184. *Structure and Antimalarial Activity. Part II.* iso*Alloxazines, Quinoxalines, and Quinoxalo*cyclo*pentadienes.*

By D. Muriel Hall and E. E. Turner.

Condensations of substituted *o*-phenylenediamines with (1) alloxan and (2) 1 : 3-diphenyl*cyclo*pentane-2 : 4 : 5-trione gave *iso*alloxazines and quinoxalo*cyclo*pentadienes. 5 : 6-Diaminoquinoline has been prepared and condensed with glucosone and other 1 : 2-diketones to give quinoxalines. 7-*Chloro*-2 : 3-*di*-(m-*aminophenyl*)-*quinoxaline* has been prepared. None of these compounds showed antimalarial activity.

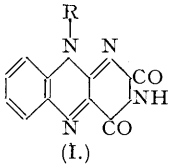
As long as the exact causes of antimalarial activity remain obscure, it is worth while to prepare compounds whose general molecular pattern has some resemblance to that of a compound of established activity, for example, atebrine. Consequently, we have investigated the possibility of obtaining 9-substituted *iso*alloxazines (I) in which R is a series of dialkylaminoalkyl groups.

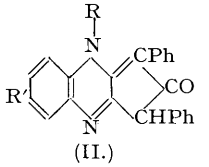
Condensation of *m*-amino-*N*-methyl-*p*-toluidine with alloxan was effected by two of the known methods for *iso*alloxazine synthesis (*A*, Kuhn and Reinemund, *Ber.*, 1934, **67**, 1932; *B*, Kuhn and Weygand, *ibid.*, 1935, **68**, 1282) to give 6 : 9-*dimethyl*iso*alloxazine*, but attempted condensation of *N*-(δ-diethylamino-α-methylbutyl)-*o*-phenylenediamine by method *A* (*i.e.*, in presence of aqueous hydrochloric acid) resulted in the elimination of the *N*-substitutent and formation of alloxazine. Method *B* (condensation in acetic-boric acid solution) led to a product, the constitution of which has not been established.

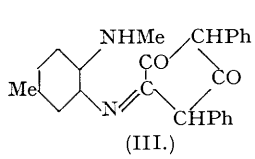
Condensation of *N*-methylalloxan with *m*-amino-*N*-methyl-*p*-toluidine by method *A* proceeded normally to give 3 : 6 : 9-*trimethyl*iso*alloxazine*, isolated as the *monohydrate*. Elimination of the *N*-substituent again occurred in an attempt to condense *N*-(δ-diethylamino-α-methylbutyl)-*o*-phenylenediamine with *N*-methylalloxan by method *A*, the product thus being 3-methylalloxazine, while method *B* led to an obscure result. Attempted condensation of 4- and 5-chloro-*N*-(δ-diethylamino-α-methylbutyl)-*o*-phenylenediamine or of *N*-(γ-diethylaminopropyl)-*o*-phenylenediamine with alloxan failed to give a definite product.

None of the compounds isolated exhibited antimalarial activity

In a second investigation alloxan was replaced by 1 : 3-diphenyl*cyclo*pentanetrione. Condensation of this ketone with *o*-phenylenediamine took place in alcoholic solution, as found by Chakravarti (*J. Indian Chem. Soc.*, 1925, **2**, 71): use of formic or acetic acid as condensation solvent led to no improvement. In this way 1 : 3-*diphenyl*-4′-β-*hydroxyethyl*-2-*keto*-1 : 2 : 3′ : 4′-*tetrahydroquinoxalo*-2′ : 3′ : 4 : 5-cyclo*pentadiene* was obtained (II; R = CH_2·CH_2·OH; R′ = H). Condensation of the trione with *m*-amino-*N*-methyl-*p*-toluidine in alcoholic-hydrochloric acid or alcoholic-glacial acetic acid gave the desired compound (II; R = R′ = CH_3) but in alcohol or in alcoholic–formic acid a second product was formed, namely 5-(2′-*methylamino*-5′-*methylanilo*)-2 : 4-*diphenyl*cyclo*pentane*-1 : 3-*dione* (III), and this compound could not be caused to undergo cyclisation to (II). A related observation was made by Kuhling and Kaselitz (*Ber.*, 1906, **39**, 1314) in connection


(I.)

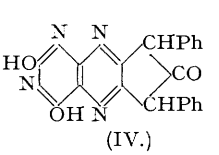

(II.)


(III.)

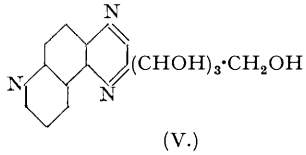
with the mode of condensation of alloxan with *N*-substituted *o*-diamines. The compound (III), which could clearly exist in numerous forms, was actually isolated in two interconvertible modifications. The various compounds of type (II) did not give water-soluble hydrochlorides and were therefore tested for antimalarial activity as suspensions in 5% aqueous gelatin. No activity was observed. Attempts to introduce as R substituent in (II) dialkylaminoalkyl groups were unsuccessful.

Condensation of 4 : 5-diaminouracil (sulphate) with 1 : 3-diphenyl*cyclo*pentanetrione in aqueous acetic acid gave 6′ : 8′-dihydroxy-1 : 3-diphenyl-2-keto-1′ : 4′ : 5′ : 7′-tetra-azanaphtho-2′ : 3′ : 4 : 5-*cyclo*pentene (IV), which was isolated as the *sodium* salt. In this form it proved to have no antimalarial activity.

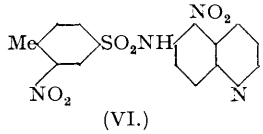
It seemed desirable to attempt the synthesis of a compound combining basic and carbohydrate function. The interaction of glucosone with 5 : 6-diaminoquinoline was investigated. The only product isolated, which appeared to be the desired substance, (V) (or the obvious structural isomeride), was formed in low yield and could not be satisfactorily purified. The quinoxalines formed by condensing 5 : 6-diaminoquinoline with benzil and with phenanthraquinone were devoid of antimalarial activity.



(IV.)



(V.)



(VI.)

During the preparation of 5 : 6-diaminoquinoline certain statements in the literature were found to be inexact. Kaufmann and Zeller (*Ber.*, 1917, **50**, 1626) reported that nitration of 6-*p*-toluenesulphonamidoquinoline with 60% nitric acid at 70° gave a product, m. p. 168—169°, which was said to analyse correctly for the mononitro-compound and which hydrolysed to give 5-nitro-6-aminoquinoline. Rudy (*Ber.*, 1938, **71**, 847) stated that the yield of nitration product by this method was variable, but he gave neither melting point nor analytical details. We find that the procedure of Kaufmann and Zeller, even with various normal modifications, leaves 6-*p*-toluenesulphonamidoquinoline unaffected. Nitration at a low temperature of the *p*-toluenesulphonyl compound with freshly distilled fuming nitric acid, freed from nitrous acid, is now found to give 5-*nitro*-6-o-*nitro*-p-*toluenesulphonamidoquinoline* (VI), which can be hydrolysed in good yield to 5-nitro-6-aminoquinoline, the constitution of which follows from its production by the nitration of 6-o-*nitro*-p-*toluenesulphonamidoquinoline*. 5-Nitro-6-aminoquinoline could not be caused to react with either *p*-toluenesulphonyl chloride or *o*-nitro-*p*-toluenesulphonyl chloride.

In a related investigation involving the use of 4-chloro-*o*-phenylenediamine it was found that the conditions given by Holleman (*Rec. trav. chim.*, 1915, **34**, 204) or de Bruyn (*ibid.*, 1916, **36**, 126) for mono-nitration of *p*-chloroacetanilide led to a mixture of mono- and di-nitro-compounds. Suitable conditions for mono-nitration are now described. From the 4-chloro-*o*-phenylenediamine, by usual methods, 7-*chloro*-2 : 3-*di*-(m-*aminophenyl*)*quinoxaline* was prepared. Its hydrochloride showed no antimalarial activity.

The pharmacological tests were carried out by Dr. Ann Bishop of the Molteno Institute on *Plasmodium relictum* and by Miss I. Tonkin of the National Institute for Medical Research on *P. gallinaceum*.

Experimental.

6 : 9-*Dimethyl*iso*alloxazine* was prepared by the method of Kuhn and Reinemund (*loc. cit.*) by dissolving *m*-amino-*N*-methyl-*p*-toluidine (1 g., 1 mol.) in concentrated hydrochloric acid (1·5 c.c.) and adding to a solution of alloxan (1·7 g., 1·1 mol.) in 5 c.c. of water. The mixture became hot and a yellow precipitate formed. After warming for 10 mins. on a water-bath the precipitate (1·4 g., 80%) was filtered off, washed, and dried. 6 : 9-*Dimethyl*iso*alloxazine* crystallised from a large volume of glacial acetic acid in yellow plates, which did not melt below 280° (Found : C, 58·9; H, 4·4; N, 23·2. $C_{12}H_{10}O_2N_4$ requires C, 59·5; H, 4·2; N 23·1%). Condensation by the method of Kuhn and Weygand (*loc. cit.*) in acetic acid solution in the presence of boric acid gave a similar yield.

The *m*-amino-*N*-methyl-*p*-toluidine, m. p. 42—43°, was obtained in 85% yield by reduction of *m*-nitro-*N*-methyl-*p*-toluidine with stannous chloride in hydrochloric acid.

3 : 6 : 9-*Trimethyl*iso*alloxazine*.—*N*-Methylalloxan (1·1 g., 1 mol.) was dissolved in 4 c.c. of water and added to *m*-amino-*N*-methyl-*p*-toluidine (0·8 g., 1 mol.) dissolved in hydrochloric acid (1·2 c.c.). The solution became yellow and after a few minutes' warming a yellow solid began to separate. 3 : 6 : 9-*Trimethyl*iso*alloxazine monohydrate* crystallised from water in orange needles (Found : C, 57·2; H, 5·2; N, 20·7. $C_{13}H_{14}O_3N_4$ requires C, 56·9; H, 5·15; N, 20·4%). It was soluble in hot water and in acids and insoluble in alkalis.

The *N*-methylalloxan was prepared from theobromine by the method of Biltz (*Ber.*, 1912, **45**, 3659).

o-*Nitro*-N-(δ-*diethylamino*-α-*methylbutyl*)*aniline Monopicrate*.—A mixture of *o*-chloronitrobenzene (20 g., 1 mol.), 2-amino-5-diethylaminopentane (20 g., 1 mol.) and anhydrous sodium acetate (12 g., 1·2 mols.) was heated at 150° for 18 hours. The deep orange product was dissolved in hydrochloric acid (1 : 1) and the solution extracted with ether to remove unchanged *o*-chloronitrobenzene. After boiling off the ether, the solution was made alkaline with sodium hydroxide and steam distilled to remove unchanged 2-amino-5-diethylaminopentane. The residual oil was extracted with ether, the solution dried over potassium carbonate, and the solvent removed on a water-bath, leaving the *o*-nitro-*N*-(δ-diethylamino-α-methylbutyl)-aniline as an orange oil. It was converted into o-*nitro*-N-(δ-*diethylamino*-α-*methylbutyl*)*aniline monopicrate* in alcoholic solution and crystallised from alcohol, m. p. 124—125°; yield, after one crystallisation, 31 g. (50%) (Found : C, 49·5; H, 5·8; N, 16·7. $C_{21}H_{28}O_9N_6$ requires C, 49·6; H, 5·55; N, 16·5%).

Reduction of the nitro-compound was carried out by (1) titanous chloride, (2) stannous chloride and hydrochloric acid, (3) zinc dust and glacial acetic acid and (4) hydrogen in alcoholic solution in the presence of Raney nickel. The resulting diamine darkened rapidly in air and neither it nor any of its derivatives could be obtained crystalline. It was therefore used for attempted condensations immediately after preparation without purification. Actually, none of the condensations proved successful.

The condensation of *N*-(δ-diethylamino-α-methylbutyl)-*o*-phenylenediamine hydrochloride with alloxan in aqueous solution gave alloxazine (Found : C, 55·5; H, 3·1; N, 25·8. Calc.: C, 56·1; H, 2·8; N, 26·2%). Condensation of the diamine hydrochloride with *N*-methylalloxan in aqueous solution gave 3-methylalloxazine (Found : C, 57·0; H, 3·9; N, 24·6. Calc.: C, 57·9; H, 3·5; N, 24·6%), with similar loss of the basic side-chain. Condensation of the diamine with alloxan or with *N*-methylalloxan in acetic acid solution in the presence of boric acid gave in each case a " glass " which could not be obtained crystalline.

4-*Chloro*-2-*nitro*-N-(δ-*diethylamino*-α-*methylbutyl*)*aniline Monopicrate*.—A mixture of 2 : 5-dichloronitrobenzene (19 g.), obtained in 97% yield by the nitration of *p*-dichlorobenzene (Holleman, *Rec. trav. chim.*, 1915, **35**, 1), 2-amino-5-diethylaminopentane (16 g.) and anhydrous sodium acetate (10 g.) was heated at 135—140° for 5 hours. The mixture

was steam distilled and the residual dark red oil extracted with ether. It was dried over potassium carbonate, the ether removed and the oil dissolved in alcohol and treated with an alcoholic solution of picric acid.

4-Chloro-2-nitro-N-(δ-*diethylamino-α-methylbutyl*)-*aniline monopicrate* crystallised from alcohol in orange needles (27·5 g., 51%), m. p. 110—111° (Found: N, 15·3. $C_{21}H_{27}O_9N_6Cl$ requires N, 15·5%).

5-Chloro-2-nitro-N-(δ-*diethylamino-α-methylbutyl*)-*aniline Monopicrate.*—The reaction was carried out exactly as for the 4-chloro-compound. 2 : 4-Dichloronitrobenzene (19 g.), obtained in 90% yield by the nitration of *m*-dichlorobenzene (Roberts and Turner, *J.*, 1925, 2004), gave crude monopicrate (31 g., 52%), but on crystallisation from alcohol a lot of tar was obtained and the yield of crystallised product was only 19 g. *5-Chloro-2-nitro*-N-(δ-*diethylamino-α-methylbutyl*)-*aniline monopicrate* was a yellow microcrystalline powder, m. p. 110—111° (Found: C, 46·6; H, 5·3; N, 15·1; Cl, 6·7. $C_{21}H_{27}O_9N_6Cl$ requires C, 46·5; H, 5·0; N, 15·5; Cl, 6·5%).

o-*Nitro*-N-(δ-*diethylaminopropyl*)-*aniline Monopicrate.*—A mixture of *o*-chloronitrobenzene (24 g.), 3-diethylaminopropylamine (20 g.) and anhydrous sodium acetate (15 g.) was heated at 150° for 17 hours. The product was treated with hydrochloric acid (1 : 1) and unchanged *o*-chloronitrobenzene extracted with ether. On cooling in ice the hydrochloride of *o*-nitro-*N*-(γ-diethylaminopropyl)-aniline crystallised as orange needles. It was filtered, decomposed separately with alkali and ether extracted. The filtrate was made alkaline, steam distilled to remove unchanged 3-diethylaminopropylamine, and extracted with ether. The ethereal extracts were evaporated and the residual yellow oil was converted into the picrate in alcoholic solution. The fraction which had not been through the solid hydrochloride gave a rather impure picrate. o-*Nitro*-N-(δ-*diethylaminopropyl*)*aniline monopicrate* crystallised from alcohol in yellow needles, m. p. 126—127° (Found: C, 48·0; H, 5·1; N, 16·7. $C_{19}H_{24}O_9N_6$ requires C, 47·5; H, 5·0; N, 17·5%).

1 : 3-Diphenyl*cyclo*pentane-2 : 4 : 5-trione was prepared by the method of Claisen and Ewan (*Annalen*, 1895, **284**, 245).

1 : 3-*Diphenyl-2-keto*-2 : 3-*dihydroquinoxalo*-2′ : 3′-4 : 5-cyclo*pentadiene.*—*o*-Phenylenediamine (1·1 g.) and 1 : 3-diphenyl*cyclo*pentane-2 : 4 : 5-trione (2·6 g.) were dissolved separately in hot alcohol and the solutions mixed and kept overnight. The yellow precipitate crystallised from acetone, in which it was sparingly soluble, in yellow rods, m. p. 249—250°; yield, 2·0 g., 60%. Chakravarti (*loc. cit.*) gives m. p. 251°.

1 : 3-*Diphenyl*-4′-β-*hydroxyethyl*-2-*keto*-1 : 2 : 3′ : 4′-*tetrahydroquinoxalo*-2′ : 3′-4 : 5-cyclo*pentadiene* (II; R = CH_2CH_2OH; R′ = H).—*o*-Nitro-β-hydroxyethylaniline (7·3 g.) was reduced with glacial acetic acid and zinc dust and the solution filtered and added to 1 : 3-diphenyl*cyclo*pentane-2 : 4 : 5-trione (10·6 g.) in hot alcohol (100 c.c.). After warming and leaving for several hours, a little water was added and the solution decanted from the separated tar. On adding more water 1 : 3-*diphenyl*-4′-β-*hydroxyethyl*-2-*keto*-1 : 2 : 3′ : 4′-*tetrahydroquinoxalo*-2′ : 3′-4 : 5-cyclo*pentadiene* crystallised. It was washed with a little alcohol, recrystallised from acetone (3·3 g., 20%) and obtained in pale yellow plates, m. p. 208—209° (Found: C, 78·8; H, 5·3; N, 7·7. $C_{25}H_{20}O_2N_2$ requires C, 78·9; H, 5·3; N, 7·4%).

The *o*-nitro-β-hydroxyethylaniline was prepared by heating ethanolamine with *o*-chloronitrobenzene in the presence of pyridine (Karrer and Naef, *Helv. Chim. Acta*, 1936, **19**, 1029).

1 : 3-*Diphenyl*-4′ : 7′-*dimethyl*-2-*keto*-1 : 2 : 3′ : 4′-*tetrahydroquinoxalo*-2′ : 3′-4 : 5-cyclo*pentadiene* (II; R = R′ = CH_3).—The condensation of 1 : 3-diphenyl*cyclo*pentane-2 : 4 : 5-trione with *m*-amino-*N*-methyl-*p*-toluidine was carried out in the following solvents: (*a*) alcohol, (*b*) alcohol–formic acid, (*c*) alcohol–hydrochloric acid, (*d*) alcohol–glacial acetic acid. In the first three cases the pure diamine was used for the condensation; in the last case the nitro-compound (1·7 g.) was reduced with glacial acetic acid and zinc dust, filtered from zinc salts and this solution used for the condensation. This last method gave the best yield (1·1 g., 30%). 1 : 3-*Diphenyl*-4′ : 7′-*dimethyl*-2-*keto*-1 : 2 : 3′ : 4′-*tetrahydroquinoxalo*-2′ : 3′-4 : 5-cyclo*pentadiene* crystallised from alcohol in yellow needles, m. p. 224—225° (Found: C, 81·8; H, 5·6; N, 8·4. $C_{25}H_{20}ON_2$ requires C, 82·4; H, 5·5; N, 7·8%).

From the experiments with solvents (*a*) and (*b*) a second substance was isolated. This crystallised from alcohol or ligroin (b. p. 60—80°) in two forms, needles, m. p. 100—101°, and plates, m. p. 106—107°. Either form could be obtained by suitable inoculation of the solution. Analysis showed it to be 5-(2′-*methylamino*-5′-*methylanilo*)-2 : 4-*diphenyl*cyclo*pentane*-1 : 3-*dione* (III) (Found: C, 78·5; H, 5·8; N, 7·3. $C_{25}H_{22}O_2N_2$ requires C, 78·6; H, 5·8; N, 7·25%).

Substance from N-(γ-*Diethylaminopropyl*)-o-*phenylenediamine.*—*o*-Nitro-*N*-(γ-diethylaminopropyl)-aniline (6·2 g.) was reduced with zinc dust and acetic acid and the filtered solution added to 1 : 3-diphenyl*cyclo*pentane-2 : 4 : 5-trione (6·5 g.) in glacial acetic acid. The solution was warmed and kept for several days. Dark crystals separated (3·0 g.) and concentration of the mother-liquors gave a further crop (1·2 g.). This *substance* was insoluble in most organic solvents and in dilute hydrochloric acid but crystallised from a large volume of glacial acetic acid as a brown powder which did not melt up to 270° (Found: C, 64·7; H, 5·2; N, 3·7%).

6′ : 8′-*Dihydroxy*-1 : 3-*diphenyl*-2-*keto*-1′ : 4′ : 5′ : 7′-*tetra-azanaphtho*-2′ : 3′-4 : 5-Δ⁴-cyclo*pentene* (IV).—4 : 5-Diaminouracil sulphate (2·0 g.), dissolved in hot 33% acetic acid (250 c.c.), and 1 : 3-diphenyl*cyclo*pentane-2 : 4 : 5-trione (2·6 g.) in hot glacial acetic acid (100 c.c.) were heated together under reflux for 2 hours. The yellow precipitate (1·7 g., 46%) was insoluble or sparingly soluble in alcohol, acetone, toluene, glacial acetic acid and dilute hydrochloric acid and did not melt below 300°. It was dissolved in boiling sodium carbonate solution, from which the *sodium* salt of 6′ : 8′-*dihydroxy*-1 : 3-*diphenyl*-2-*keto*-1′ : 4′ : 5′ : 7′-*tetra-azanaphtho*-2′ : 3′-4 : 5-Δ⁴-cyclo*pentene* crystallised on cooling. This crystallised from water in orange-yellow thin rods (Found: C, 62·8; H, 3·8; N, 14·9. $C_{12}H_{13}O_3N_4Na,\frac{1}{2}H_2O$ requires C, 62·8; H, 3·5; N, 14·0%).

The 4 : 5-diaminouracil was prepared from cyanoacetic acid by the synthesis of Kuhn and Cook (*Ber.*, 1937, **70**, 761). From the acid (65 g.) 4 : 5-diaminouracil sulphate (44 g., 31%) was obtained. 6-Nitroquinoline was obtained in 66% yield by the method of Knueppel (*Ber.*, 1896, **29**, 703).

6-Nitroquinoline (226 g. in 2 lots) was reduced with iron, water, and acetic acid and the 6-aminoquinoline converted into the *p*-toluenesulphonyl derivative, using *p*-toluenesulphonyl chloride in the presence of sodium carbonate and a little water. Crystallisation from alcohol gave pure 6-*p*-toluenesulphonamidoquinoline (258 g., 67%), m. p. 197—198°. The method of Kaufmann and Zeller (*loc. cit.*) gave lower yields.

Nitration of 6-p-*Toluenesulphonamidoquinoline.*—6-*p*-Toluenesulphonamidoquinoline (32·5 g.) was added gradually to stirred nitric acid (*d* 1·52, 162·5 g.) at − 10° to 0°. The nitric acid had been freshly prepared by distillation of 70% nitric acid from an equal volume of concentrated sulphuric acid and was freed from nitrous acid by treatment with urea. The solution was left for about 10 minutes, then poured on to ice and the precipitate filtered and washed with water. It crystallised from alcohol in brownish-yellow regular prisms (31 g., 73%), m. p. 199—200°, and proved to be 5-*nitro*-6-*o*-*nitro*-p-*toluenesulphonamidoquinoline* (VI) (Found: C, 50·1; H, 3·2; N, 14·8. $C_{16}H_{12}O_6N_4S$ requires C, 49·5; H, 3·1; N, 14·4%). Hydrolysis of the dinitro-compound (30 g.) by heating at 100° with concentrated sulphuric acid for 1 hour gave 5-nitro-6-aminoquinoline (12·3 g., 84%), which was crystallised from benzene. It had m. p. 175—176°.

Attempts to prepare the *p*-toluenesulphonyl and *o*-nitro-*p*-toluenesulphonyl derivatives of 5-nitro-6-aminoquinoline by the action of the corresponding sulphonyl chloride in the presence of sodium carbonate or pyridine were unsuccessful; the former method gave in each case 5-*nitro*-6-*aminoquinoline monohydrochloride*, which was also prepared for comparison by the addition of concentrated hydrochloric acid to a solution of the base in acetone. It crystallised from alcohol in yellow plate-like needles, m. p. 258° (decomp.) (Found: C, 48·3; H, 3·5; N, 18·7. $C_9H_8O_2N_3Cl$ requires C, 47·9; H, 3·6; N, 18·6%).

To confirm the orientation of the dinitro-compound, 6-aminoquinoline was treated with *o*-nitro-*p*-toluenesulphonyl chloride in the presence of sodium carbonate and a little water, giving 6-o-*nitro*-p-*toluenesulphonamidoquinoline*, which crystallised from methyl alcohol in rectangular plates, m. p. 191—192° (Found: C, 55·4; H, 4·2; N, 11·9. $C_{16}H_{13}O_4N_3S$ requires C, 56·0; H, 3·8; N, 12·2%). Nitration of this compound with freshly distilled nitric acid (*d* 1·52) gave 5-nitro-6-*o*-nitro-*p*-toluenesulphonamidoquinoline, m. p. and mixed m. p. with the previous specimen, 199—200°.

Reduction of 5-nitro-6-aminoquinoline with stannous chloride and hydrochloric acid (Rudy, *loc. cit.*) was unsatisfactory and was carried out with iron, water, and acetic acid. Alcohol and ammonia were added and, after boiling, the solution was filtered from iron oxides. Most of the alcohol was distilled off rapidly and the solution taken down to dryness in a vacuum. The crude residue, 5 : 6-diaminoquinoline, was used for the following condensations.

Condensation of 5 : 6-*Diaminoquinoline with Glucosone.*—5 : 6-Diaminoquinoline (0·5 g.) was dissolved in boiling alcohol and the hot filtered solution added to glucosone (0·56 g.) dissolved in slightly aqueous alcohol. The solution was warmed on a water-bath for 5 minutes, left for 1 hour and the slight precipitate filtered off. On leaving overnight a larger amount of solid separated; this was filtered and boiled with a large volume of dry acetone. The filtered acetone solution on cooling and concentrating deposited a jelly-like precipitate which dried to a light brown microcrystalline powder in a vacuum, m. p. 222—225° (decomp.), with previous softening. There was insufficient of this *compound* for further investigation [Found: C, 58·5; H, 5·2; N, 15·3. The expected product (V), $C_{15}H_{15}O_4N_3$ requires C, 59·8; H, 5·0; N, 14·0%].

The glucosone was obtained in 29% yield by the hydrolysis with hydrochloric acid (Fischer, *Ber.*, 1889, **22**, 87) of glucosazone, prepared by the method Fischer (*ibid.*, 1884, **17**, 579). The identity of the glucosone was proved by condensation with *o*-phenylenediamine in aqueous alcohol to give 2-(1-d-arabo-1 : 2 : 3 : 4-*tetrahydroxy*-n-*butyl*)-*quinoxaline*, which crystallised from alcohol in needles, m. p., after drying in a vacuum, 194° with charring (Found: C, 57·6; H, 5·4; N, 11·25. $C_{12}H_{14}O_4N_2$ requires C, 57·6; H, 5·6; N, 11·2%). This condensation was first described by Fischer (*ibid.*, 1889, **22**, 87) (cf. Griess and Harrow, *ibid.*, 1887, **20**, 2205), who gave no m. p. or analysis. The monohydrate, m. p. 187—188° (decomp.), of the quinoxaline was later prepared by Ohle (*Ber.*, 1934, **67**, 155) from fructose.

2 : 3-*Diphenylpyrido*-2′ : 3′-7 : 8-*quinoxaline.*—An alcoholic solution of 5 : 6-diaminoquinoline (2·0 g.) and benzil (2·6 g.) was boiled until the separation of solid was complete. The 2 : 3-*diphenylpyrido*-2′ : 3′-7 : 8-*quinoxaline* (1·4 g., 33%) crystallised from alcohol in slightly yellow plates, m. p. 205—206° (Found: C, 82·3; H, 3·9. $C_{23}H_{15}N_3$ requires C, 82·9; H, 4·5%). It was soluble in concentrated hydrochloric acid but reprecipitated on dilution with water.

1 : 2 : 3 : 4-*Dibenzopyrido*-2′ : 3′-8 : 9-*phenazine.*—An alcoholic solution of 5 : 6-diaminoquinoline (1·6 g.) and phenanthraquinone (2·0 g.) was boiled until the separation of solid was complete. The 1 : 2 : 3 : 4-*dibenzopyrido*-2′ : 3′-8 : 9-*phenazine* crystallised from benzene or glacial acetic acid in light brown needles (1·5 g., 47%), m. p. 294° (Found: C, 83·0; H, 4·1. $C_{23}H_{13}N_3$ requires C, 83·4; H, 4·0%). Kaufmann and Zeller (*loc. cit.*) describe the condensation product of 5 : 6-diaminoquinoline and phenanthraquinone as yellow needles, m p. 287—288°, but give no analysis.

p-Chloroacetanilide (50 g.) was dissolved in nitric acid (*d* 1·42) (500 g.), cooled to − 10° and fuming nitric acid (*d* 1·49) (500 g.) added gradually with stirring, the temperature being kept below 0°. Stirring was continued for 15 minutes after all the acid had been added and the solution then poured on ice. The *p*-chloro-*o*-nitroacetanilide was washed free from acid and hydrolysed by heating for a short time with 70% sulphuric acid at <120°. The *p*-chloro-*o*-nitroaniline (42·5 g., 85%) was crystallised from aqueous alcohol; it had m. p. 116—117°.

p-Chloro-*o*-nitroaniline (10 g.) was reduced in alcoholic solution with hydrogen in the presence of Raney nickel catalyst. 4-Chloro-*o*-phenylenediamine (6 g.), m. p. 73—74°, was obtained by crystallisation from ligroin (b. p. 100—120°).

7-*Chloro*-2 : 3-*di*-(m-*nitrophenyl*)*quinoxaline.*—An alcoholic solution of 4-chloro-*o*-phenylenediamine (3·0 g.) and 3 : 3′-dinitrobenzil (6·3 g.) was boiled for 3 hours. The precipitate was crystallised by dissolving in acetone (1 l.) under reflux and then distilling off most of the solvent. 7-*Chloro*-2 : 3-*di*-(m-*nitrophenyl*)-*quinoxaline* crystallised from the concentrated solution in almost colourless, diamond-shaped plates (7·6 g., 90%), m. p. 224—225° (Found: N, 13·9. $C_{20}H_{11}O_4N_4Cl$ requires N, 13·8%).

7-*Chloro*-2 : 3-*di*-(m-*aminophenyl*)*quinoxaline.*—The above dinitro-compound (3 g.) was suspended in glacial acetic acid (15 c.c.) and added gradually to a boiling solution of stannous chloride (11 g.) in hydrochloric acid (14 c.c.). The reddish-brown solution was poured into excess of 10% sodium hydroxide solution and the yellow precipitate filtered, dissolved in dilute hydrochloric acid and reprecipitated with ammonia. Crystallisation from methyl alcohol gave orange plates (1·8 g., 60%) of 7-*chloro*-2 : 3-*di*-(m-*aminophenyl*)*quinoxaline* (+ $2CH_3OH$), melting at 80—81° with loss of methyl alcohol (Found: N, 13·9. $C_{20}H_{15}N_4Cl,2CH_3OH$ requires N, 13·6%. Found, with material freed from methyl alcohol by vacuum drying at 100°: C, 69·9; H, 4·5. $C_{20}H_{15}N_4Cl$ requires C, 69·3; H, 4·4%). Catalytic reduction of a suspension of the dinitro-compound in alcohol using Raney nickel gave a similar yield.

Microanalyses were carried out by Drs. G. Weiler and F. B. Strauss of Oxford.

We thank the Department of Scientific and Industrial Research, the Medical Research Council and Imperial Chemical Industries, Ltd., for grants.

The work was carried out in the University Chemical Laboratory, Cambridge during the period 1941—1944.

BEDFORD COLLEGE, UNIVERSITY OF LONDON. [*Received, June 15th*, 1945.]