative is soluble in aqueous sodium hydroxide and gives a blue-violet colour with nitric acid. 3 : 4-*Dihydro*-3-*keto*-4-*phenylquinoxaline*-2-*carboxyureide* was obtained in 50% yield from the amine and alloxan in aqueous ethanol (cf. Kühling and Kaslitz, *loc. cit.*). The reaction is much faster in aqueous ethanol (*ca.* ½ hour), and the product is not contaminated with the dark green impurity otherwise formed. Crystallisation from aqueous acetic acid gave the ureide (VI; R = Ph) in yellow prisms, m. p. 244° (Found: C, 62·8; H, 3·6; N, 18·2. $C_{16}H_{12}O_3N_4$ requires C, 62·3; H, 3·9; N, 18·2%). Light absorption in 95% ethanol: maxima at 230 mμ (ε = 20,100), 310 mμ (ε = 6600), and 378 mμ (ε = 3960); and minima at 220 mμ (ε = 18,800), 268 mμ (ε = 3680), and 350 mμ (ε = 3450).

A solution of the ureide (0·5 g.) in aqueous sodium hydroxide (25 c.c.; N) was filtered after 3 days from red needles of *N*-phenyl-*o*-phenylenediamine (0·081 g., 27%); acidification of the filtrate gave 3 : 4-dihydro-3-keto-4-phenylquinoxaline-2-carboxylic acid (0·185 g., 43%), m. p. of the unpurified acid 158—160° (decomp.) (cf. Kühling and Kaselitz, *loc. cit.*).

3 : 4-*Dihydro*-3-*keto*-4-*phenylquinoxaline*-2-*carboxydimethylureide*.—The ureide (VI; R = Ph) (8 g.), anhydrous potassium carbonate (24 g.), methyl iodide (24 g.), and acetone (70 c.c.) were refluxed for 18 hours. After addition of water, the product was isolated with chloroform, and when crystallised gave 3 : 4-*dihydro*-3-*keto*-4-*phenylquinoxaline*-2-*carboxydimethylureide* (7·7 g., 88%) as colourless prisms, m. p. 209° (Found: C, 64·0; H, 4·7; N, 16·8; NMe, 12·1. $C_{18}H_{16}O_3N_4$ requires C, 64·1; H, 5·1; N, 16·8; NMe, 17·3%). Light absorption in 95% ethanol: maximum at 301 mμ (ε = 3525); minimum at 279 mμ (ε = 1800).

This carboxydimethylureide (3·4 g.) was heated with ethanol (60 c.c.) and aqueous sodium hydroxide (60 c.c.; 2N) for 3 hours, and the alcohol removed by evaporation on a steam-bath. Extraction of the aqueous solution with ether gave *N*-phenyl-*o*-phenylenediamine (1·4 g., 75%). The base (1·1 g.) was heated on a steam-bath for ½ hour with toluene-*p*-sulphonyl chloride (1·2 g.) and pyridine (5 ml.), and the mixture poured into ice–water. Crystallisation of the precipitate from aqueous ethanol (charcoal) gave 2-(toluene-p-sulphonamido)diphenylamine (0·8 g.) in needles, m. p. 132° alone or mixed with the authentic specimen already described.

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