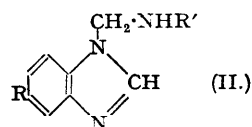
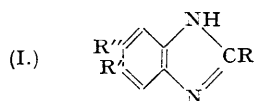


314. Structure and Antimalarial Activity. Part IV. Benziminazoles and Mercaptodihydroglyoxalines.

By A. T. JAMES and E. E. TURNER.

Various derivatives of benziminazole substituted in positions 1, 2, 4, 5, and 6 have been prepared and slight antimalarial activity has been demonstrated in certain of them. A small number of 4 : 5-dihydroglyoxalines substituted in position 1 or 2 has been prepared and slight activity has been found in one or two cases.

BENZIMINAZOLES bearing aliphatic chains in position 2 have been shown by Clemo and Swan (J., 1944, 274) and by Turner and Hall (J., 1948, 1909) to be inactive against *Plasmodium relictum* and *Plasmodium gallinaceum* in chicks. This result was confirmed when 5(or 6)-chloro-6(or 5)-methoxy-2-methylbenziminazole (I; R = Me, R' = Cl, R'' = MeO) and 5-chloro-2-pentadecylbenziminazole (I; R = C₁₅H₃₁, R' = Cl, R'' = H) were found to be inactive. Introduction of a carboxyl group at position 2 to give β-(5-chlorobenziminazol-2-yl)propionic acid (I; R = CH₂·CH₂·CO₂H, R' = Cl, R'' = H) failed to induce activity, as did similar introduction of a hydroxymethyl group.

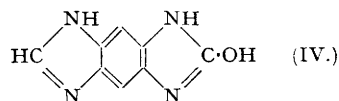
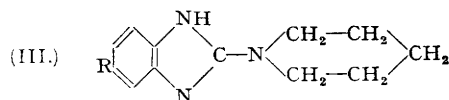


Woolley (J. Biol. Chem., 1944, 152, 225) has shown that benziminazole and 4-nitro- and 4-amino-benziminazole inhibited the growth of certain yeasts and bacteria, the inhibition being reversed by the purines adenine and guanine.

The similarity of the structures of these purines and 4- and 5-amino- and -nitro-benziminazoles suggested that these compounds might display some activity against avian malaria. However, 5-amino- (I; R = R'' = H, R' = NH₂), 5-nitro-2-mercapto- (I; R = SH, R' = NO₂, R'' = H), and 5-amino-2-mercaptobenziminazole (I; R = SH, R' = NH₂, R'' = H) all proved to be inactive.

Slight antimalarial activity was found in the following benziminazoles: 1-(2-pyridylamino-methyl)- (II; R = H, R' = 2-pyridyl), 4-nitro-1-(2-pyridylaminomethyl)- (II; R = NO₂, R' = 2-pyridyl), and 4-nitro-1-(2-hydroxyethylaminomethyl)-benziminazole (II; R = NO₂, R' = CH₂·CH₂·OH).

5-Nitro-2-aminobenziminazoles were next selected for trial as they possess a cyclic guanide structure. Attempts to synthesise such compounds by the cyclisation of the appropriate *o*-aminophenylureas failed, though a variety of condensing agents including sodium propionate in propionic acid, phosphorus oxychloride, sulphuric acid, and zinc chloride was used. The most effective method for the synthesis of these compounds was that described by Kym and Ratner (Ber., 1912, 45, 3238), consisting in heating the appropriate amine with 2-chlorobenziminazole. In this way 5-nitro-2-(*p*-chloroanilino)benziminazole (I; R = *p*-Cl·C₆H₄·NH, R' = NO₂, R'' = H) and 5-nitro-2-piperidinobenziminazole (III; R = NO₂) were prepared. Both substances were soluble in alkali to give deeply coloured solutions and were tested as such since the hydrochlorides were not very soluble in water. Reduction of the nitro-group to give 5-amino-2-piperidinobenziminazole (III; R = NH₂) failed to induce any activity.



Mono-, di-, and tri-nitro-derivatives of 2-hydroxybenziminazole were readily prepared. The action of nitric acid (*d* 1·42) on 2-hydroxybenziminazole afforded 5-nitrobenziminazolone, nitration with fuming nitric acid afforded 5 : 6-dinitrobenziminazolone, and nitration with a mixture of concentrated sulphuric and nitric acids afforded 4 : 5 : 6-trinitrobenziminazolone.

The reaction between dinitrobenziminazolone and aromatic amines, reported by Kym and Ratner (*loc. cit.*) to result in the replacement of one of the nitro-groups by an amine residue, was found to be complex and to give rise, in the case of *p*-chloroaniline, to a variety of coloured products. No indication of simple replacement of one of the nitro-groups was found with

5-Nitrobenziminazolone proved to be inactive, 6-chloro-5-nitrobenziminazolone showed slight antimalarial activity. Slight activity was also displayed by dinitro-*p*-chloroanilino-benziminazolone, and dinitroisopropylaminobenziminazolone. Trinitrobenziminazolone was inactive, as was 2-hydroxyglyoxalino(4':5'-5:6)benziminazole (IV). All these derivatives, except (IV), dissolved readily in weakly alkaline solutions to give intensely coloured solutions, and were tested as such.

$$\begin{array}{ccc}
 \begin{array}{c} \text{CH}_2\text{-NH} \\ | \\ \text{CH}_2\text{-N} \end{array} \text{C}=\text{SR} & \begin{array}{c} \text{CH}_2\text{-N} \cdot \text{CH}_2\text{-N} \\ | \quad \quad | \\ \text{CH}_2\text{-N} \quad \text{C}=\text{SH} \end{array} \begin{array}{c} \text{CH}_2\text{-CH}_2 \\ | \\ \text{CH}_2\text{-CH}_2 \end{array} \text{CH}_2 & \begin{array}{c} \text{CH}_2\text{-NH} \\ | \\ \text{CH}_2\text{-N} \end{array} \text{C}=\text{S}-\text{C}=\begin{array}{c} \text{NH-CH}_2 \\ | \\ \text{N-CH}_2 \end{array} \\
 \text{(V.)} & \text{(VI.)} & \text{(VII.)}
 \end{array}$$

The pharmacological tests were carried out by Drs. Hawking and W. M. Perry of the National Institute for Medical Research.

(All m. p.s are uncorrected. Analyses are by Drs. Weiler and Strauss, Oxford.)

2-Chloro-4-nitroanisole.—*o*-Chloroanisole (1 mol.) was nitrated in glacial acetic acid with nitric acid (2.5 mols.; d 1.42) by heating the mixture under reflux for 2 hours (cf. Reverdin and Eckhard, *Ber.*, 1899, **32**, 2622). On cooling, needles of 2-chloro-4-nitroanisole (52%) separated and after crystallisation from alcohol had m. p. 93–94°.

2-Chloro-4-acetamidooanisole.—2-Chloro-4-nitroanisole was reduced with iron filings and very dilute hydrochloric acid. After neutralisation with aqueous ammonia, alcohol was added and the iron, etc., were removed by filtration. The brownish product obtained after removal of the alcohol was acetylated with acetic anhydride. Crystallisation from water (charcoal) gave a product, m. p. 94° (Reverdin and Eckhard, *loc. cit.*).

2-Chloro-5-nitro-4-acetamidoanisole.—Nitration of 2-chloro-4-acetamidoanisole in a mixture of concentrated sulphuric and nitric acids below 20° gave a brown crystalline product when the mixture was poured on crushed ice. Crystallisation from glacial acetic acid afforded yellow needles, m. p. 158°. Hydrolysis with concentrated hydrochloric acid gave 2-chloro-5-nitro-4-aminoanisole, m. p. 133° after crystallisation from alcohol (Found: N, 13.6; Cl, 17.1. $C_7H_7O_3N_2Cl$ requires N, 13.8; Cl, 17.5%).

2-Chloro-5-amino-4-acetamidobenzonitrile.—2-Chloro-5-nitro-4-acetamidobenzonitrile was reduced in alcoholic solution with hydrogen in the presence of Raney nickel. The base obtained after removal of the nickel and alcohol crystallised from water as lozenges, m. p. 157° (Found: N, 13.2%. $C_9H_7ClO_2N_3$ requires N, 13.1%). The hydrochloride, m. p. 252° (decomp.), was obtained by passage of hydrogen chloride into a solution of the base in alcohol, followed by precipitation by ether (Found: C, 43.6; H, 4.8; N, 11.0%. $C_9H_{12}O_2N_3Cl_2$ requires C, 43.0; H, 4.8; N, 11.2%).

5-Chloro-6-methoxy-2-methylbenzimidazole.—2-Chloro-5-amino-4-acetamidoanisole was heated in propionic acid with fused sodium propionate. Neutralisation and crystallisation from alcohol gave 5-chloro-6-methoxy-2-methylbenzimidazole, converted into the *hydrochloride*, m. p. 262° (Found: N, 12.0. $C_9H_{10}ON_2Cl_2$ requires N, 12.0%).

4-Chloro-2-nitropalmitoanilide.—4-Chloro-2-nitroaniline (5 g.) was heated in dry toluene with palmitoyl chloride (8 g.) for 1 hour. On evaporation of the toluene and crystallisation of the product twice from alcohol and then from acetone-light petroleum, a pale yellow crystalline *anilide* (10 g.), m. p. 76°, was obtained (Found: N, 6.5. $C_{22}H_{35}O_3N_2Cl$ requires N, 6.8%).

4-Chloro-2-aminopalmitoanilide.—4-Chloro-2-nitropalmitoanilide (7.5 g.) was reduced in alcoholic solution with hydrogen in the presence of Raney nickel. Removal of the nickel and alcohol, followed by crystallisation from aqueous alcohol, gave a crystalline *product* (4.6 g.), m. p. 103° (Found: N, 6.9. $C_{22}H_{37}ON_2Cl$ requires N, 7.4%).

25-Chloro-2-pentadecylbenzimidazole.—4-Chloro-2-aminopalmitoanilide (5 g.) was heated in propionic acid with fused sodium propionate (1 g.) for 1 hour. The solution was then diluted and neutralised with 10% sodium hydroxide solution. The precipitate was crystallised twice from aqueous alcohol, giving needles, m. p. 68° (3 g.). Recrystallisation from light petroleum gave a benzimidazole with m. p. 71° (Found: N, 7.5. $C_{22}H_{35}N_2Cl$ requires N, 7.7%). The hydrochloride, m. p. 211°, was prepared by passing dry hydrogen chloride into a solution of the base in benzene (Found: N, 7.0. $C_{22}H_{35}N_2Cl_2$ requires N, 7.0%).

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added until the solution grew turbid. Cooling the solution caused the deposition of brown crystals. Crystallisation from water (charcoal) afforded *p*-(5-chlorobenziminazol-2-yl)propionic acid, plates, m. p. 190—191° (12 g.). The *hydrochloride*, m. p. 257°, was obtained by the action of hydrogen chloride on a suspension of the base in chloroform (Found : N, 11.0. $C_{10}H_{10}O_2N_2Cl_2$ requires N, 10.7%).

5-Chloro-2-hydroxymethylbenziminazole.—4-Chloro-*o*-phenylenediamine (5.3 g.) and glycollic acid (3.9 g.) were heated for 30 minutes in 4*N*-hydrochloric acid (40 c.c.) (Phillips, *J.*, 1928, 2393). Neutralisation of the solution with aqueous ammonia gave a brownish crystalline product which had m. p. 205° after crystallisation from aqueous alcohol (5 g.). The *hydrochloride*, m. p. 246°, was precipitated from an acetone solution of the base by the action of hydrogen chloride (Found : C, 43.1; H, 3.6; N, 12.4. $C_8H_8ON_2Cl_2$ requires C, 43.8; H, 3.6; N, 12.8%).

5-Nitrobenziminazole.—4-Nitro-*o*-phenylenediamine (7 g.) was heated in formic acid solution (60 c.c.) with fused sodium formate (2 g.) for 30 minutes. Dilution of the solution, followed by neutralisation with aqueous ammonia, gave a precipitate which on crystallisation from aqueous alcohol gave 5-nitrobenziminazole (5 g.), yellow, m. p. 204—205° (cf. Bamberger and Berle, *Annalen*, 1891, 273, 340).

4-Nitrobenziminazole.—Benziminazole (10 g.) was dissolved in nitric acid (*d* 1.42) cooled below 40°. Dilution of the solution and neutralisation with aqueous ammonia, followed by crystallisation of the precipitate from aqueous alcohol, afforded 4-nitrobenziminazole (7 g.), m. p. 210—212°. A mixture with 5-nitrobenziminazole had m. p. 198°.

5-Aminobenziminazole. 5-Nitrobenziminazole (2 g.) was reduced with hydrogen in alcoholic solution in the presence of Raney nickel. Filtration and evaporation of the alcohol afforded 5-aminobenziminazole (1.5 g.), m. p. 160° after crystallisation from aqueous alcohol (cf. Woolley, *loc. cit.*).

5-Nitro-2-mercaptobenziminazole.—4-Nitro-*o*-phenylenediamine (10 g.) was heated with carbon disulphide (7 g.) in alcohol (100 c.c.) for 3 hours in the presence of sodium hydroxide. The carbon disulphide and alcohol were removed under reduced pressure and the residue was crystallised from aqueous alcohol (charcoal), giving 5-nitro-2-mercaptobenziminazole (6 g.), m. p. 282° (Found : N, 21.2. Calc. for $C_7H_5O_2N_2S$: N, 21.5%).

5-Amino-2-mercaptobenziminazole.—5-Nitro-2-mercaptobenziminazole was reduced with hydrogen in alcoholic solution over Raney nickel. The nickel was removed by filtration and hydrogen chloride was passed into the alcoholic solution. Precipitation with ether, followed by crystallisation from water, afforded 5-amino-2-mercaptobenziminazole *hydrochloride*, m. p. 220° (Found : C, 41.4; H, 4.0; S, 15.8. $C_7H_8N_2ClS$ requires C, 41.5; H, 4.4; S, 15.9%).

N-*p*-Chlorophenyl-N'-(4-chloro-2-nitrophenyl)urea.—4-Chloro-2-nitrophenyl isocyanate (5 g.) was heated in toluene with *p*-chloroaniline (7 g.) and three drops of pyridine on the water-bath for 2 hours. On cooling of the solution a yellow precipitate formed, which on crystallisation from alcohol afforded N-*p*-chlorophenyl-N'-(4-chloro-2-nitrophenyl)urea (6 g.), yellow, m. p. 228° (Found : N, 12.9; Cl, 21.5. $C_{15}H_9O_3N_3Cl_2$ requires N, 12.9; Cl, 21.8%).

N-*p*-Chlorophenyl-N'-(4-chloro-2-aminophenyl)urea.—The above compound was reduced in ethyl acetate over Raney nickel with hydrogen under pressure. Removal of the nickel by filtration, followed by crystallisation of the product from alcohol gave N-*p*-chlorophenyl-N'-(4-chloro-2-aminophenyl)urea, m. p. 235° (Found : N, 14.0. $C_{15}H_{11}ON_3Cl_2$ requires N, 14.2%).

N-(4-Chloro-2-nitrophenyl)-N'-isopropylurea.—The reaction between 4-chloro-2-nitrophenyl isocyanate and isopropylamine was carried out as described for *p*-chloroaniline. The product was yellow and had m. p. 183—184° (Found : N, 16.5. $C_{11}H_{13}O_3N_3Cl$ requires N, 16.3%).

N-Pentamethylene-N'-(4-chloro-2-nitrophenyl)urea.—The reaction between 4-chloro-2-nitrophenyl isocyanate and piperidine afforded a product, m. p. 89° (Found : N, 14.1. $C_{12}H_{14}O_3N_3Cl$ requires N, 14.8%).

Attempted Cyclisation of N-*p*-Chlorophenyl-N'-(4-chloro-2-aminophenyl)urea.—(a) The amine (6 g.) was heated in propionic acid (50 g.) with fused sodium acetate (2 g.) for 1 hour. The solution was diluted, made alkaline with 10% sodium hydroxide solution, and extracted with benzene. The benzene was removed *in vacuo* and the brownish residue crystallised from aqueous alcohol (charcoal) and then from carbon tetrachloride. The substance isolated in this way melted at 230°.

(b) The amine (5 g.) was heated in dry toluene (120 c.c.) with phosphorus oxychloride for 2 hours. After evaporation under reduced pressure the residue was crystallised twice from chloroform. The product obtained melted at 232°. A mixture of the product and N-*p*-chlorophenyl-N'-(2-amino-4-chlorophenyl)urea melted at 235°.

(c) A solution of the base (3 g.) in dry toluene (100 c.c.) was heated with zinc chloride for 1 hour. The solution was cooled and filtered, and the toluene evaporated off. Repeated crystallisation of the residue from alcohol afforded a product melting at 230°. A mixture of the product and the original amine melted at 233°.

2-Hydroxybenziminazole.—A mixture of *o*-phenylenediamine (1 mol.) and urea (3 mols.) was heated at 170—180° (Kym and Ratner, *loc. cit.*) until the liquid had set to a hard crystalline mass. This was cooled, dissolved in 5% sodium hydroxide solution (charcoal), and precipitated with 30% hydrochloric acid, affording 2-hydroxybenziminazole as a micro-crystalline solid, m. p. 290° (70%).

5-Nitro-2-hydroxybenziminazole. 2-Hydroxybenziminazole (20 g.) was dissolved in nitric acid (*d* 1.42; 150 c.c.) at room temperature. After some minutes the solution became turbid and a yellow solid separated. The solution was poured on crushed ice and filtered and the solid crystallised from alcohol, affording the pale yellow 5-nitro-2-hydroxybenziminazole, m. p. >295° in 75% yield (cf. Hager, *Ber.*, 1884, 17, 2630) (Found : N, 24.5. Calc. for $C_7H_5O_3N_3$: N, 23.5%).

The preparation was also carried out by fusing a mixture of 4-nitro-*o*-phenylenediamine and excess of urea at 170—180°. The cooled solid mass was dissolved in 5% sodium hydroxide solution (charcoal) to give a red solution; the colour disappeared on acidification and pale yellow 5-nitro-2-hydroxybenziminazole, m. p. >290°, was precipitated (cf. Kym and Ratner, *loc. cit.*).

2-Chloro-5-nitrobenziminazole.—5-Nitro-2-hydroxybenziminazole (15 g.) was heated under reflux with phosphorus oxychloride (30 g.) until dissolution was complete (3 hours). After evaporation *in vacuo* the residual hardened foam was washed rapidly with ice-water and then crystallised from alkaline

aqueous alcohol. Cooling the solution caused the deposition of colourless 2-chloro-5-nitrobenziminazole, m. p. 220° (Kym and Ratner, *loc. cit.*).

5-Nitro-2-*p*-chloroanilobenziminazole.—2-Chloro-5-nitrobenziminazole (10 g.) was heated at 180° with excess of *p*-chloroaniline (75 g.) for 2 hours. The dark brown melt was cooled and steam-distilled to remove the excess of *p*-chloroaniline, and the residue dissolved in concentrated hydrochloric acid. Neutralisation with aqueous ammonia afforded a yellowish-brown product (15 g.), which on crystallisation from alcohol gave 5-nitro-2-*p*-chloroanilobenziminazole as an orange-red micro-crystalline powder, m. p. 260° (decomp.) (Found: N, 19.8. $C_{13}H_9O_2N_4Cl$ requires N, 19.5%).

5-Nitro-2-piperidinobenziminazole.—2-Chloro-5-nitrobenziminazole (6 g.) was heated in piperidine (20 c.c.) for 2 hours. The residue obtained after evaporation of the piperidine was dissolved in concentrated hydrochloric acid and carefully neutralised with sodium carbonate. The orange-yellow precipitate obtained, crystallised from aqueous methanol, gave 5-nitro-2-piperidinobenziminazole as small yellow needles, m. p. >260° (Found: N, 21.8. $C_{15}H_{14}O_2N_4$ requires N, 22.8%).

5-Amino-2-piperidinobenziminazole.—5-Nitro-2-piperidinobenziminazole (5 g.) was reduced in alcoholic solution with hydrogen in the presence of Raney nickel. Removal of the nickel and passage of hydrogen chloride, followed by addition of ether, precipitated the dihydrochloride. Crystallisation from water afforded 5-amino-2-piperidinobenziminazole dihydrochloride as a trihydrate, m. p. 190° (Found: C, 42.8; H, 5.9; N, 16.4. $C_{11}H_{16}N_4Cl_2 \cdot 3H_2O$ requires C, 42.2; H, 6.4; N, 16.4%).

1-(2-Pyridylaminomethyl)benziminazole.—Benziminazole (0.01 mol.) was dissolved in methyl alcohol (100 c.c.), together with 2-aminopyridine (0.011 mol.). 40% Aqueous formaldehyde (0.012 mol.) was added and the solution kept overnight (Bachman and Heisey, *J. Amer. Chem. Soc.*, 1946, **68**, 2496). Removal of the methyl alcohol by distillation, followed by crystallisation from aqueous alcohol, afforded 1-(2-pyridylaminomethyl)benziminazole as needles, m. p. 190–192° (Found: C, 70.0; H, 5.5; N, 24.6. $C_{13}H_{12}N_4$ requires C, 69.7; H, 5.6; N, 24.9%).

4-Nitro-1-(2-pyridylaminomethyl)benziminazole.—Starting with 4-nitrobenziminazole the preparation was carried out as described above for benziminazole. Crystallisation of the product from aqueous alcohol afforded 4-nitro-1-(2-pyridylaminomethyl)benziminazole as plates, m. p. 207–208° (Found: C, 58.0; H, 3.8. $C_{13}H_{11}O_2N_5$ requires C, 58.0; H, 4.1%).

4-Nitro-1-(2-hydroxyethylaminomethyl)benziminazole.—Under the conditions described above, ethanolamine, 4-nitrobenziminazole, and formaldehyde afforded 4-nitro-1-(2-hydroxyethylaminomethyl)benziminazole as needles, m. p. 205°. The monohydrochloride had m. p. 260° (decomp.) (Found: N, 19.9. $C_{10}H_{13}O_3N_4Cl$ requires N, 20.6%).

5:6-Dinitro-2-hydroxybenziminazole.—5-Nitrobenziminazole (7 g.) was dissolved in fuming nitric acid (50 c.c.) (Kym and Ratner, *loc. cit.*). After 2 hours the solution was poured on crushed ice, and the yellow product dissolved in ammonia solution (d 0.88). After acidification with concentrated hydrochloric acid, followed by filtration, the solution deposited orange crystals of 5:6-dinitro-2-hydroxybenziminazole (3 g.), which after crystallisation from alcohol did not melt up to 260° (Found: C, 37.6; H, 1.9; N, 24.0. Calc. for $C_7H_4O_3N_4$: C, 37.6; H, 1.8; N, 25.0%).

5:6:7-Trinitro-2-hydroxybenziminazole.—5-Nitro-2-hydroxybenziminazole (5 g.) was dissolved in concentrated sulphuric acid (50 c.c.), and concentrated nitric acid (d 1.42; 10 c.c.) added. After $\frac{1}{2}$ hour, the solution was poured on crushed ice. The yellow precipitate (6 g.) was washed free from acid and dissolved in 10% sodium hydroxide solution, and the solution filtered and acidified. The resulting yellow solid dissolved in 5% sodium carbonate solution to give a deep-red solution. Cautious acidification with dilute hydrochloric acid afforded a crystalline orange-yellow precipitate of 5:6:7-trinitro-2-hydroxybenziminazole, m. p. >300° (Found: C, 31.2; H, 1.2; N, 25.4. $C_7H_3O_7N_5$ requires C, 31.2; H, 1.1; N, 25.9%).

Reaction between *p*-Chloroaniline and 5:6-Dinitro-2-hydroxybenziminazole.—*p*-Chloroaniline (20 g.) was mixed with 5:6-dinitro-2-hydroxybenziminazole (3 g.) and heated in a bath at 140° for 1 hour. The melt was cooled and then steam-distilled to remove excess of *p*-chloroaniline. The dark residue was dissolved in 3*N*-sodium hydroxide solution, and the solution filtered and acidified. The dark red product crystallised from aqueous alcohol to give a semi-crystalline mass which could be further fractionated by careful precipitation by acid of a solution in sodium carbonate solution. The products were all dark and contained from 38.0 to 52.0% of carbon and 22.0 to 25.0% of nitrogen. No substance corresponding to the expected nitro-*p*-chloroanilobenziminazolone could be isolated. Slight antimalarial activity was displayed by the fractions.

Dinitro-*p*-chloroanilobenziminazolone.—5:6:7-Trinitrobenziminazolone (5 g.) was heated with *p*-chloroaniline (30 g.) at 180° for 1 hour. Extraction of the solid product with dilute hydrochloric acid to remove excess of base, followed by dissolution of the residue in 10% sodium hydroxide solution, gave a reddish-purple solution. On acidification a red powder was precipitated; this was dissolved in dilute aqueous ammonia, and the solution filtered and acidified with dilute acid; a micro-crystalline precipitate of dinitro-*p*-chloroanilobenziminazolone, m. p. >290° (Found: C, 44.2; H, 1.6; N, 19.8. $C_{13}H_9O_5N_5Cl$ requires C, 44.7; H, 2.3; N, 20.0%), was obtained.

Dinitroisopropylaminobenziminazolone.—Addition of 5:6:7-trinitrobenziminazolone (5 g.) to *iso*-propylamine (20 g.) provoked a violent reaction, giving a deep-red solution. When the reaction had ceased, the solution was diluted with alcohol and then acidified with dilute hydrochloric acid; there resulted an immediate precipitate of the bright red dinitroisopropylaminobenziminazolone (3 g.), m. p. 242° (Found: N, 25.1. $C_{10}H_{11}O_5N_5$ requires N, 25.0%).

6-Chloro-5-nitrobenziminazolone.—5-Chlorobenziminazolone (from 4-chloro-*o*-phenylenediamine and urea) was dissolved in nitric acid (d 1.42) at room temperature and set aside for 1 hour. The yellow precipitate obtained by pouring the acid solution on crushed ice was dissolved in 10% sodium carbonate solution, and the solution filtered. On acidification, 5-chloro-6-nitrobenziminazolone was precipitated; it sinters at 200° (Found: N, 19.8. $C_7H_4O_3N_3Cl$ requires N, 19.6%).

2-Hydroxyglyoxalino(4':5'-5:6)benziminazole.—5:6-Dinitrobenziminazolone (6 g.) was reduced with iron filings and hydrochloric acid as described by Kym and Ratner (*loc. cit.*) to give 5:6-diaminobenziminazolone. The dihydrochloride of the base was obtained as a brownish crystalline solid, and

without further purification was heated in formic acid solution with fused sodium formate. Neutralisation of the solution gave a dark precipitate which was dissolved in dilute hydrochloric acid. The solution was treated with charcoal, filtered, and evaporated almost to dryness *in vacuo*; this gave the hydrochloride of 2-hydroxyglyoxalino(4':5'-5:6)benziminazole as needles, m. p. 280° (Found : N, 27.4. Calc. for $C_8H_8ON_4 \cdot HCl$: N, 26.6%).

(4:5-Dihydroglyoxalin-2-ylthio)acetic acid.—The reaction between 2-mercapto-4:5-dihydroglyoxaline and chloroacetic acid as described by Johnson and Edens (*J. Amer. Chem. Soc.*, 1942, **64**, 2706) afforded 4:5-dihydroglyoxaline-2-thiolacetic acid hydrochloride, m. p. 222° after crystallisation from alcohol (Found: C, 30.8; H, 4.9; N, 13.6. Calc. for $C_8H_8O_2N_2S \cdot HCl$: C, 30.8; H, 4.6; N, 14.3%).

Bis-4:5-dihydroglyoxalin-2-yl Disulphide Periodide.—2-Mercapto-4:5-dihydroglyoxaline, treated with iodine in potassium iodide solution (Johnson and Edens, *loc. cit.*) gave the periodide, m. p. 118°.

Bis-4:5-dihydroglyoxalin-2-yl Sulphide.—The above periodide, digested with boiling water (Johnson and Edens, *loc. cit.*), gave bis-4:5-dihydroglyoxalin-2-yl sulphide as its hydriodide, m. p. 282° (Found: N, 18.7. Calc. for $C_8H_{10}N_4S \cdot HI$: N, 18.8%).

2-Mercapto-1-piperidinomethyl-4:5-dihydroglyoxaline.—2-Mercapto-4:5-dihydroglyoxaline was treated with formaldehyde and piperidine in methyl alcohol as described before. The base had m. p. 118°. The dihydrochloride, m. p. 200°, was prepared by the action of hydrogen chloride on an alcoholic solution of the base (Found: N, 15.0. $C_9H_{13}N_3SCl_2$ requires N, 15.4%).

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