34. *The Constitution of Products formed from o-Phenylenediamines and Alloxan in Neutral Solution. Part II.* Rudy and Cramer's "bis-Barbiturylidene Ether."*

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

The compound previously described as "bis-[5-(1-methyl-2 : 3-dihydrobenzimidazolyl-3)barbituryl-5] ether" (Rudy and Cramer, *Ber.*, 1939, **72**, 227, 728) is shown to be the anhydride of 1 : 2 : 3 : 4-tetrahydro-3-hydroxy-4-methylquinoxaline-2-*spiro*-5'-(hexahydro-2' : 4' : 6'-triketopyrimidine). Similarly, a *pseudo*-base structure, *viz.*, 6 : 7-dichloro-1 : 2 : 3 : 4-tetrahydro-3-hydroxy-4-methylquinoxaline-2-*spiro*-5'-(hexahydro-2' : 4' : 6'-triketopyrimidine), or its anhydride, may be attributed to a previously unidentified product obtained from alloxan and 4 : 5-dichloro-2-dimethylaminoaniline (Barlow, *J.*, 1951, 2226; Barlow, Ing, and Lewis, *ibid.*, p. 3142).

By the action of acetic anhydride on certain quinoxaline-2-carboxyureides, quinoxaline-2-carboxyacetamides are obtained.

It has recently been proved (King and Clark-Lewis, *J.*, 1951, 3080) that the initial condensation product of alloxan with *o*-dimethylaminoaniline is not the anil (I), as supposed by Rudy and Cramer (*Ber.*, 1938, **71**, 1234; 1939, **72**, 227, 728), but the spiran (II; R = H) formed in a unique ring-closure involving an *N*-methyl group. Accompanying the spiran is a sparingly-soluble by-product described by Rudy and Cramer as a "bis-barbiturylidene ether" and believed by them to have the constitution (III). Since the so-called ether can also be prepared merely by the action of molecular oxygen or of alloxan on the primary condensation product, the two compounds are presumably in close structural relationship and it is therefore difficult, with the adoption of the revised expression (II; R = H), to accept the formula (III). On the other hand, oxidation under the specified mild conditions is readily explicable in terms of the spiran structure (II), and further investigation has shown that the supposed ether is the anhydride (IV) of a carbinol-amine (V; R = H) similar in structure to the initial spiran (II; R = H).

The light absorption of the colourless carbinol-amine (V; R = H), which is quite different from that of the yellow spiran (II; R = H) or of the quinoxalinecarboxyureides (King and Clark-Lewis, *J.*, 1951, 3379), resembles the absorption of a product $C_{12}H_{12}O_4N_4Cl_2$ obtained from alloxan and 4 : 5-dichloro-2-dimethylaminoaniline (Barlow, *J.*, 1951, 2226). The dichloro-compound shows a bathochromic shift of about 20 mμ in the position of two subsidiary maxima, but the similarity in light absorption and in the method of preparation clearly favours the analogous structure (V; R = Cl) and this has been confirmed by catalytic dechlorination to (V; R = H). The expression (V; R = Cl) implies an empirical formula $C_{12}H_{10}O_4N_4Cl_2$, which is in better agreement with the reported analytical figures than is the constitution $C_{12}H_{12}O_4N_4Cl_2$ (Barlow, *loc. cit.*; Barlow, Ing, and Lewis, *J.*, 1951, 3242).

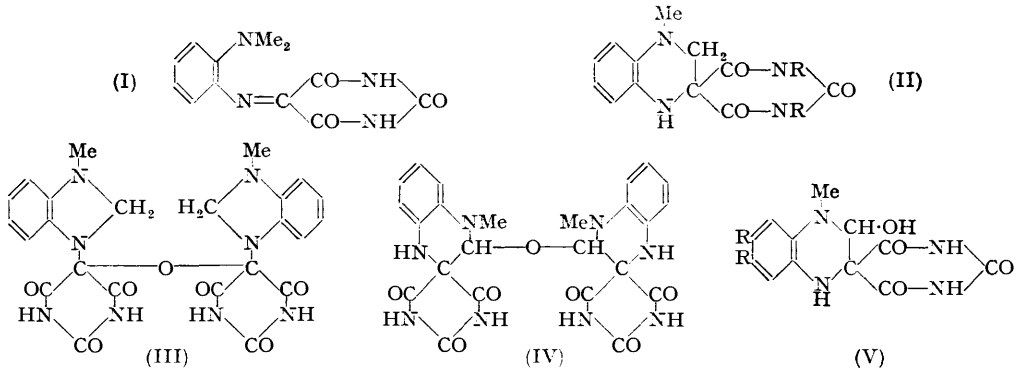
The carbinol-amine (V; R = H) crystallises as a monohydrate, and analyses and a molecular-weight determination by *X*-ray diffraction are in agreement with the molecular formula $C_{12}H_{12}O_4N_4,H_2O$ but the possibility, although remote, that the compound is the anhydride trihydrate cannot be entirely excluded since attempts to obtain the anhydrous base invariably result in the formation of the dimeric anhydride, $C_{24}H_{22}O_7N_8$ (IV). The low solubility of the compound affects the reliability of molecular-weight determinations and the published values (Rudy and Cramer, *loc. cit.*) are discordant and inaccurate. The carbinol-amine $C_{12}H_{10}O_4N_4Cl_2$ which is not solvated similarly yields an anhydride, $C_{24}H_{18}O_7N_8Cl_4$.

The formation of the carbinol-amine (V; R = H) by oxidation with molecular oxygen is comparable with the preparation from strychnine of *pseudo*strychnine (Leuchs, *Ber.*, 1937, **70**, 1543). Proof of the constitution (V; R = H) has been obtained by alkaline hydrolysis which affords 3 : 4-dihydro-3-keto-4-methylquinoxaline-2-carboxylic acid and formic acid. The liberation of formic acid, which also occurs with the dichloro-compound (V; R = Cl), results from the instability of the β-aldehydo-dicarboxylic acid generated on

* Part I, *J.*, 1951, 3379.

hydrolysis of the quinoxaline ring; with the loss of the formyl group, recyclisation and atmospheric oxidation follow, giving the quinoxalinecarboxylic acid.

Salts of the carbinol-amine (V; R = H) are almost completely hydrolysed in water but a hydrogen sulphate of the corresponding anhydro-base was prepared by dissolving the amine in sulphuric acid and then diluting with ethanol. Both carbinol-amines (V; R = H and R = Cl) are resistant to acid hydrolysis, and this provides further evidence against the dihydrobenziminazole structure (III), which, viewed as a diaza-acetal, would be expected to yield formaldehyde under acid conditions. It also indicates that the barbiturate ring is intact in these amines since the ureide side-chain of quinoxaline-2-carboxyureides is readily cleaved by acids (Part I).



Vigorous oxidation of (V; R = H) with hydrogen peroxide in acetic acid yields 1-methylbenziminazole as the final product. Formation of the latter was considered by Rudy and Cramer to be evidence for the dihydrobenziminazole nuclei postulated in their structure (III), but as the compound (II; R = H) behaves similarly under these conditions it is clear that the 1-methylbenziminazole is produced by secondary reactions. Both carbinol-amines failed to give ethers with the simple alcohols, but this may be attributed to their very low solubility in these solvents.

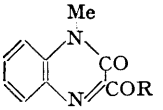
Oxidation of the *NN*-dimethyl derivative (II; R = Me) with molecular oxygen likewise gave a compound resembling the other carbinol-amines, and which from its analysis is either the carbinol-amine hemihydrate, $C_{14}H_{16}O_4N_4,\frac{1}{2}H_2O$, or an ether dihydrate, $C_{28}H_{30}O_7N_8,2H_2O$. 1 : 2 : 3 : 4 : 2′ : 4′-Hexahydro-2′ : 4′-diketo-4 : 3′-dimethylglyoxalino-(1′ : 5′-1 : 2)quinoxaline (*J.*, 1951, 3081, formula III), on the other hand, did not form a carbinol-amine but was oxidised to the orange 2 : 3-dehydro-derivative (*loc. cit.*, formula VII).

It has been observed that in the preparation of the 6 : 7-dichloro-carbinol-base with acetic acid as solvent, a highly coloured by-product is obtained (Barlow, *loc. cit.*); this has now been identified as 6 : 7-dichloro-9-methyl*iso*alloxazine. These two compounds were also formed in aqueous ethanol, but in neither experiment was any of the dichloro-analogue of (II; R = H) detected, apparently because of its great ease of oxidation. The work of Rudy and Cramer (*loc. cit.*) affords other examples, in the 6 : 7-dimethyl series, of this ready oxidation.

As precautions were taken to eliminate secondary amine, it is unlikely that the formation of 6 : 7-dichloro-9-methyl*iso*alloxazine arose from the presence of this impurity; moreover, alloxan and primary-secondary *o*-diamines in neutral solution afford 3-keto-3 : 4-dihydro-4-alkyl(or -aryl)quinoxaline-2-carboxyureides (Part I). Rudy and Cramer have reported the formation of an *iso*alloxazine from the bis-barbiturylidene ether (III) by boiling sodium carbonate solution, and it presumably occurs through hydrolysis to a 5-(*o*-methylamino-phenylamino)barbituric acid followed by cyclisation to the corresponding dihydro*iso*-alloxazine which is then oxidized, *e.g.*, by air. The 6 : 7-dichloro-9-methyl*iso*alloxazine isolated in the present work, therefore, is probably a secondary product derived from the carbinol-amine (V; R = Cl).

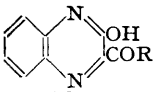
Acetolysis of Quinoxaline-2-carboxyureides.—Condensation of *N*-methyl-*o*-phenylene diamine with alloxan in neutral solution yields 3 : 4-dihydro-3-keto-4-methylquinoxaline-2-

carboxyureide (VI ; R = NH·CO·NH_2) (see Part I), erroneously supposed by Kühling and Kaselitz (*Ber.*, 1906, **39**, 1314) to be an anil. According to these authors the " anil " yields an acetyl derivative, which was represented as (VII) (cf. Barlow, Ing, and Lewis, *J.*, 1951, 3242). We have investigated the action of acetic anhydride on (VI ; R = NH·CO·NH_2) and also on the hydroxyquinoxaline-carboxyureide (VIII ; R = NH·CO·NH_2). Acetolysis occurred in each case, and the structure of the products (VI and VIII ; R = NH·COMe) has



(VI)

(VII ; R = ·NH·CO·NH_2)



(VIII)

been established by synthesis. Thus 3-acetylcarbamyl-1 : 2-dihydro-2-keto-1-methylquinoxaline (VI ; R = NH·COMe) was obtained by the action of acetic anhydride on 3-carbamyl-1 : 2-dihydro-2-keto-1-methylquinoxaline (VI ; R = NH_2), and similarly 3-carbamyl-2-hydroxyquinoxaline (VIII ; R = NH_2) gave 3-acetylcarbamyl-2-hydroxyquinoxaline (VIII ; R = NH·COMe), the products being identical with those derived from the corresponding ureides.

As previously reported (Part I), methylation of the ureides (VI and VIII ; R = NH·CO·NH_2) with methyl iodide affords the identical 3 : 4-dihydro-3-keto-4-methylquinoxaline-2-carboxydimethylureide (VI ; R = dimethylureido), and Zerewitinoff determination has now confirmed the presence of one active hydrogen atom per molecule. Among structures which may be written for a dimethylureide side chain, those containing methoxyl groups can be eliminated since Zeisel determination gave negative results and it is known that compounds of this type containing methoxyl groups readily yield methyl halides (Curd, Davy, and Richardson, *J.*, 1949, 1732, and references quoted there). Two possibilities remain, *viz.*, –CO·NMe·CO·NHMe and –CO·NH·CO·NMe_2. The quinoxaline-carboxydimethylureide (VI ; R = dimethylureido) and its 4-phenyl analogue have now been found to be inert towards acetic anhydride under conditions which cause cleavage of the –CO·NH·CO– group in the unmethylated ureides. It seems probable, therefore, that the grouping –CO·NH·CO– is not present in the dimethylureides (VI), which accordingly must have the alternative side-chain R = NMe·CO·NHMe.

The ultra-violet spectra of (VIII and VI ; R = NH·CO·NH_2) in neutral solution are indistinguishable, but differ from that of 3-methoxyquinoxaline-2-carboxyureide, so that the compound represented as (VIII ; R = NH·CO·NH_2) is probably the alternative 3 : 4-dihydro-3-keto-quinoxaline-2-carboxyureide, *i.e.*, (VI ; R = NH·CO·NH_2, with NH for NMe). The predominance of the lactam over the lactim form has been established in several other heterocyclic systems recently investigated (Marshall and Walker, *J.*, 1951, 1004 ; Hearn, Morton, and Simpson, *ibid.*, p. 3318, 3329).

Experimental

1 : 2 : 3 : 4-*Tetrahydro*-3-*hydroxy*-4-*methylquinoxaline*-2-spiro-5′-(*hexahydro*-2′ : 4′ : 6′-*triketopyrimidine*) (V ; R = H).—(*a*) Alloxan hydrate (40 g., 1·3 mol.), dissolved in water (60 c.c.), was added to a mixture of *o*-dimethylaminoaniline (26·2 g., 1 mol.), ethanol (250 c.c.), and 10N-hydrochloric acid (10 drops), and the solution was kept at room temperature. Filtration after 3 days yielded a mixture from which the yellow spiran (II ; R = H) was extracted with pyridine as previously described (*J.*, 1951, 3080 ; Rudy and Cramer, *loc. cit.*). A solution of the residue (8 g., 15%) in boiling water (charcoal) slowly deposited 1 : 2 : 3 : 4-*tetrahydro*-3-*hydroxy*-4-*methylquinoxaline*-2-spiro-5′-(*hexahydro*-2′ : 4′ : 6′-*triketopyrimidine*) *monohydrate* (6 g., 11%) in colourless needles or prisms, m. p. from 370—375° (decomp.) [Found : C, 48·7 ; H, 5·0 ; N, 18·4 ; NMe, 7·0% ; *M* (by *X*-ray diffraction), 1204/*n* (determination by Dr. S. C. Wallwork). $C_{12}H_{12}O_4N_4,H_2O$ requires C, 49·0 ; H, 4·8 ; N, 19·0 ; NMe, 9·9% ; *M*, 294·2]. Light absorption in H_2O (and in N-HCl) : max. at 250 (ε = 22,800), 270 (ε = 8750), and 277 (ε = 7430) ; min. at 227 mμ (ε = 9250), 268 (ε = 8500), and 274 mμ (ε = 6840).

(*b*) A slow stream of oxygen was passed through a suspension of the spiran (II ; R = H) (1·5 g.) in boiling water (50 c.c.). The yellow solid dissolved during 3—4 hours, and the cold solution deposited the carbinol-base (V ; R = H) (0·9 g., 55%) identical with that obtained by method (*a*) (cf. Rudy and Cramer, *loc. cit.*).

(*c*) The dichloro-compound (V; R = Cl) (1 g.), sodium acetate (1 g., 2·7 mol.), sodium hydrogen carbonate (0·5 g., 2·05 mol.), Raney nickel, and water (60 c.c.) were shaken with hydrogen at 100° ± 10°/120 atm. for 10 hours. The catalyst was removed by filtration (kieselguhr) and washed with hot water, and the combined filtrate was concentrated to 50 c.c. Crystallisation of the deposited solid afforded the hydrated carbinol (II; R = H) (0·239 g., 29%), m. p. and mixed m. p. 372—374° (decomp.). The carbinol does not give the violet colour with hydrogen peroxide–hydrochloric acid characteristic of the spiran (II; R = H). When dried at 160° *in vacuo* for 1 hour or to constant weight at 100—120°, the carbinol-amine hydrate is converted into *di*[(*barbituric acid*)-5-spiro-2′-(1′ : 2′ : 3′ : 4′-*tetrahydro-4′-methylquinoxalin-3′-yl*)] *ether* (IV), m. p. from 370—375° (decomp.) (Found: C, 54·1; H, 4·6; N, 21·4. $C_{24}H_{22}O_7N_8$ requires C, 53·9; H, 4·2; N, 21·0%).

A solution of the carbinol hydrate (1 g.) in concentrated sulphuric acid (5 c.c.) was poured into ethanol. The precipitate (*ca.* 0·5 g.) was collected after 24 hours, and washing with ethanol gave the *quinoxalinium hydrogen sulphate*, decomp. 254° (Found: C, 40·8; H, 3·8; S, 8·2. $C_{12}H_{11}O_3N_4,HSO_4$ requires C, 40·4; H, 3·4; S, 9·0%).

Hydrolysis of 1 : 2 : 3 : 4-*Tetrahydro-3-hydroxy-4-methylquinoxaline*-2-spiro-5′-(*hexahydro-2′ : 4′ : 6′-triketopyrimidine*) (V; R = H).—(*a*) The carbinol-amine (1·25 g.) was boiled with 5N-sodium hydroxide (25 c.c.) until evolution of ammonia ceased. After acidification with 10N-hydrochloric acid the solution was extracted with chloroform from which was isolated 3 : 4-dihydro-3-keto-4-methylquinoxaline-2-carboxylic acid (0·35 g., 38%), crystallising from water in needles, m. p. 170° (decomp.) alone or with an authentic specimen (m. p. and mixed m. p. of the methyl ester, 125°).

(*b*) The carbinol-amine (V; R = H) (1 g.) was hydrolysed as described in (*a*), and the solution acidified with 2N-sulphuric acid. The quinoxaline-carboxylic acid was collected after 24 hours and the filtrate concentrated, the distillation being continued after addition of water (20 c.c.). After titration with 0·1N-sodium hydroxide (32·3 c.c.; 1 mol. of formic acid requires 34·0 c.c.), the resulting sodium salt gave *NN′*-di-*p*-tolylformamidine, m. p. 140—141°, not depressed by admixture with a genuine specimen (Whalley, *J.*, 1948, 1014).

The carbinol-base was not affected by boiling with 2N-hydrochloric acid (3 hours) or ethanolic hydrogen chloride (5%) (8 hours).

1 : 2 : 3 : 4-*Tetrahydro-3-hydroxy-4-methylquinoxaline*-2-spiro-5′-(*hexahydro-2′ : 4′ : 6′-triketo-1′ : 3′-dimethylpyrimidine*).—To 1 : 2 : 3 : 4-tetrahydro-4-methylquinoxaline-2-*spiro*-5′-(hexahydro-2′ : 4′ : 6′-triketo-1′ : 3′-dimethylpyrimidine) (II; R = Me) (0·53 g.) (*J.*, 1951, 3080), dissolved in acetic acid (10 c.c.), water (20 c.c.) was added and oxygen was passed through the boiling solution for 5 hours. Evaporation left a residue which crystallised from 2N-hydrochloric acid, affording 1 : 2 : 3 : 4-*tetrahydro-3-hydroxy-4-methylquinoxaline*-2-spiro-5′-(*hexahydro-2′ : 4′ : 6′-triketo-1′ : 3′-dimethylpyrimidine*) as prisms, m. p. 306—307° (Found: C, 54·1; H, 5·03; N, 18·0. $C_{14}H_{16}O_4N_4,\frac{1}{2}H_2O$ requires C, 53·7; H, 5·47; N, 17·9%). Light absorption in H_2O: max. at 253 (ε = 21,800) and 272 (ε = 7500); min. at 227—228 mμ (ε = 9000) (Found: loss at 110° *in vac.*, 5·0. Formation of $C_{28}H_{30}O_7N_8$ requires loss, 5·8%).

Oxidation of 1 : 2 : 3 : 4-*Tetrahydro-3-hydroxy-4-methylquinoxaline*-2-spiro-5′-(*hexahydro-2′ : 4′ : 6′-triketopyrimidine*) (V; R = H).—Hydrogen peroxide (15%; 3·3 c.c.) was added to aqueous acetic acid (50%; 20 c.c.) containing the carbinol-amine (V; R = H) (3 g.), and the solution evaporated to dryness after 1 hour's boiling. The residue was heated on a steam-bath for 5 hours, than basified with 2N-sodium hydroxide, and the whole extracted with ether. Distillation gave 1-methylbenziminazole (0·6 g., 45%), m. p. 58°, characterised by the picrate, m. p. 247° (decomp.) (Found: C, 47·2; H, 2·9; N, 19·7. Calc. for $C_8H_8N_2,C_6H_3O_7N_3$: C, 46·6; H, 3·1; N, 19·4%), and *picrolonate*, decomp. 254° (Found: C, 54·5; H, 3·9; N, 21·4. $C_8H_8N_2,C_{10}H_8O_5N_4$ requires C, 54·6; H, 4·1; N, 21·2%). M. p.s with specimens prepared from authentic 1-methylbenziminazole were not depressed.

Oxidation of 1 : 2 : 3 : 4-*Tetrahydro-4-methylquinoxaline*-2-spiro-5′-(*hexahydro-2′ : 4′ : 6′-triketopyrimidine*) (II; R = H).—A solution of the spiran (II; R = H) (1 g.) in acetic acid (50%, 40 c.c.) was boiled for 1 hour with hydrogen peroxide (15%, 1 c.c.). 1-Methylbenziminazole (0·25 g., 50%) was isolated and identified as described under (*a*).

4 : 5-*Dichloro*-NN-*dimethyl*-2-*nitroaniline*.—(*a*) 1 : 2 : 4-Trichlorobenzene (100 g.) was slowly poured into nitric acid (*d* 1·5; 300 c.c.), the solution being kept in cold water for 20 minutes. 1 : 2 : 4-Trichloro-5-nitrobenzene, obtained by pouring the solution on ice, crystallised from methanol in needles, m. p. 55—56° (77 g., 61%; cf. Barlow and Ing, *J.*, 1950, 713). A solution of 1 : 2 : 4-trichloro-5-nitrobenzene (52 g., 1 mol.) and dimethylamine (10·3 g., 1 mol.) in ethanol (250 c.c.) was heated in a closed container at 100° for 24 hours. After removal of the solvent,

the residue was extracted with 10N-hydrochloric acid to separate the product from trichloronitrobenzene (25·2 g., 49%). Diluting the acid solution to 2 l. gave 4 : 5-*dichloro*-NN-*dimethyl*-2-*nitroaniline* (20·3 g., 38%; m. p. 82—91°), which separated from light petroleum as orange prisms, m. p. 99—100° (Found: C, 41·2; H, 3·1; N, 11·9%. $C_8H_8O_2N_2Cl_2$ requires C, 40·9; H, 3·4; N, 11·9%). The light petroleum filtrate deposited an isomer (0·7 g.), probably 2 : 5-*dichloro*-NN-*dimethyl*-4-*nitroaniline*, which crystallised in lemon-yellow plates, m. p. 106—107° (Found: C, 41·2; H, 3·5; N, 12·1%). After filtration from the dichloronitro-amines the diluted aqueous solution was extracted with chloroform, to yield a further product (*ca.* 6%), probably 1-*chloro*-2 : 4-*bisdimethylamino*-5-*nitrobenzene*, which crystallised from light petroleum in yellow prisms, m. p. 87—88° (Found: C, 49·8; H, 6·1; N, 17·5. $C_{10}H_{14}O_2N_3Cl$ requires C, 49·3; H, 5·8; N, 17·2%).

(*b*) Heating 1 : 2 : 4-trichloro-5-nitrobenzene (34·2 g.) with dimethylamine in pyridine as described for the preparation of *NN*-dimethyl-*o*-nitroaniline by Campbell (*J. Amer. Chem. Soc.*, 1949, **71**, 740) yielded, after removal of pyridine by distillation, a mixture of bases (34 g.) which was separated as under (*a*) into 4 : 5-dichloro-*NN*-dimethyl-2-nitroaniline (18·1 g., 51%, after crystallisation) and 1-chloro-2 : 4-bisdimethylamino-5-nitrobenzene (7·6 g., 21%). This method is more convenient in manipulation than (*a*).

4 : 5-Dichloro-*NN*-dimethyl-2-nitroaniline was treated with toluene-*p*-sulphonyl chloride in pyridine; the product was indistinguishable from the original nitro-amine (m. p. 99—100°) and no toluene-*p*-sulphonanilide was isolated.

4 : 5-*Dichloro*-2-*dimethylaminoaniline*.—4 : 5-Dichloro-2-nitrodimethylaniline (40 g.) in ethanol (100 c.c.) was reduced with hydrogen at 6 atm. over Raney nickel in 3 hours at room temperature. The catalyst was removed by filtration (kieselguhr), and evaporation gave 4 : 5-*dichloro*-2-*dimethylaminoaniline* (32 g., 92%), b. p. 174—178°/20 mm., n_D^{19} 1·5982, as a colourless oil darkening rapidly in air (Found: C, 46·8; H, 4·8; N, 13·3. $C_8H_{10}N_2Cl_2$ requires C, 46·9; H, 4·9; N, 13·7%). After treatment with toluene-*p*-sulphonyl chloride, the nitro-amine gave 4 : 5-dichloro-2-dimethylaminoaniline, b. p. 166—170°/17 mm., n_D^{25} 1·5985, d^{20} 1·2864, R_D 54·45 (Calc.: R_D 54·71). The *picrate* crystallised from ethanol in yellow prisms, m. p. 179° (Found: C, 39·1; H, 3·1; N, 16·2. $C_8H_{10}N_2Cl_2,C_6H_3O_7N_3$ requires C, 38·7; H, 3·0; N, 16·1%).

6 : 7-*Dichloro*-1 : 2 : 3 : 4-*tetrahydro*-3-*hydroxy*-4-*methylquinoxaline*-2-spiro-5′-(*hexahydro*-2′ : 4′ : 6′-*triketopyrimidine*) (V; R = Cl).—Alloxan hydrate (35 g.), dissolved in water (50 c.c.) containing concentrated hydrochloric acid (5 drops), was added to a solution of 4 : 5-dichloro-2-dimethylaminoaniline (25 g.) in ethanol (250 c.c.). The crystalline product (22·5 g.) was collected after 2 days at room temperature, and further quantities (16 and 5·9 g.) were obtained after 6 and 28 days respectively. The solid, which was insoluble in pyridine, was extracted with boiling acetic acid, leaving the crude *iso*alloxazine (below). The product from the cold solution, after 2 further crystallisations from acetic acid (*ca.* 50 c.c./g.), gave 6 : 7-*dichloro*-1 : 2 : 3 : 4-*tetrahydro*-3-*hydroxy*-4-*methylquinoxaline*-2-spiro-5′-(*hexahydro*-2′ : 4′ : 6′-*triketopyrimidine*) (17 g., 40%) as a felted mat of needles, m. p. 400° (decomp.) (Found: N, 13·6; Cl, 17·3; NMe, 7·4. $C_{12}H_{10}O_4N_4Cl_2,CH_3{\cdot}CO_2H$ requires N, 13·8; Cl, 17·5; NMe, 7·2; loss, 14·8. Found, after drying at 110°: C, 41·5; H, 3·1; N, 16·1; Cl, 20·6; loss, 15·9. $C_{12}H_{10}O_4N_4Cl_2$ requires C, 41·8; H, 2·9; N, 16·2; Cl, 20·6; loss, 14·8%). By more prolonged drying (3 hours at 110°) the carbinol is converted into the anhydride, *di*[(*barbituric acid*)-5-spiro-2′-(6′ : 7′-*dichloro*-1′ : 2′ : 3′ : 4′-*tetrahydro*-4′-*methylquinoxalin*-3′-*yl*)] *ether*, m. p. 400° (decomp.) (Found: C, 42·6; H, 3·0; N, 16·6. $C_{24}H_{18}O_7N_8Cl_4$ requires C, 42·9; H, 2·7; N, 16·7%). The ether was also obtained as rectangular plates, m. p. 400° (decomp.), by boiling the carbinol (V; R = Cl) with nitromethane for 5 minutes (Found: C, 43·7; H, 2·7; Cl, 22·0. Calc. for $C_{24}H_{18}O_7N_8Cl_4$: C, 42·9; H, 2·7; Cl, 21·1%). Ultra-violet light absorption of the carbinol-amine in H_2O: max. at 208 (ε = 30,000), 249 (ε = 18,650), 288 (ε = 6730), and 297 mμ (ε = 6360); min. at 233 (ε = 13,000), 272 (ε = 4010), and 293 mμ (ε = 5720). Comparison of m. p. and ultra-violet light absorption with those of a sample kindly provided by Dr. R. B. Barlow (*loc. cit.*) showed their identity. The carbinol-amine was boiled with 5N-sodium hydroxide for 3 hours, and formic acid identified as in the case of (V; R = H) by conversion into *NN′*-di-*p*-tolylformamidine, m. p. and mixed m. p. 140—141°. The carbinol-amine yields colourless solutions in hot acetic acid and in hot water; it is almost insoluble in the usual organic solvents.

Crystallisation of the reaction product less soluble in acetic acid afforded 6 : 7-*dichloro*-9-*methyl*iso*alloxazine* (*ca.* 2·5 g., 7%), m. p. 346° (decomp.) (Found: C, 44·6; H, 2·1; N, 19·0. $C_{11}H_6O_2N_4Cl_2$ requires C, 44·5; H, 2·0; N, 18·9%). Light absorption in 95% EtOH: max. at 224 (ε = 27,700), 272 (ε = 32,000), 336 (ε = 6540), and 451 mμ (ε = 9410); min. at 240 (ε = 10,200), 302 (ε = 2840), and 376 mμ (ε = 1950).

Oxidation of 1 : 2 : 3 : 4 : 2′ : 4′-*Hexahydro*-2′ : 4′-*diketo*-4 : 3′-*dimethylglyoxalino*(1′ : 5′-1 : 2)-*quinoxaline*.—Oxygen was passed through a boiling solution of the hydantoin (0·85 g.) in acetic acid (10 c.c.) for 1 hour. The solution rapidly developed a dark orange colour, and evaporation to dryness and washing (alcohol) left an orange solid (0·8 g.), m. p. *ca.* 240°. Fractional crystallisation from alcohol and aqueous alcohol removed a small quantity of impure hexahydro-compound (m. p. 146—148°), giving 1 : 4 : 2′ : 4′-tetrahydro-2′ : 4′-diketo-4 : 3′-dimethylglyoxalino(1′ : 5′-1 : 2)quinoxaline, m. p. 256°, not depressed by the authentic material, m. p. 260° (*J.*, 1951, 3080). Similarly the light absorptions of both specimens in alcoholic solution were identical: light absorption of an $8·77 \times 10^{-5}$ M-solution in 95% EtOH: max. at 218 (ε = 15,650), 225—226 (ε = 15,230), 266 (ε = 12,700), 281·5 (ε = 12,500), 343 (ε = 5470), and 437 mμ (ε = 6390); min. at 216 (ε = 14,850), 224 (ε = 15,100), 245 (ε = 8220), 278 (ε = 12,080), 307 (ε = 1700), and 365 mμ (ε = 1280). The extinction coefficients decreased with dilution, presumably owing to a diminished association of the molecules.

3-*Acetylcarbamyl*-1 : 2-*dihydro*-2-*keto*-1-*methylquinoxaline* (VI; R = NH·COMe).—(*a*) 3 : 4-Dihydro-3-keto-4-methylquinoxaline-2-carboxyureide (VI; R = NH·CO·NH_2) (3 g.) was boiled with acetic anhydride (50 c.c.) for 3½ hours, *i.e.*, 1 hour after solution was complete. A product (2 g., 66%) separated in the cold as yellow needles, m. p. 190°; recrystallisation from ethanol gave 3-*acetylcarbamyl*-1 : 2-*dihydro*-2-*keto*-1-*methylquinoxaline* in yellow needles, m. p. 222° (Found: C, 58·7; H, 4·6; N, 17·2. $C_{12}H_{11}O_3N_3$ requires C, 58·8; H, 4·5; N, 17·1%). After storage for 3 months the material formerly melting at 190° had m. p. 222°.

(*b*) Methyl 3 : 4-dihydro-3-keto-4-methylquinoxaline-2-carboxylate (0·5 g.) (*J.*, 1951, 3379) was dissolved in excess of alcoholic ammonia (10%), and the precipitate was collected after 4 hours. 3-*Carbamyl*-1 : 2-*dihydro*-2-*keto*-1-*methylquinoxaline* (VI; R = NH_2) crystallised from water in pale yellow needles (0·25 g., 50%), m. p. 254—255° (Found: C, 59·2; H, 4·5; N, 20·2. $C_{10}H_9O_2N_3$ requires C, 59·1; H, 4·5; N, 20·7%). The amide (0·13 g.) was boiled with acetic anhydride (5 c.c.) for 30 minutes and the acetyl derivative (0·075 g., 48%), m. p. 190°, collected from the cold solution (Found: C, 58·4; H, 4·4; N, 17·0%). Crystallised from ethanol, it had m. p. 222° alone or mixed with the material prepared by method (*a*).

2-*Acetylcarbamyl*-3-*hydroxyquinoxaline* (VIII; R = NH·COMe).—(*a*) 3-Hydroxyquinoxaline-2-carboxyureide (VIII; R = NH·CO·NH_2) (3 g.) dissolved in *ca.* 5 hours when boiled with acetic anhydride (50 c.c.); boiling was then continued for 1 hour. Later, 2-*acetylcarbamyl*-3-*hydroxyquinoxaline* (0·8 g., 26%) was collected, and it crystallised from ethanol in yellow leaflets, m. p. 268° (decomp.) (Found: C, 57·5; H, 4·2; N, 18·1. $C_{11}H_9O_3N_3$ requires C, 57·1; H, 3·9; N, 18·2%). Evaporation of the filtrate and extraction of the residue with ethanol yielded further quantities of (VIII; R = NH·COMe), together with a colourless compound (0·4 g., 13%), rapid m. p. 266—267° (decomp.), probably an *acetyl* derivative of 3-hydroxyquinoxaline-2-carboxylic acid (Found: C, 56·9; H, 3·8; N, 12·1. $C_{11}H_8O_4N_2$ requires C, 56·9; H, 3·5; N, 12·1%).

(*b*) Ethyl 3-hydroxyquinoxaline-2-carboxylate (Gowenlock, Newbold, and Spring, *J.*, 1945, 622—625) (3 g.) in alcohol (20 c.c.) was mixed with alcoholic ammonia (10%; 50 c.c.). Amide formation (0·8 g., 31% after 4 hours; 98% after 72 hours) was much slower than with (VI; R = OMe) (above). 2-*Carbamyl*-3-*hydroxyquinoxaline*, which is sparingly soluble in hot water, crystallised in pale yellow needles, m. p. 308° (decomp.) (Found: C, 57·3; H, 3·7; N, 21·8. $C_9H_7O_2N_3$ requires C, 57·1; H, 3·7; N, 22·2%). Acetylation by boiling acetic anhydride for 30 minutes gave 2-acetylcarbamyl-3-hydroxyquinoxaline (68%), yellow leaflets, m. p. 266° (decomp.), alone and when mixed with the material obtained by method (*a*).

3-Hydroxyquinoxaline-2-carboxylic acid resists acetylation, the acid being recovered from short boiling with acetic anhydride. After 2½ hours' boiling, 2-hydroxyquinoxaline (25%), m. p. 270°, was obtained. Ethyl 3-hydroxyquinoxaline-2-carboxylate (2 g.) was boiled with acetic anhydride (20 c.c.) for 3 hours and the solution then evaporated to dryness. Repeated crystallisation from aqueous ethanol yielded original material (1·4 g., 70% recovery) and the more soluble *ethyl* 3-*acetoxyquinoxaline*(or 4-*acetylquinoxalone*)-2-*carboxylate* in colourless needles, m. p. 88—90°, clearing at *ca.* 130° (Found: C, 60·3; H, 4·3; N, 11·3. $C_{13}H_{12}O_4N_2$ requires C, 60·0; H, 4·6; N, 10·8%).

Quinoxaline-2-*carboxydimethylureides and Acetic Anhydride*.—3 : 4-Dihydro-3-keto-4-methylquinoxaline-2-carboxydimethylureide, which contains one active hydrogen atom (Found: active H, 0·46. Calc. for $C_{13}H_{14}O_3H_4$: active H, 0·36%), was recovered (75%) after 2½ hours' heating with acetic anhydride. In a similar experiment with the 4-phenyl analogue (Part I) the recovery was 80%.

THE UNIVERSITY, NOTTINGHAM. [*Received, September 19th*, 1952.]