## 60. The Application of the Hofmann Reaction to the Synthesis of Heterocyclic Compounds. Part I. Synthesis of Alloxazine from Quinoxaline-2 : 3-dicarboxylic Acid.

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Quinoxaline-2 : 3-dicarboxylic acid is converted into *methyl quinoxaline-2 : 3-dicarboxylate* and thence into *quinoxaline-2 : 3-dicarboxyamide* (X). Treatment of this diamide with two molecular proportions of potassium hypobromite in excess of alkali yields alloxazine (XII) in 60% yield. When treated with one molecular proportion of potassium hypobromite in excess of alkali, the diamide (X) yields 2-aminoquinoxaline-3-carboxylic acid (XI, R = H) in 70% yield.

Various preparations of 2 : 4-dihydroxypyrimidine derivatives by the action of alkaline hypohalite solution upon 1 : 2-dicarboxyamides have been described in the literature.* The first example of the reaction was observed by Hoogewerff and van Dorp (*Rec. Trav. chim.*, 1891, **10**, 4; 1896, **15**, 107), who obtained 2 : 4-dihydroxyquinazoline (II) by the interaction of equimolecular proportions of potassium hypobromite and phthalamide (I) in alkaline solution. Similarly, cinchomeronamide (IV), when treated with two molecular proportions of potassium hypobromite in alkaline solution, gives a mixture of 3-aminopyridine-4-carboxylic acid and 2 : 4-dihydroxycopazoline (V) (Blumenfeld, *Monatsh.*, 1895, **16**, 702; Gabriel and Colman, *Ber.*, 1902, **25**, 2831). The general reaction has been applied to succinamide and *C*-substituted succinamides, which give dihydrouracil and substituted dihydrouracils respectively (Weidel and Roitner, *Monatsh.*, 1896, **17**, 174; van Dam, *Rec. Trav. chim.*, 1896, **15**, 101; McRae, Weston, and Hubbs, *Canadian J. Res.*, 1937, **15**, B, 434; McRae and McGinnis, *ibid.*, 1940, **18**, B, 90), to maleamide, which is thereby converted into uracil (Rinkes, *Rec. Trav. chim.*, 1927, **46**, 268), and to pyrazine-2 : 3-dicarboxyamide (VI), which yields 2 : 4-dihydroxypteridine (VII) (Gabriel and Sonn, *Ber.*, 1907, **40**, 4857). A variation of the general reaction is the conversion of *o*-cyanobenzamide (III) into 2 : 4-dihydroxyquinazoline (II) (Braun and Tcherniac, *Ber.*, 1907, **40**, 2709) and of 5-cyano-2-methyl*iso*nicotinamide (VIII) into 2 : 4-dihydroxy-6-methylcopazoline (IX) (Reider and Elderfield, *J. Org. Chem.*, 1942, **7**, 286).

This series of investigations was undertaken in order to examine the scope of the general reaction, more particularly to examine its application to the synthesis of condensed pyrimidine ring systems of the type present in certain naturally occurring products, and finally to examine obvious modifications of the general reaction with a view to the synthesis of heterocyclic systems other than pyrimidine. The present communication describes a synthesis of alloxazine (XII) by the action of alkaline potassium hypobromite upon quinoxaline-2 : 3-dicarboxyamide (X).

(I.) (II.) (III.) (IV.) (V.)

(VI.) (VII.) (VIII.) (IX.)

(X.) (XI.) (XII.)
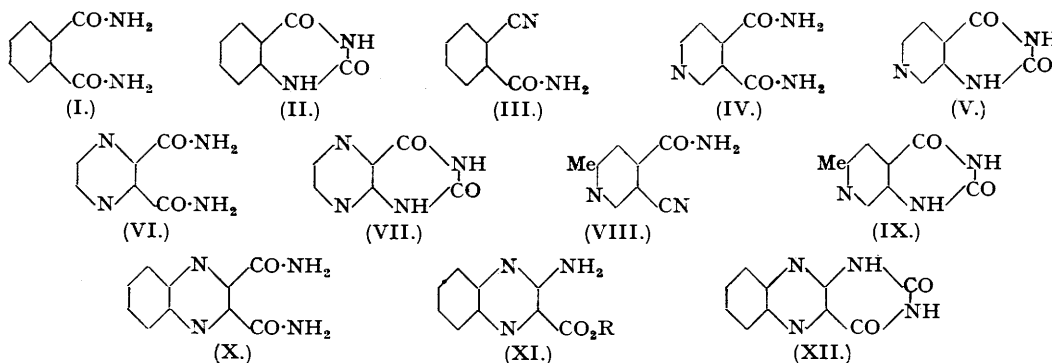
Methyl quinoxaline-2 : 3-dicarboxylate has been prepared by Ohle and Gross (*Ber.*, 1935, **68**, 2262) and the corresponding ethyl ester has been prepared by Chattaway and Humphrey (*J.*, 1929, 645). Ohle and Gross obtained the methyl ester by condensing *o*-phenylenediamine with the crude product obtained by oxidation of methyl dihydroxymaleate with quinone, presumably a condensation of methyl diketosuccinate with *o*-phenylenediamine. According to these authors methyl quinoxaline-2 : 3-dicarboxylate has m. p. 325° and is insoluble in alcohol. Chattaway and Humphrey obtained the ethyl ester by direct esterification of quinoxaline-2 : 3-dicarboxylic acid and according to these authors it has m. p. 83° and is very easily soluble in alcohol. We attempted to prepare the ethyl ester by condensing *o*-phenylenediamine with ethyl diketosuccinate. The crude product was difficult to purify and after many crystallisations gave 2 : 3-dihydroxyquinoxaline. Many variations in the conditions employed for the condensation did not lead to the required ester. The condensation of ethyl 1-chloro-2-ketobutyrate with *o*-phenylenediamine was then examined in order to establish conditions for the direct synthesis of ethyl 2-methylquinoxaline-3-carboxylate, a reaction which involves oxidation and is analogous to a number of well-known pyrazine syntheses. It was hoped that a similar condensation of ethyl chloro-oxaloacetate with *o*-phenylenediamine would give ethyl quin-

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* The corresponding reaction leading to the formation of 5-substituted hydantoins from *C*-substituted malonamides will be discussed in a later communication.

oxaline-2 : 3-dicarboxylate. In alcoholic solution ethyl 1-chloro-2-ketobutyrate and *o*-phenylenediamine gave a high yield of 2-methylbenziminazole hydrochloride. When the condensation was carried out in the presence of an aqueous suspension of calcium carbonate, the required ethyl 2-methylquinoxaline-3-carboxylate was obtained. The yield, however, was extremely low and the route was abandoned in favour of the successful one described below.

We next investigated the direct esterification of quinoxaline-2 : 3-dicarboxylic acid with methyl alcohol, this alcohol being chosen since in general methyl esters are amidated more easily than ethyl esters. *Methyl quinoxaline*-2 : 3-*dicarboxylate* was obtained in high yield, but the properties of this ester—m. p. 130°, easily soluble in alcohol—are markedly different from those of the product described under this name by Ohle and Gross. Methyl quinoxaline-2 : 3-dicarboxylate was characterised by hydrolysis to quinoxaline-2 : 3-dicarboxylic acid and by conversion into *quinoxaline*-2 : 3-*dicarboxyamide* (X), m. p. 328°, by treatment with methanolic ammonia.

Treatment of quinoxaline-2 : 3-dicarboxyamide with one molecular proportion of potassium hypobromite in alkaline solution gave 2-aminoquinoxaline-3-carboxylic acid (XI) in 70% yield. When treated with two molecular proportions of hypobromite in alkaline solution, however, the diamide gave alloxazine (XII) in similar yield; the alloxazine was characterised by conversion into its dimethyl derivative by treatment with diazomethane. The same remarkable difference in the course of the reaction between a dicarboxyamide and alkaline hypobromite solution according as one or two molecular proportions of the latter are employed has been previously observed in the case of pyrazine-2 : 3-dicarboxyamide by Gabriel and Sonn (*loc. cit.*) and confirmed in this laboratory by Mr. G. T. Newbold.

The conversion of a 1 : 2-dicarboxyamide into a 2 : 4-dihydroxypyrimidine derivative is an intramolecular application of the reaction whereby a monocarboxyamide is converted into an alkyl acylurea (Hofmann, *Ber.*, 1881, **14**, 2725; 1882, **15**, 407, 752, 762; Turpin, *Ber.*, 1888, **21**, 2488; Odenwald, *Annalen*, 1918, **416**, 228; 1919, **418**, 316) by successive treatment with bromine and alkali :
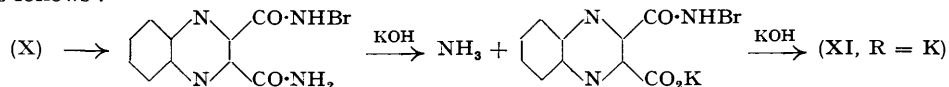
$$2R \cdot CO \cdot NH_2 + Br_2 + 2KOH \longrightarrow R \cdot CO \cdot NH \cdot CO \cdot NHR + 2KBr + 2H_2O \quad (A).$$

Applied to a dicarboxyamide, this reaction is expressed by the formula :

$$X\!\!<^{CO \cdot NH_2}_{CO \cdot NH_2} + Br_2 + 2KOH \longrightarrow X\!\!<^{CO-NH}_{NH \cdot CO} + 2KBr + 2H_2O$$
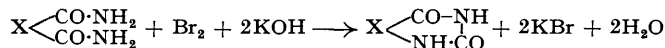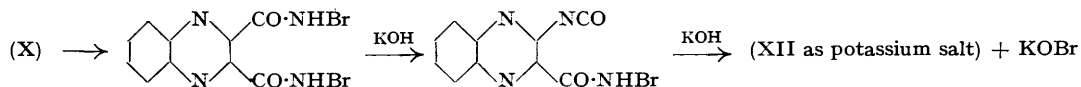
It has been assumed that the formation of an alkyl acylurea is to be attributed to the addition of acid amide to the intermediate *iso*cyanate (Hofmann, *loc. cit.*; see also Hoogewerff and van Dorp, *Rec. Trav. chim.*, 1896, **15**, 111; Graebe and Rostovzeff, *Ber.*, 1902, **35**, 2747), but this suggested mechanism cannot be considered satisfactory since Jeffreys (*Amer. Chem. J.*, 1899, **22**, 14) and Stieglitz and Earle (*ibid.*, 1903, **30**, 412) have shown that an *iso*cyanate does not react with an acid amide under conditions comparable with those employed in the Hofmann reaction. Stieglitz and Earle showed that an *iso*cyanate reacts vigorously with a *N*-halogen acid amide in the presence of alkali with formation of an alkyl acylurea :

$$R \cdot NCO + R \cdot CO \cdot NHBr + KOH \longrightarrow R \cdot NH \cdot CO \cdot NH \cdot COR + KOBr$$
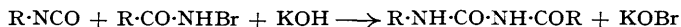
and assumed that the regenerated hypohalite reacts with more acid amide, the reaction proceeding to completion according to the proportions expressed in (*A*). This suggested mechanism offers an equally satisfactory explanation of the formation of 2 : 4-dihydroxyquinazoline (II) from phthalamide by treatment with one molecular proportion of hypohalite. A significant fact in considering the abnormal behaviour of quinoxaline-2 : 3-dicarboxyamide is that when this compound is treated in the cold with one molecular proportion of hypobromite in excess of alkali, ammonia is immediately produced, although no such evolution of ammonia occurs on dissolving the amide either in alkali alone or in a solution containing two molecular proportions of hypobromite in excess of alkali. This behaviour suggests that the " one mole " reaction proceeds as follows :

(X) $\longrightarrow$ [structure: quinoxaline with CO·NHBr and CO·NH₂] $\xrightarrow{KOH}$ NH$_3$ + [structure: quinoxaline with CO·NHBr and CO₂K] $\xrightarrow{KOH}$ (XI, R = K)

the mono-*N*-bromoamide being hydrolysed in alkaline solution with evolution of ammonia, the formation of which limits the reaction to amino-acid formation and excludes alloxazine formation. The " two mole " reaction is assumed to proceed by the steps :

(X) $\longrightarrow$ [structure: quinoxaline with CO·NHBr and CO·NHBr] $\xrightarrow{KOH}$ [structure: quinoxaline with NCO and CO·NHBr] $\xrightarrow{KOH}$ (XII as potassium salt) + KOBr

This reaction proceeds under very mild reaction conditions. In one experiment the diamide was treated with two molecular proportions of potassium hypobromite in alkaline solution at 0°, and the resulting solution maintained at this temperature for 72 hours; the potassium salt of alloxazine had then separated in 60% yield. After removal of this salt the resulting solution contained only one-fifth of a mole of hypobromite. The explanation of this low hypobromite content was forthcoming when it was found that, after

a suspension of equimolecular proportions of alloxazine in alkaline potassium hypobromite solution had been maintained at 0° for 24 hours, the hypobromite content of the solution fell to half the original value.

<div align="center">EXPERIMENTAL.</div>

2-Methylbenziminazole from o-*Phenylenediamine and Ethyl* 1-*Chloro*-2-*ketobutyrate*.—A solution of the ester (3·4 g.; 1/50 mol.) and the diamine (2·2 g.; 1/50 mol.) in absolute alcohol (10 c.c.) was refluxed for 3 hours. The residue obtained after evaporation (vacuum) of the mixture on the steam-bath was triturated with ether (50 c.c.). The solid product, which contained nitrogen and chlorine, was collected and washed with ether. It was very soluble in water and alcohol and insoluble in ether and benzene and did not melt below 300° (yield, 2·5 g.). This hydrochloride was dissolved in the minimum volume of water, and the base liberated by the addition of sodium hydroxide solution; 2-methylbenziminazole separated as needles, m. p. 173—175°, which after one recrystallisation from benzene–light petroleum attained the constant m. p. 175°, undepressed by an authentic specimen (Found : C, 72·3; H, 6·2. Calc. for $C_8H_8N_2$: C, 72·7; H, 6·1%).

Ethyl 2-*Methylquinoxaline*-3-*carboxylate frôm* o-*Phenylenediamine and Ethyl* 1-*Chloro*-2-*ketobutyrate*.—A mixture of the diamine (2·2 g.), the ester (3·4 g.), calcium carbonate (1 g.), and water (25 c.c.) was heated on the steam-bath for 8 hours. Carbon dioxide was slowly evolved. After standing overnight, the product crystallised. It was collected, washed with a little water, and recrystallised from hot water to give ethyl 2-methylquinoxaline-3-carboxylate as feathery needles, m. p. 72—73° (yield, 10%), which gave a negative halogen test. After sublimation at 60—70°/760 mm. the ester was obtained as long needles, m. p. 73°. Wahl and Doll (*Bull. Soc. chim.*, 1913, **13**, 468) give m. p. 73° for ethyl 2-methylquinoxaline-3-carboxylate obtained by condensation of o-phenylenediamine with ethyl diketobutyrate (Found : N, 13·4. Calc. for $C_{12}H_{12}O_2N_2$: N, 13·0%).

2 : 3-*Dihydroxyquinoxaline from* o-*Phenylenediamine and Ethyl Diketosuccinate*.—A solution of the ester (3·85 g.) in absolute alcohol (5 c.c.) was added to a warm solution of the diamine (2·2 g.) in absolute alcohol (10 c.c.). Reaction was instantaneous and proceeded with evolution of heat and the separation of a solid. When the reaction was complete the solid (3·5 g.) was collected and washed with alcohol. After repeated crystallisation from water it gave 2 : 3-di-hydroxyquinoxaline as long needles not melting above 360°. It was freely soluble in dilute sodium hydroxide solution; its appearance and solubility properties were indistinguishable from those of an authentic specimen (Found : C, 59·05; H, 3·9; N, 17·7. Calc. for $C_8H_6O_2N_2$: C, 59·3; H, 3·7; N, 17·3%). The condensation was also effected (*a*) in benzene solution, (*b*) in aqueous suspension, and (*c*) in aqueous-alcoholic solution, in each case with the same result. Condensation of o-phenylenediamine and ethyl diketosuccinate under the conditions used by Wahl and Doll (*loc. cit.*) for the preparation of ethyl 2-methylquinoxaline-3-carboxylate from ethyl 1 : 2-diketobutyrate and o-phenylenediamine, also led to 2 : 3-dihydroxyquinoxaline.

Methyl Quinoxaline-2 : 3-*dicarboxylate*.—Quinoxaline-2 : 3-dicarboxylic acid was prepared by the method of Chattaway and Humphrey (*loc. cit.*); it had m. p. 190° (decomp.) and was characterised by conversion into the anhydride (yellow needles, m. p. 251°) by treatment with acetic anhydride. The acid (2 g.) was heated under reflux with methanolic hydrogen chloride (2%; 20 c.c.) for 2 hours. The solution was concentrated to half bulk (vacuum) and then poured into saturated sodium bicarbonate solution (20 c.c.). The ester was collected by filtration and purified by crystallisation from methanol, *methyl quinoxaline*-2 : 3-*dicarboxylate* (1·8 g.) separating as plates, m. p. 130° (Found : C, 58·7; H, 4·3; N, 11·2. $C_{12}H_{10}O_4N_2$ requires C, 58·5; H, 4·1; N, 11·4%). The methyl ester was converted into quinoxaline-2 : 3-dicarboxylic acid (m. p. and mixed m. p.) by heating with 10% aqueous potassium hydroxide solution for 1 hour on the water-bath, followed by acidification of the solution.

Quinoxaline-2 : 3-*dicarboxyamide*.—A solution of methyl quinoxaline-2 : 3-dicarboxylate (1·7 g.) in cold absolute methanol (70 c.c.) was saturated with dry ammonia. The product began to separate almost immediately and after standing overnight it was collected. After one recrystallisation from water the *diamide* separated as needles, m. p. 328° (decomp.) (yield, 93%) (Found : C, 55·6; H, 3·9. $C_{10}H_8O_2N_4$ requires C, 55·55; H, 3·7%).

2-*Aminoquinoxaline*-3-*carboxylic Acid*.—Quinoxaline-2 : 3-dicarboxyamide (1·08 g.) was dissolved with cooling in a mixture of water (14 c.c.) and potassium hypobromite solution (14 c.c.; 1 mol.); ammonia was immediately evolved. [The hypobromite solution used in this and the next experiment was prepared by adding bromine (16 g.) to aqueous potassium hydroxide solution (10%; 280 c.c.) at 0°. The hypobromite present was estimated by titration, and the solution found to contain 13·2 g. of potassium hypobromite.] The solution was kept at 0° overnight and then heated for 1 hour at 75—80°. No separation of solid had occurred at 0° after several hours. The clear solution was acidified with acetic acid, and the yellow solid collected, washed with water, and crystallised from aqueous acetic acid, 2-amino-quinoxaline-3-carboxylic acid separating as yellow needles, m. p. 212—213° (decomp.) either alone or when mixed with a specimen prepared by Mr. A. H. Gowenlock, using an unambiguous route to be described later (yield, 70%). Philips (*Ber.*, 1895, **28**, 1657) gives m. p. 210° (decomp.) for 2-aminoquinoxaline-3-carboxylic acid (Found : N, 22·4. Calc. for $C_9H_7O_2N_3$: N, 22·2%).

Alloxazine.—Quinoxaline-2 : 3-dicarboxyamide (1·08 g.) was dissolved at 0° in potassium hypobromite solution (28 c.c.; 2 mols.; see previous experiment) and maintained at this temperature overnight. The formation of ammonia could not be detected. The mixture was then maintained at 75—80° for 1 hour and cooled to 0°. After standing overnight, a heavy precipitate of the potassium salt of alloxazine had separated. This was collected, washed with ice-water (halogen test negative), dissolved in a minimum volume of hot water, and the solution acidified with acetic acid. The precipitated alloxazine was collected and combined with the material obtained by acidification of the mother-liquor from the potassium salt. It was purified by solution in aqueous sodium hydroxide (5%) and acidification of this solution with acetic acid. Alloxazine was obtained as a pale yellow powder which blackened above 300° but did not melt below 360° (yield, 60%) (Found : C, 55·8; H, 3·1; N, 26·2. Calc. for $C_{10}H_6O_2N_4$: C, 56·1; H, 2·8; N, 26·2%). A suspension of this product (0·15 g.) in dry ether (50 c.c.) was treated with an ethereal solution of diazomethane (from 2 c.c. of nitrosomethylurethane). The slow evolution of nitrogen was complete after standing overnight. The mixture was evaporated to dryness, and the residue washed with dilute sodium hydroxide solution and water and crystallised from alcohol to give 2 : 3-dimethylalloxazine as small yellow prisms, m. p. 236—237°, undepressed by a specimen prepared by methylation of authentic alloxazine; Kuhn and Bar (*Ber.*, 1934, **67**, 904) give m. p. 238° (corr.) for dimethylalloxazine (Found : C, 59·8; H, 4·4; N, 22·7. Calc. for $C_{12}H_{10}O_2N_4$: C, 59·5; H, 4·1; N, 23·1%).

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