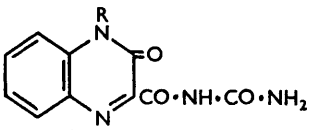
78. *Quinoxaline Derivatives. Part III.* Cyclisation of 3 : 4-Dihydro-3-oxoquinoxaline-2-carboxyureides to 1 : 2 : 3 : 4-Tetrahydro-3-oxoquinoxaline-2-spiro-5′-hydantoins.*

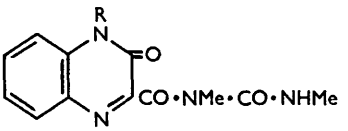
By J. W. Clark-Lewis.

The cyclisation named in the title occurs rapidly under the influence of aqueous sodium carbonate. Methylation of the yellow ureides in acetone–potassium carbonate leads by a similar cyclisation to colourless methyl derivatives of the *spiro*-hydantoins (*e.g.*, III). The constitution of 2 : 2′-*spiro*di-(1 : 2 : 3 : 4-tetrahydro-3-oxoquinoxaline) is discussed.

Reaction of diprimary and primary-secondary *o*-phenylenediamines with alloxan in neutral aqueous or aqueous-ethanolic solution leads to 3 : 4-dihydro-3-oxoquinoxaline-2-carboxyureides [1,2] (I; R = H, alkyl, or aryl), and not to anils as previously assumed.[3–5] The ureides are readily hydrolysed to the carboxylic acids by aqueous sodium hydroxide or acid, and with boiling acetic anhydride give *N*-acylacetamides.[6] Methylation [1] of the yellow ureides (I; R = H and Me) gave the same colourless compound tentatively regarded [6] as the " dimethylureide " (II; R = Me) but now proved to be 1 : 2 : 3 : 4-tetrahydro-4 : 1′ : 3′-trimethyl-3-oxoquinoxaline-2-*spiro*-5′-hydantoin (III; R = Me); an analogous structure (III; R = Ph) is proposed for the colourless " dimethylureide " [6] obtained by methylation [1] of the ureide (I; R = Ph).



(I)



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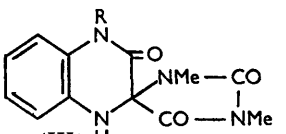

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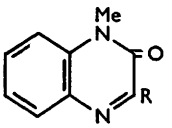

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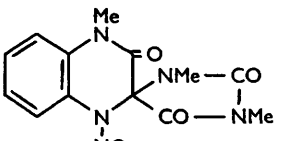

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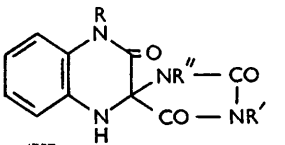


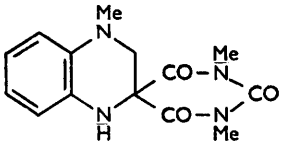
(VI)

The *spiro*hydantoin (III; R = Me) contained one active hydrogen (Zerewitinoff) and three *N*-methyl groups, but no methoxyl groups (Zeisel), and alkaline hydrolysis gave the quinoxaline-2-carboxylic acid (IV; R = CO_2H) as previously reported.[1] Proof of the revised constitution (III; R = Me) was obtained by examination of the *N*-nitroso-compound which, if a nitrosomethylureide derived from (II; R = Me), should yield diazomethane. Alkaline hydrolysis of the nitroso-derivative (V) did not yield diazomethane but gave methylamine (one equivalent) and 1 : 2-dihydro-1-methyl-3-methylamino-2-oxoquinoxaline (IV; R = NHMe) (53%), which was identified by synthesis. These observations show that the methylated ureides have the tricyclic structures (III; R = Me and Ph) formed by cyclisation under the methylation conditions (acetone–potassium carbonate). The acid chloride (IV; R = COCl) derived from synthetic 3 : 4-dihydro-4-methyl-3-oxoquinoxaline-2-carboxylic acid reacted with *NN*′-dimethylurea to

* Parts I and II, King and Clark-Lewis, *J.*, 1951, 3379; *J.*, 1953, 172.

[1] King and Clark-Lewis, *J.*, 1951, 3379.
[2] Hinsberg, *Ber.*, 1885, **18**, 1228; *Annalen*, 1896, **292**, 245.
[3] Kühling, *Ber.*, 1893, **26**, 540; Rudy and Cramer, *Ber.*, 1938, **71**, 1234; 1939, **72**, 227, 728; *Oesterr. Chem.-Ztg.*, 1939, **42**, 329 (cf. ref. 5); Kuhn and Reinemund, *Ber.*, 1934, **67**, 1932; Kuhn, Rudy, and Weygand, *Ber.*, 1935, **68**, 633; Tishler, Wellman, and Ladenburg, *J. Amer. Chem. Soc.*, 1945, **67**, 2165.
[4] Kühling and Kaselitz, *Ber.*, 1906, **39**, 1314.
[5] King and Clark-Lewis, *J.*, 1951, 3080.
[6] *Idem*, *J.*, 1953, 172.

give the *spiro*hydantoin (III; R = Me) directly. Methylation of the ureide side chain is not a prerequisite for cyclisation, however, as the ureide (I; R = Me) gave the tricyclic isomer (VI; R = Me, R′ = R″ = H) when heated with acetone and potassium carbonate, and methylation of the product gave the compound (III; R = Me). Triethylamine proved ineffective as a substitute for potassium carbonate. The *spiro*hydantoins (VI; R′ = R″ = H, R = H, Me, and Ph) are conveniently obtained by warming the ureides (I; R = H, Me, and Ph) with aqueous sodium carbonate, the initially insoluble ureides dissolving as cyclisation proceeds. The light absorption of the *spiro*hydantoins differs from that of the isomeric ureides and is discussed below. The cyclisation of quinoxalonecarboxyureides appears to be a general reaction, and also a new type of hydantoin ring closure; the hydantoins react with diazomethane, as expected, to give the 3′-methyl derivatives (VI; R = alkyl or aryl, R′ = Me, R″ = H). 3-Hydroxyquinoxaline-2-carboxyureide cyclises less readily than the 4-alkyl-3-oxo- and 4-aryl-3-oxo-derivatives, presumably owing to reduction in the double-bond character of the 1 : 2-bond in the former due to lactim–lactam tautomerism. 3-Methoxyquinoxaline-2-carboxyureide did not cyclise but was hydrolysed rapidly to 3-methoxyquinoxaline-2-carboxylic acid by warm aqueous sodium carbonate.



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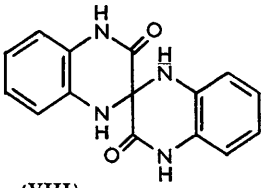
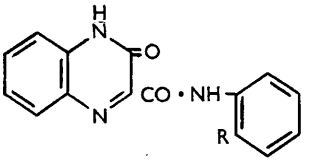


(VIII)



(IX)

The secondary amino-group of the tetrahydroquinoxaline*spiro*hydantoin (III; R = Me) failed to react with acetic anhydride [6] and is therefore sterically hindered to a greater degree than in the analogous *spiro*barbituric acid [5] (VII). The *spiro*hydantoin (III; R = Me) with boiling acetyl chloride gave the 1-acetyl derivative in good yield but was otherwise difficult to acylate (see Experimental section). It was hoped that degradation of derivatives of the hydrazine corresponding to the nitroso-compound (V) would locate the active hydrogen of the secondary amine group in the *spiro*hydantoin (III; R = Me), but zinc–acetic acid reduction of the nitroso-compound did not yield the hydrazine and catalytic hydrogenation at room temperature gave a quantitative recovery of the parent amine.

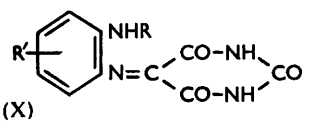
The tetrahydroquinoxaline*spiro*hydantoin (III; R = Me) is more resistant to acid hydrolysis than the ureides (I) and it was recovered (60%) after being boiled for 5 hr. with aqueous-ethanolic hydrochloric acid. It did not however survive the acid hydrolytic conditions necessary for the removal of a toluene-*p*-sulphonyl group and, as it also failed to react with toluene-*p*-sulphonyl chloride, a projected unequivocal synthesis of the 1-toluene-*p*-sulphonyl derivative of (III; R = Me) was abandoned. After the *spiro*hydantoin (III; R = Me) had been heated at 100° with sulphuric and acetic acid the only product isolated was 3 : 4-dihydro-4-methyl-3-oxoquinoxaline-2-carboxymethylamide (IV; R = CO·NHMe) (5%), a compound previously obtained [4] by interaction of *N*-methyl-*o*-phenylenediamine and 1 : 3-dimethylalloxan (which readily undergoes ring fission [7, 8]). This and some related amides were obtained in small yields (in a single experiment) by the reaction of amines with the mixed carboxylic anhydride (IV; R = CO·O·COBu^n), and were prepared more satisfactorily by other standard methods.

1 : 2-Dihydro-1-methyl-3-methylamino-2-oxoquinoxaline (IV; R = NHMe), obtained by degradation of the nitroso-compound (V), was easily prepared by reaction of the corresponding 3-chloro-compound (IV; R = Cl) with aqueous-methanolic methylamine.

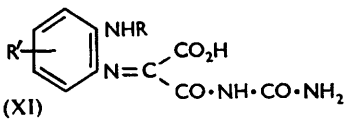
[7] Bredereck and Pfleiderer, *Chem. Ber.*, 1954, **87**, 1119.
[8] Pfleiderer, *ibid.*, 1955, **88**, 1625.

Reaction under similar conditions with ammonia, a weaker base, gave the known 3-methoxyquinoxalone (IV; R = OMe) (88%) and only traces of the 3-amino-compound (IV; R = NH_2).[9]

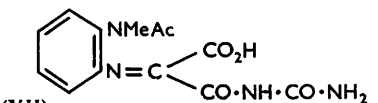
The cyclisation of quinoxalone-2-carboxyureides (I) to tetrahydroquinoxaline-2-*spiro*-5'-hydantoins (VI; R' = R'' = H) is analogous to the formation of 2 : 2'-*spiro*di-(1 : 2 : 3 : 4-tetrahydro-3-oxoquinoxaline) (VIII) from *o*-phenylenediamine (2 mol.) and diethyl mesoxalate (1 mol.). Ohle and Gross [10] have represented the colourless product of this reaction as 2'-amino-3-hydroxyquinoxaline-2-carboxyanilide (IX; R = NH_2) and postulated tautomerism of this with the spiran (VIII). The light absorption is consistent with the existence of the product predominantly or even exclusively as the spiran (VIII), as the absorption is closely similar to that of the tetrahydroquinoxaline*spiro*hydantoins and different from that of the authentic, yellow anilide (IX; R = H), which was prepared for comparison. The resistance of the compound to hydrolysis is also consonant [10] with the spiran structure (VIII). Some reactions of the spiran proceed with fission of one pyrazine ring, *e.g.*, the diacetyl derivative is yellow and its light absorption is closely similar to that of the anilide (IX; R = H), which indicates that it is an acetyl derivative of the *o*-aminoanilide (IX; R = NH_2) and this conclusion is supported by the ready hydrolysis [10] to 3-hydroxyquinoxaline-2-carboxylic acid. The development of a yellow colour when the spiran is heated may also be due to formation of the anilide (IX; R = NH_2) (cf. Ohle and Gross [10]); a similar colour change is seen when the tetrahydroquinoxaline*spiro*hydantoins are heated. There is however no precise evidence for thermodynamically reversible tautomerism of these compounds of the type postulated by Ohle and Gross.[10]



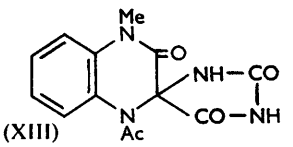
(X)



(XI)



(XII)



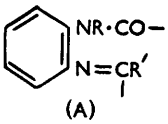
(XIII)

It now appears certain that tetrahydroquinoxaline-2-*spiro*-5'-hydantoins have been obtained previously without recognition of their true nature. Bednarczyk and Marchlewski [11] condensed *o*-phenylenediamine hydrochloride with alloxan in the presence of an excess of sodium acetate and formulated the product as (I; R = H), but the reported light absorption is closely similar to that of the tricyclic isomer (VI; R = R' = R'' = H) which differs considerably from that of the authentic ureide (I; R = H), so that cyclisation of the latter has clearly occurred under the influence of sodium acetate. Kühling and Kaselitz [4] obtained colourless compounds from each of four yellow quinoxalonecarboxyureides by treating them with dilute aqueous sodium hydroxide, but as they regarded the ureides as anils [1] (X) the products were also formulated as anils (XI). From elementary analyses it was concluded that the compounds (XI) suffered partial (in one case complete) dehydration when dried in a desiccator, and that ring closure to the starting materials or " anhydrides " (X) had occurred. The " anhydrides " described by Kühling and Kaselitz are clearly the tetrahydroquinoxaline-2-*spiro*-5'-hydantoins (VI; R' = R'' = H; R = Me and Ph) and 1 : 2 : 3 : 4-tetrahydro-6(and 7)-methyl-3-oxo-4-*p*-tolylquinoxaline-2-*spiro*-5'-hydantoin. The hydrated forms of these " anhydrides " must now be regarded as incompletely dried specimens of the *spiro*hydantoins which, as a class, appear to lose water of crystallisation

[9] Cheeseman, *J.*, 1955, 1804.
[10] Ohle and Gross, *Ber.*, 1935, **68**, 2262; Simpson, " Condensed Pyridazine and Pyrazine Rings," Interscience Publ. Inc., London, 1953, p. 240.
[11] Bednarczyk and Marchlewski, *Bull. Acad. polon. Sci.*, 1938, **506**, *A*, 529.

relatively slowly at 100°. This revision of the structures of the " anhydrides " of (XI) to *spiro*hydantoins instead of anils (X) removes an outstanding anomaly [6,12] in the evidence for the ureide structures (I) of the products formed from *o*-phenylenediamines and alloxan under neutral conditions. It was reported by Kühling and Kaselitz [4] that reaction of the ureide (I; R = Me) with acetic anhydride and acetyl chloride gave an acetyl derivative, which the authors represented as the conversion (X ⟶ XII), involving an improbable hydrolysis under dehydrating conditions. The authentic ureide (I; R = Me) failed to give the reported acetyl derivative, but the isomeric *spiro*hydantoin (VI; R = Me, R′ = R″ = H) reacted rapidly to give the 1-acetyl derivative (XIII), the structure of which was confirmed by methylation to the 1-acetyl derivative of (III; R = Me). As Kühling and Kaselitz failed to distinguish between the *spiro*hydantoin and the ureide there can be little doubt that they used the former in the acetylation and that their acetyl derivative was (XIII).

The light absorption of 1 : 2 : 3 : 4-tetrahydro-3-oxoquinoxaline derivatives (*e.g.*, the *spiro*hydantoins) is of simple aromatic type whereas the derivatives of 3 : 4-dihydro-3-oxoquinoxaline have three bands of absorption which are characteristic and are attributed to the chromophore (A) (Table). The two types of compound are therefore easily distinguished by examination of the absorption spectra. The light absorption of the colourless dimethylamide and methylanilide of 3 : 4-dihydro-4-methyl-3-oxoquinoxaline-2-carboxylic acid is similar to that of the yellow amides, monoalkylamides, and ureides, except for a hypsochromic shift in the position of the absorption maxima in the two longer-wavelength bands.



(A)

Light absorption (*in* 95% *ethanol*). *Wavelength* (mμ) *of maximum absorption* (ε *in parentheses*).

3 : 4-*Dihydro*-3-*oxoquinoxaline derivatives.*

I; R = Me	236 (26,000)	317 (9000)	387 (5900)
IV; R = CO·NH_2	234 (21,000)	301 (7300)	370 (5200)
IV; R = CO·NHMe	234 (20,500)	302 (8900)	369 (6200)
IV; R = CO·NMe_2	232 (23,000)	288 (8100)	353 (6800)
IV; R = CO·NMePh	232 (20,500)	292 (6800)	354 (6700)
IV; R = H	230 (20,300)	282 (5200)	346 (5300)
IX; R = H	233 (35,000)	312 (12,250)	368 (12,600)

1 : 2 : 3 : 4-*Tetrahydro*-3-*oxoquinoxaline derivatives.*

VI; R = Me; R′ = R″ = H	219 (21,300)	300 (4400)
VI; R = R′ = R″ = Me	225 (26,500)	301 (4000)
VI; R = R′ = R″ = H	225 (21,600)	301 (4000)
IV; 1 : 2-dihydro, R = CO·NMePh*	227 (30,000)	300 (3400)
VIII	227 (47,700)	301 (10,200)

* See *J.*, 1957, 439.

Experimental

Light-absorption spectra were determined on solutions in 95% EtOH with a Hilger Uvispek spectrophotometer.

1 : 2 : 3 : 4-*Tetrahydro*-4 : 1′ : 3′-*trimethyl*-3-*oxoquinoxaline*-2-spiro-5′-*hydantoin* (III; R = Me).—(*a*) Heating a stirred mixture of 3-hydroxyquinoxaline-2-carboxyureide [1,2] (40 g.), anhydrous potassium carbonate (75 g.), methyl iodide (32 c.c.), and acetone (500 c.c.) for 24 hr. gave 1 : 2 : 3 : 4-*tetrahydro*-4 : 1′ : 3′-*trimethyl*-3-*oxoquinoxaline*-2-spiro-5′-*hydantoin* (III; R = Me) (41 g., 87%) which crystallised from methanol in prisms, m. p. 194° alone and when mixed with the " dimethylureide " [1,6] prepared from 3 : 4-dihydro-4-methyl-3-oxoquinoxaline-2-carboxyureide (Found : NMe, 27·5; active H, 0·57; OMe, 0. $C_{13}H_{14}O_3N_4$ requires NMe, 31·8; active H, 0·36%). Light absorption : max. 225 (ε 26500) and 301 mμ (ε 4000); min. 276 mμ (ε 1700). The *spiro*hydantoin failed to react at room temperature with acetic anhydride–pyridine, formic–acetic anhydride, toluene-*p*-sulphonyl chloride–pyridine (85% recoveries) and

[12] Barlow, Ing, and Lewis, *J.*, 1951, 3242.

with the last reagent at 100° for 4 hr. (75% recovery). The 1-*acetyl derivative*, obtained by heating the *spiro*hydantoin (2 g.) with boiling acetyl chloride (25 c.c.) for 2 hr., crystallised from methanol in prisms, m. p. 206° (1·85 g., 80%) (Found : C, 57·2; H, 5·2; N, 17·9. $C_{15}H_{16}O_4N_4$ requires C, 57·0; H, 5·1; N, 17·7%). Light absorption : max. 235 (ε 26,000) and infl. 260—270 mμ (ε 6300).

(*b*) A mixture of 3 : 4-dihydro-4-methyl-3-oxoquinoxaline-2-carboxylic acid (2 g.), dry benzene (20 c.c.), and thionyl chloride (10 c.c.) was heated on a steam-bath for 2 hr. before evaporation to dryness under reduced pressure. Dry benzene (40 c.c.) and molten *NN'*-dimethylurea (2 g.) were added to the solid residue, and the mixture (two liquid phases) was boiled for 3 hr. and then kept at room temperature for 14 hr. Evaporation of the organic solution, after washing with aqueous sodium hydrogen carbonate and water, left a residue which crystallised from methanol (charcoal) in colourless prisms (1·8 g., 67%), m. p. 194° alone and when mixed with the compound prepared by method (*a*).

Hydrolyses of the spiro*Hydantoin* (III; R = Me).—(*a*) A solution of the *spiro*hydantoin (2 g.) in ethanol (50 c.c.) and concentrated hydrochloric acid (50 c.c.) developed an orange colour when boiled for 5 hr. After removal of the ethanol, extraction of the aqueous solution with chloroform afforded the *spiro*hydantoin (1·2 g., 60% recovery), m. p. and mixed m. p. 194°, and no acidic material was isolated.

(*b*) A solution of the *spiro*hydantoin (2 g.) in ethanol (90 c.c.) and 10N-sodium hydroxide (10 c.c.) was heated on a steam-bath for 3 hr., then diluted with water (30 c.c.), and the ethanol removed by distillation. Acidification of the aqueous solution with 12N-hydrochloric acid and crystallisation of the precipitate from boiling water (50 c.c.; charcoal) gave 3 : 4-dihydro-4-methyl-3-oxoquinoxaline-2-carboxylic acid (0·58 g., 40%) which crystallised from methanol in large, yellow prisms, m. p. and mixed m. p. 175° (decomp.); decarboxylation at the m. p. afforded 1 : 2-dihydro-1-methyl-2-oxoquinoxaline [4,9] which crystallised from benzene–light petroleum in needles, m. p. 120—121°. Light absorption : max. 230 (ε 20,300), 282 (ε 5200), and 346 mμ (ε 5300); min. 260 (ε 2700) and 308 mμ (ε 2700).

(*c*) A solution of the *spiro*hydantoin (3 g.) in a mixture (12 c.c.) of sulphuric acid (100 c.c.) and acetic acid (45 c.c.) was heated at 100° for 75 min., then poured into ice-water (100 c.c.). The dark solution was kept for 14 hr. before extraction with chloroform, and the residue obtained by evaporation of the chloroform consisted of 3 : 4-dihydro-4-methyl-3-oxoquinoxaline-2-carboxymethylamide [4,8] which crystallised from methanol and from water as a *monohydrate*, yellow prisms (0·122 g., 5%), m. p. 165—166° alone and when mixed with the synthetic material described below (Found : C, 56·7; H, 5·5; N, 18·0. $C_{11}H_{11}O_2N_3,H_2O$ requires C, 56·2; H, 5·6; N, 17·9%). The aqueous solution remaining after extraction with chloroform was basified with sodium hydroxide and extracted with chloroform. Evaporation of the chloroform left a negligible residue, with a carbylamine odour, which was discarded.

1 : 2 : 3 : 4-*Tetrahydro*-4 : 1′ : 3′-*trimethyl*-1-*nitroso*-3-*oxoquinoxaline*-2-spiro-5′-*hydantoin* (V) *and its* 4-*Phenyl Analogue*.—Sodium nitrite (2·2 g.) in water (10 c.c.) was added to a solution of the *spiro*hydantoin (III; R = Me) (6 g.) in acetic acid (40 c.c.) cooled in water; precipitation commenced almost immediately and the *nitroso-compound* (6·4 g., 96%) was collected after 30 min. It decomposed at *ca.* 170°, dissolved with decomposition (nitrous fumes) in hot acetic acid, and crystallised in sparingly soluble yellow elongated leaflets from ethanol (Found : C, 52·1; H, 4·5; N, 23·1. $C_{13}H_{13}O_4N_5$ requires C, 51·5; H, 4·3; N, 23·1%). Hydrogenation of the nitroso-compound (5 g.) in acetic acid over palladised charcoal (5%) gave 3 : 4-dihydro-4 : 1′ : 3′-trimethyl-3-oxoquinoxaline-2-*spiro*-5′-hydantoin (4·5 g., *ca.* 100%), m. p. and mixed m. p. 194°. Reduction of the nitroso-compound suspended in ethanol with zinc dust and acetic acid at room temperature gave smaller recoveries of the *spiro*hydantoin but none of the required hydrazine.

1 : 2 : 3 : 4-*Tetrahydro*-1′ : 3′-*dimethyl*-1-*nitroso*-3-*oxo*-4-*phenylquinoxaline*-2-spiro-5′-*hydantoin* (0·35 g., 65%), which crystallised from methanol in yellow prisms decomposing (gas) indefinitely above 200°, was similarly prepared by the addition of aqueous sodium nitrite to an acetic acid (10 c.c.) solution of 1 : 2 : 3 : 4-tetrahydro-1′ : 3′-dimethyl-3-oxo-4-phenylquinoxaline-2-*spiro*-5′-hydantoin (0·5 g.), which was previously formulated as the isomeric dimethylureide [1,6] (Found : N, 19·2. $C_{18}H_{15}O_4N_5$ requires N, 19·2%).

1 : 2-*Dihydro*-1-*methyl*-3-*methylamino*-2-*oxoquinoxaline* (IV; R = NHMe).—(*a*) 1 : 2 : 3 : 4-Tetrahydro-4 : 1′ : 3′-trimethyl-1-nitroso-3-oxoquinoxaline-2-*spiro*-5′-hydantoin (V) (4·3 g.) was treated with aqueous potassium hydroxide (50%) and covered with ether, and the mixture

was distilled. The ethereal distillate contained methylamine, but no diazomethane, and distillation was continued until no further methylamine distilled (titration equiv., 11·3 c.c. of N-acid; calc. for 1 equiv., 11·3 c.c.). Evaporation of the neutralised distillate left methylamine hydrochloride, m. p. 228°. The needles (1·5 g., 53%) which remained in the distillation flask were collected by filtration, and crystallisation of the solid from methanol afforded 1 : 2-*dihydro*-1-*methyl*-3-*methylamino*-2-*oxoquinoxaline* (1·1 g.), needles, m. p. 158°, which effloresced during drying (Found, in material dried at 80°/vac. : C, 63·4; H, 5·7; N, 22·4%; *M*, 198. $C_{10}H_{11}ON_3$ requires C, 63·5; H, 5·9; N, 22·2%; *M*, 189·2). The m. p. was unaltered by admixture of the product with that synthesised by method (*b*).

(*b*) 3-Chloro-1 : 2-dihydro-1-methyl-2-oxoquinoxaline [9] (0·5 g.) was heated for 2 hr. on a steam-bath with methanol (40 c.c.) and aqueous 25% methylamine (40 c.c.), and the solution was evaporated to dryness under reduced pressure. The residue dissolved completely in 2N-hydrochloric acid and the base was recovered by basification with aqueous ammonia. Crystallisation of the precipitate from water (300 c.c.) afforded needles of 1 : 2-dihydro-1-methyl-3-methylamino-2-oxoquinoxaline (0·4 g., 82%), m. p. 157—158° (Found, in material dried at 110° : C, 63·3; H, 6·0. Calc. for $C_{10}H_{11}ON_3$: C, 63·5; H, 5·9%). The compound sublimes in m. p. capillaries, and at 100° on a water-pump. The *acetyl derivative* crystallised from methanol in needles, m. p. 205°, not depressed by admixture with a specimen prepared by acetylation of the free base obtained by method (*a*) (Found : N, 18·4. $C_{12}H_{13}O_2N_3$ requires N, 18·2%).

1 : 2-Dihydro-3-methoxy-1-methyl-2-oxoquinoxaline [9] (88%), m. p. 123°, was obtained when 3-chloro-1 : 2-dihydro-2-oxoquinoxaline (0·5 g.) was treated with methanol and aqueous ammonia (*d* 0·88) under conditions which with methylamine afforded the 3-methylamino-derivative (Found : OMe, 15·9. Calc. for $C_{10}H_{10}O_2N_2$: OMe, 16·3%). A few mg. of acid-soluble 3-amino-1 : 2-dihydro-1-methyl-2-oxoquinoxaline,[9] m. p. 278° (copper block), were obtained.

1 : 2 : 3 : 4-*Tetrahydro*-4-*methyl*-3-*oxoquinoxaline*-2-spiro-5′-*hydantoin* (VI; R = Me, R′ = R″ = H).—A suspension of 3 : 4-dihydro-4-methyl-3-oxoquinoxaline-2-carboxyureide [1] (2 g.) in water (50 c.c.) containing sodium carbonate (*ca.* 1·5 equiv.) was warmed for a few minutes until dissolution was complete. The filtered solution was acidified with 2N-hydrochloric acid, and the precipitate (1·8 g., 90%) was collected, washed with water, and dried at 110°. This *spiran* crystallised from aqueous ethanol in fine needles, m. p. 238° (decomp.) after becoming yellow above 200° (Found, on material dried for 1 hr. at 110° : C, 52·1; H, 4·4; N, 22·2. $C_{11}H_{10}O_3N_4,\frac{1}{2}H_2O$ requires C, 51·8; H, 4·4; N, 22·0. Found, in material dried at 110°/vac. : C, 52·9; H, 4·4; N, 22·2. $C_{11}H_{10}O_3N_4$ requires C, 53·7; H, 4·1; N, 22·8%). Light absorption : max. 219 (ε 21,000) and 300 mμ (ε 4400); min. 276 mμ (ε 1400). The *spiro*hydantoin was also obtained by heating a suspension of the ureide and potassium carbonate in acetone for 14 hr.

The compound, m. p. 224°, described by Kühling and Kaselitz [4] as " methylaminophenylimino-alloxansäure " is considered to be an imperfectly dried specimen of the above *spiro*hydantoin.

1-*Acetyl*-1 : 2 : 3 : 4-*tetrahydro*-4-*methyl*-3-*oxoquinoxaline*-2-spiro-5′-*hydantoin* (XIII).—The above 4-methylquinoxalone-2-*spiro*-5′-hydantoin (0·3 g.) dissolved during 45 min. in boiling acetyl chloride (3 c.c.) and acetic anhydride (3 c.c.), and the resulting solution was evaporated to dryness under reduced pressure. Crystallisation of the residue from water afforded 1-*acetyl*-1 : 2 : 3 : 4-*tetrahydro*-4-*methyl*-3-*oxoquinoxaline*-2-spiro-5′-*hydantoin* (0·17 g., 50%) in needles, m. p. 294° (decomp., after darkening above 280°), which dissolved readily in aqueous sodium carbonate (Found : C, 54·3; H, 4·4; N, 19·9. $C_{13}H_{12}O_4N_4$ requires C, 54·2; H, 4·2; N, 19·4%). 3 : 4-Dihydro-4-methyl-3-oxoquinoxaline-2-carboxyureide failed to dissolve (1½ hr.) when similarly treated with the acetylating mixture, and apparently unchanged ureide was recovered. It is considered that the acetyl derivative, decomp. 265—270°, described by Kühling and Kaselitz (ref. 4, p. 1324) consisted of the above acetyl*spiro*hydantoin (XIII), notwithstanding the lower decomposition temperature and the recorded percentage of nitrogen.

The acetyl*spiro*hydantoin (0·130 g.) was methylated with methyl iodide by the acetone–potassium carbonate technique, and the suspension was filtered after 14 hr. Evaporation of the acetone and washing of the residue with water left insoluble 1-acetyl-1 : 2 : 3 : 4-tetrahydro-4 : 1′ : 3′-trimethyl-3-oxoquinoxaline-2-*spiro*-5′-hydantoin (0·083 g.), m. p. 204°, which crystallised from methanol in prisms (0·061 g.), m. p. 206° alone and when mixed with the authentic material described above.

1 : 2 : 3 : 4-*Tetrahydro*-4 : 3′-*dimethyl*-3-*oxoquinoxaline*-2-spiro-5′-*hydantoin* (VI; R = R′ = Me, R″ = H).—The *spiro*hydantoin (VI; R = Me, R′ = R″ = H) (1 g.) was treated with an excess of ethereal diazomethane during 48 hr. and the suspension was filtered from a solid (0·5 g.), m. p. 265°. Evaporation of the filtrate and addition of methanol gave a further crop (0·3 g.), m. p. 268°. 1 : 2 : 3 : 4-*Tetrahydro*-4 : 3′-*dimethyl*-3-*oxoquinoxaline*-2-spiro-5′-*hydantoin* is sparingly soluble in water and in ethanol, and crystallises from both solvents in minute needles; it is readily soluble in dimethylformamide and crystallised from aqueous dimethylformamide in needles, m. p. 272—273° (Found: C, 55·7; H, 4·7; NMe, 22·0. $C_{12}H_{12}O_3N_4$ requires C, 55·4; H, 4·7; NMe, 22·3%). The 4 : 3′-dimethyl*spiro*hydantoin (0·3 g.) was methylated with an excess of methyl iodide, acetone, and potassium carbonate for 14 hr., the suspension filtered when cold, and the residue washed with acetone. The acetone filtrate was evaporated and the residue was washed with water and dried at 110°. The product consisted of 1 : 2 : 3 : 4-tetrahydro-4 : 1′ : 3′-trimethyl-3-oxoquinoxaline-2-*spiro*-5′-hydantoin (0·32 g., *ca.* 100%), m. p. 191° alone and when mixed with the material described above. Recrystallisation from methanol raised the m. p. to 194°.

1 : 2 : 3 : 4-*Tetrahydro*-3-*oxoquinoxaline*-2-spiro-5′-*hydantoin* (VI; R = R′ = R″ = H).—A suspension of 3-hydroxyquinoxaline-2-carboxyureide (6·2 g.) in aqueous sodium carbonate was warmed until the solid dissolved and the filtered solution was acidified with 12N-hydrochloric acid. The pale yellow precipitate of 1 : 2 : 3 : 4-*tetrahydro*-3-*oxoquinoxaline*-2-spiro-5′-*hydantoin* (5 g., 82%) was collected and the filtrate (*ca.* 500 c.c.) was discarded. The *spiro*hydantoin crystallised from water containing ethanol, or from aqueous dimethylformamide, in almost colourless fine needles, m. p. 250° (decomp.; yellow above 200°), consisting of the hemihydrate (Found: C, 50·2; H, 4·0; N, 23·0. $C_{10}H_8O_3N_4,\frac{1}{2}H_2O$ requires C, 49·8; H, 3·8; N, 23·2. Found, on material dried at 110°/vac.: C, 51·4; H, 3·8; N, 23·5; loss 3·5. $C_{10}H_8O_3N_4$ requires C, 51·7; H, 3·5; N, 24·1; loss, 3·7%). Light absorption: max. 225 (ε 21,600) and 301 mμ (ε 4000); min. 279 mμ (ε 2800). This *spiro*hydantoin has been described [11] as the isomeric ureide.

The *spiro*hydantoin (1 g.) reacted vigorously with ethereal diazomethane (contrast the isomeric ureide [1]) and after 24 hr. the suspension was filtered from the 4 : 3′-dimethyl derivative (0·1 g.), m. p. 266—268°, raised to m. p. 272—273° by recrystallisation. Evaporation of the filtrate yielded further small quantities of the 4 : 3′-dimethyl compound and a residual gum (0·8 g.) presumably containing the 3-methoxy-3′-methyl isomer, which failed to crystallise.

1 : 2 : 3 : 4-*Tetrahydro*-3-*oxo*-4-*phenylquinoxaline*-2-spiro-5′-*hydantoin* (VI; R = Ph, R′ = R″ = H).—3 : 4-Dihydro-3-oxo-4-phenylquinoxaline-2-carboxyureide [1] (0·1 g.) was dissolved in boiling water (*ca.* 40 c.c.) containing sodium carbonate (*ca.* 1·5 equiv.), and the solution was filtered before acidification with 2N-sulphuric acid. The white precipitate of 1 : 2 : 3 : 4-*tetrahydro*-3-*oxo*-4-*phenyl*-2-spiro-5′-*hydantoin* (0·09 g., 90%), m. p. 225—226° (decomp.), was collected after 24 hr. The compound is freely soluble in ethanol and crystallised from aqueous ethanol in needles, m. p. 225—226° (decomp.) (Found, after prolonged drying at 110°: C, 62·6; H, 4·0; N, 17·9. $C_{16}H_{12}O_3N_4$ requires C, 62·3; H, 3·9; N, 18·2%). The compound, m. p. 228°, described by Kühling and Kaselitz [4] as " phenylamino-phenylimino-alloxansäure " is considered to be an imperfectly dried specimen of the *spiro*hydantoin.

3-*Methoxyquinoxaline*-2-*carboxyureide*, m. p. 225°, was obtained as previously described.[1] Light absorption: max. 246 (ε 20,100), 309 (ε 6500), and 340 mμ (ε 5200); min. 268 (ε 2400) and 330 mμ (ε 5000). It was hydrolysed rapidly by warm aqueous sodium carbonate to 3-methoxyquinoxaline-2-carboxylic acid (67%), m. p. and mixed m. p. 140—142° (decomp.) [lit.,[1] m. p. 132° (decomp.)]. The methyl ester, prepared by reaction with diazomethane, melted at 107° alone and when mixed with methyl 3-methoxyquinoxaline-2-carboxylate.[1]

Amides of 3-*Hydroxyquinoxaline*-2-*carboxylic Acid*.—3-Hydroxyquinoxaline-2-carboxyamide [6] (80%), m. p. and mixed m. p. 308° (decomp.), was prepared by the addition of an excess of aqueous ammonia (*d* 0·880) to ethyl 3-hydroxyquinoxaline-2-carboxylate [13] dissolved in a little methanol. The ammonolysis was quicker than with ethanolic ammonia,[6] and the product was collected after 14 hr. and washed with 2N-hydrochloric acid and with water.

3-*Hydroxyquinoxaline*-2-*carboxymethylamide*. A mixture of ethyl 3-hydroxyquinoxaline-2-carboxylate (2 g.) and aqueous 25% methylamine (20 c.c.) was acidified with 12N-hydrochloric acid after 8 hr. at room temperature; crystallisation of the precipitate (1·6 g.) from water or

[13] Gowenlock, Newbold, and Spring, *J.*, 1945, 622.

aqueous methanol gave 3-hydroxyquinoxaline-2-carboxymethylamide (1·2 g., 65%) in pale yellow prisms, m. p. 310—311° (decomp.; copper block) (Found: C, 59·3; H, 4·5; N, 21·2. Calc. for $C_{10}H_9O_2N_3$: C, 59·1; H, 4·5; N, 20·7%). This amide, m. p. 305—312° (decomp.), was recently obtained [7,8] by interaction of *o*-phenylenediamine and 1 : 3-dimethylalloxan.

3-*Hydroxyquinoxaline*-2-*carboxyanilide* (IX; R = H). 3-Hydroxyquinoxaline-2-carboxyamide (1 g.) was boiled with aniline (10 c.c.) until evolution of ammonia ceased (8—10 hr.) and the cooled mixture was added to an excess of 2N-hydrochloric acid before collection of the crystalline product (1·4 g., *ca.* 100%), m. p. 340° (decomp.). The *anilide* is sparingly soluble in most solvents except dimethylformamide and boiling aniline, and crystallised from aqueous dimethylformamide in yellow needles (1 g.), m. p. 343—345° (decomp.) (Found: C, 68·0; H, 4·0; N, 16·2. $C_{15}H_{11}O_2N_3$ requires C, 67·9; H, 4·2; N, 15·8%). Light absorption: max. 233 (ε 35,000), 312 (ε 12,250), and 368 mμ (ε 12,600); min. 267 (ε 3900) and 334 mμ (ε 11,000).

Amides of 3 : 4-*Dihydro*-4-*methyl*-3-*oxoquinoxaline*-2-*carboxylic Acid*.—3 : 4-*Dihydro*-4-*methyl*-3-*oxoquinoxaline*-2-*carboxyamide* (IV; R = CO·NH_2). A mixture of 3-hydroxyquinoxaline-2-carboxyamide (3·6 g.), anhydrous potassium carbonate (4 g.), dimethyl sulphate (2·0 c.c., 1·1 equiv.), and acetone (100 c.c.) was boiled for 3 hr. and then filtered while hot. The residue was treated with 2N-hydrochloric acid, and the suspension was filtered from the amide (3·2 g., 83%) which crystallised from water in yellow needles, m. p. 254—255° alone and when mixed with a sample prepared [6] by ammonolysis. It was recovered (90%) after attempted further methylation by the same procedure with dimethyl sulphate (2·2 equiv.). Light absorption: max. 234 (ε 21,000), 301 (ε 7300), and 370 mμ (ε 5200); min. 262 (ε 2200) and 332 mμ (ε 3200).

3 : 4-*Dihydro*-4-*methyl*-3-*oxoquinoxaline*-2-*carboxydimethylamide* (IV; R = CO·NMe_2). A solution of the mixed carboxylic anhydride (IV; R = CO·O·COBu^n) was prepared by the addition of triethylamine (1 equiv.) and *n*-butyl chloroformate (1 equiv.) to a dry chloroform solution of 3 : 4-dihydro-4-methyl-3-oxoquinoxaline-2-carboxylic acid (4·5 g.) at 0—10°. After 10 min. an aliquot part (one-third) was treated with an excess of aqueous dimethylamine. The solution was kept for 14 hr. and washed with 2N-hydrochloric acid, aqueous sodium hydrogen carbonate, and water. Evaporation of the organic layer left a residue of the *dimethylamide* (0·32 g., 19%), which crystallised from benzene–light petroleum in needles, m. p. 115° (Found: N, 18·2. $C_{12}H_{13}O_2N_3$ requires N, 18·3%). The dimethylamide is readily soluble in water and in alcohols. Light absorption: max. 232 (ε 23,000), 288 (ε 8100), and 353 mμ (ε 6800); min. 218 (ε 16,100), 264 (ε 4800), and 317 mμ (ε 4300).

3 : 4-*Dihydro*-4-*methyl*-3-*oxoquinoxaline*-2-*carboxymethylamide* (IV; R = CO·NHMe). The methylamide [4,7] (0·66 g., 70%), which crystallised from methanol as the monohydrate in pale yellow needles, m. p. 167—168°, was prepared by methylation of 3-hydroxyquinoxaline-2-carboxymethylamide (0·9 g.) with dimethyl sulphate as described above for the analogous 2-carboxyamide. The compound did not depress the m. p. of the product obtained by hydrolysis of 1 : 2 : 3 : 4-tetrahydro-4 : 1′ : 3′-trimethyl-3-oxoquinoxaline-2-*spiro*-5′-hydantoin as already described, or the m. p. of the methylamide (0·142 g., 9%), m. p. 165—166°, obtained by adding an excess of aqueous methylamine to an aliquot part of the mixed carboxylic anhydride solution prepared as described above for the dimethylamide. Light absorption: max. 234 (ε 20,500), 302 (ε 8900), and 369 mμ (ε 6200); min. 262 (ε 2100) and 332 mμ (ε 4200).

3 : 4-*Dihydro*-4-*methyl*-3-*oxoquinoxaline*-2-*carboxymethylanilide* (IV; R = CO·NMePh). 3 : 4-Dihydro-4-methyl-3-oxoquinoxaline-2-carboxylic acid (3 g.) was warmed with thionyl chloride (10 c.c.) and benzene (20 c.c.) on a steam-bath for 2 hr., and the residue obtained by evaporation to dryness under reduced pressure was dissolved in benzene containing methylaniline. The benzene solution was washed with 2N-hydrochloric acid, aqueous sodium hydrogen carbonate, and water, and then evaporated. The residue of *methylanilide* crystallised from benzene–light petroleum in needles (3·2 g., 75%), m. p. 165° raised to 169° by recrystallisation from the same solvent, or from ethanol in which it is more soluble (Found: C, 70·1; H, 5·1; N, 14·8. $C_{17}H_{15}O_2N_3$ requires C, 69·6; H, 5·2; N, 14·3%). Light absorption: max. 232 (ε 20,500), 292 (ε 6800), and 354 mμ (ε 6700); min. 218 (ε 14,500), 264 (ε 3000), and 318 mμ (ε 4200). The methylanilide (0·23 g., 11%) was also obtained by the addition of methylaniline to an aliquot part of the mixed anhydride solution as described above for the dimethylamide.

2 : 2′-spiro*Di*-(1 : 2 : 3 : 4-*tetrahydro*-3-*oxoquinoxaline*) (VIII).—Ethyl 3-hydroxyquinoxaline-2-carboxylate (1 g.), *o*-phenylenediamine (0·5 g.), ethanol (8 c.c.), and 1 : 1 aqueous acetic acid (2·5 c.c.) were heated at 100° for 20 hr., and the solid was collected by filtration of the hot suspension, washed with acetic acid, and extracted with boiling ethanol (150 c.c.) to remove

coloured impurities. The colourless residue (1 g., 77%) was moderately soluble in hot dimethylformamide and pyridine, and sparingly soluble in other solvents; addition of ethanol to the dimethylformamide solution precipitated 2 : 2′-spiro*di*-(1 : 2 : 3 : 4-*tetrahydro*-3-*oxoquinoxaline*) as a white powder (0·7 g.) which became yellow when heated at 200—250°, and changed form with some decomp. at *ca.* 350°, but did not melt below 375° (Found : C, 63·7; H, 4·7; N, 19·7. $C_{15}H_{12}O_2N_4$ requires C, 64·3; H, 4·3; N, 20·0%). Light absorption : max. 227 (ε 47,700) and 301—302 mμ (ε 10,200); min. 275 mμ (ε 5200). The same compound was obtained by the method described by Ohle and Gross [10] for 2′-amino-3-hydroxyquinoxaline-2-carboxyanilide.

The *spiro*-compound (0·5 g.) was heated with acetyl chloride–acetic anhydride on a steam-bath for 6 hr. The product (0·3 g.) was collected by filtration of the cold suspension and crystallisation from ethanol (50 c.c.) afforded 3-*acetoxyquinoxaline*-2-*carboxy*-o-*acetamidoanilide* (0·15 g.) in yellow needles, m. p. 230° (decomp.) (Found : C, 62·5; H, 4·6; N, 15·1. $C_{19}H_{16}O_4N_4$ requires C, 62·6; H, 4·4; N, 15·4%). Light absorption : max. 232 (ε 33,300), 314 (ε 9400), and 352 mμ (ε 9000); min. 268 (ε 5100) and 332 mμ (ε 8800). The *spiro*-compound dissolved rapidly in boiling acetic anhydride, and crystallisation from ethanol of the residue remaining after evaporation of the acetic anhydride under reduced pressure afforded the *o*-acetamidoanilide, m. p. and mixed m. p. 230° (decomp.).

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