275. *Benziminazole Analogues of Paludrine.*

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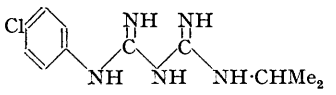
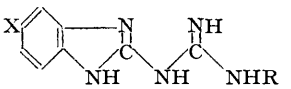
A series of 2-guanidinobenziminazoles has been prepared by the action of *o*-phenylenediamines on dicyandiamide and on iso*propyldicyandiamide*. When attempting an alternative method of synthesis from *o*-phenylenediamine and dicyanimide, 2 : 4-*diaminobenzo*-1 : 3 : 5-*triazepine*, a derivative of a new heterocyclic system, was obtained.

Despite their close structural relationship to the antimalarial diguanides, the guanidinobenziminazoles, with the exception of the slightly active 5 : 6-dichloro-compounds, have no plasmodicidal properties.

Although little is known as to the mechanism of their action, the biological activity of the quinoline and acridine anti-malarials is generally believed to be connected with their structural relationship to riboflavin. The diguanides, on the other hand, do not appear to function as riboflavin antagonists (see Curd and Rose, *Nature*, 1946, **158**, 707), and the antiplasmodial properties of paludrine (I) therefore seem to be due to the inhibition of some other growth factor at present unrecognised. Curd and Rose (*loc. cit.*) have suggested that this substance may be a highly specific porphyrin, since there is evidence that the antimalarial can associate into a bimolecular complex similar in structure to the porphyrin ring-system.



(I.)



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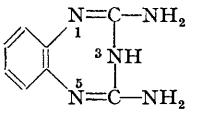

(III.)

It is possible, however, to draw somewhat different conclusions as to the nature of the inhibited substance, depending on the resemblance of paludrine to other biologically significant structures, for example, benziminazole. Thus, the compound (II; R = $CHMe_2$, X = Cl) is the exact analogue in the benziminazole series of the N^1-phenyldiguanide, paludrine (I), and its formulation from the latter requires no rearrangement of groups, being merely the result of ring-closure between the aromatic ring and its adjacent nitrogen atom N^2 with the loss of two atoms of hydrogen. Woolley (*J. Biol. Chem.*, 1944, **152**, 225) has already recorded the growth-inhibitory action of benziminazole for certain micro-organisms, and the fact that it is caused by interference with the utilisation of guanine and adenine might indicate that paludrine functions as an antagonist of a purine essential to the growth of the malaria parasite. In any event, in view of their close relationship to paludrine, it was clearly desirable to determine whether the 2-guanidinobenziminazoles were biologically active. The view expressed by Hawking (*Nature*, 1947, **159**, 409) that the drug is not itself an antimalarial agent but is converted into an active compound *in vivo* adds further interest to the guanidinobenziminazole (II; R = $CHMe_2$, X = Cl) as a possible intermediate in the metabolism of paludrine. A series of 2-guanidino- and 2-(N^3-*iso*propylguanidino)-benziminazoles has therefore been synthesised, consisting of the 5-*chloro*-, 5-*methoxy*- and 5-*methyl*, and of the 5 : 6-*dichloro*-, 5 : 6-dimethoxy- and 5 : 6-*dimethyl* derivatives.

2-Guanidinobenziminazole (II; R = H, X = H) was first obtained by Ziegelbauer

(*Sitzungber. Akad. Wiss. Wien*, 1896, **105**, 640) from dicyandiamide and *o*-phenylenediamine dihydrochloride in ethanol at 105°, although he assigned to the product the structure (III). This was later corrected by Pellizzari (*Gazetta*, 1921, **51**, 89) who also (*ibid.*, p. 140) improved the method of preparation by refluxing the reactants in boiling water. It has been found that a considerable reduction in time is possible, and better yields are obtained, by using more concentrated solutions. The product (II; R = X = H) was identified by means of the nitrate and picrate, and the other compounds of type (II; R = H), which were similarly prepared, were characterised by means of their *picrates* and *mono-* or *di-hydrochlorides*.

For the series represented by (II; R = $CHMe_2$), the hitherto undescribed iso*propyldicyandiamide*, $CHMe_2$·NH·C(:NH)·NH·CN, was required; in the course of unsuccessful experiments on the preparation of such a monoalkyl derivative from dicyandiamide, the latter was found to react with formic acid giving *guanylurea formate*. The employment of dicyanimide was then considered since the sodium salt is known to react with two equivalents of alkylamine hydrochloride forming dialkyldiguanides (Slotta and Tschesche, *Ber.*, 1929, **62**, 1394), and attempts were made to obtain the required monoalkyldicyandiamide by using one molecular proportion of alkylamine. The sodium dicyanimide used in these experiments was kindly supplied by Imperial Chemical Industries Limited who had earlier used it for the same and related purposes. By the action of ammonium chloride on sodium dicyanimide in boiling *n*-butanol, dicyandiamide was obtained in small yields, and similar condensations with *iso*propylamine and *n*-butylamine hydrochlorides gave good yields of *iso*propyl- and *n*-butyldicyandiamides as glassy solids, the *iso*propyl derivative ultimately crystallising. *iso*Propyldicyandiamide reacted vigorously with acetic anhydride giving a solid, which by analogy with the product prepared by Andreasch (*Sitzungsber. Akad. Wiss. Wien*, 1927, **136**, 145) from dicyandiamide, is believed to be 2-iso*propylamino*-6-*hydroxy*-4-*methyltriazine*.

From *iso*propyldicyandiamide and the appropriate *o*-diamine hydrochlorides in boiling aqueous solution 2-(N^3-*iso*propylguanidino)benziminazole (II; R = $CHMe_2$, X = H) and the 5-chloro-derivative (II; R = $CHMe_2$, X = Cl) were obtained as crystalline *dihydrochlorides*, but the bases, liberated by the addition of alkali to the reaction mixtures, generally failed to crystallise at this stage. Purification through copper derivatives was possible, as with the diguanides (Curd and Rose, *J.*, 1946, 732), but undoubtedly the most successful method of isolation consisted in preparing the easily crystallisable picrates. Of these, 2-(N^3-iso*propylguanidino*)-5-*methoxybenziminazole picrate* was readily converted into its *dihydrochloride* by aqueous hydrochloric acid, but with the more insoluble iso*propylguanidino*-5 : 6-*dimethoxybenziminazole picrate*, treatment with *iso*propanolic hydrogen chloride in 2-ethoxyethanol was necessary, and, on adding ether, the *dihydrochloride* was quantitatively precipitated. Similarly purified were the *dihydrochlorides* of 2-(N^3-*iso*propylguanidino)-5-methyl-, 5 : 6-dichloro-2-(N^3-*iso*propylguanidino)-, and 2-(N^3-*n*-butylguanidino)-5 : 6-dimethoxy-benziminazole; the 2-(N^3-*iso*propylguanidino)-5 : 6-dimethyl derivative separated from its reaction mixture as a hydrated *monohydrochloride*. From the purified hydrochlorides the free bases were readily obtained as crystalline solids.

Later, experiments were made with the intention of carrying out the synthesis of 2-(N^3-alkylguanidino)benziminazoles in the reverse direction, starting from *o*-phenylenediamine hydrochloride and sodium dicyanimide, but instead of the expected 2-cyanaminobenziminazole, an addition product, $C_8H_9N_5$, was isolated. The new amine, characterised by its *nitrate* and *picrate*, is isomeric with 2-guanidinobenziminazole, but it differs from this compound in failing to react with nitrous acid, which, as shown by Pellizzari (*loc. cit.*) and now confirmed, converts the 2-guanidino-compound into 2-cyanaminobenziminazole. To the addition product $C_8H_9N_5$ we therefore ascribe the only likely alternative structure (III), the formation of a 7-ring from *o*-phenylenediamine having an analogy in the reaction of this substance with ethyl malonate (Meyer, *Annalen*, 1906, **347**, 17).

The production of (III) instead of the expected 2-cyanaminobenziminazole thus vitiates the alternative scheme for the synthesis of N^3-alkylguanidinobenziminazoles : it is in any case excluded by the inertness of 2-cyanaminobenziminazole, which failed to undergo the necessary reaction with *iso*propylamine hydrochloride, even on prolonged heating in boiling *n*-propyl alcohol with copper sulphate.

Of the fifteen 2-guanidinobenziminazoles which have been described, the hydrochlorides of (II; R = H, X = H), (II; R = H, X = Cl), (II; R = $CHMe_2$, X = Cl), (II; R = H, X = OMe) and (II, R = $CHMe_2$, X = OMe) were tested against *P. gallinaceum* infections in chicks, and the remainder against *P. relictum* in canaries. None of the compounds is appreciably more toxic than paludrine, yet even at the maximum tolerated dosages those used

in the *P. gallinaceum* tests, as already briefly reported (*Nature*, 1947, **160**, 53), were devoid of antimalarial action. Among those tested against *P. relictum*, the 5 : 6-dichloro-2-guanidino- and 5 : 6-dichloro-2-(N^3-*iso*propylguanidino)-benziminazoles showed slight activity, but the remainder were ineffective.

The contrast between these results and those given by the N^1-phenyldiguanides indicates the high specificity of the latter group. This is particularly remarkable with regard to the derivative (I) and its benziminazole counterpart (II; R = $CHMe_2$, X = Cl), where the close resemblance between the two structures can be seen in their similar capacity for tautomerism, and in the formation by the guanidinobenziminazole of a *copper* derivative, in which two molecules of the base are associated in a porphyrin-like structure presumably identical in shape with that of the diguanide (I).

No precise explanation can be given for this marked difference in biological properties, but the inactivity of the benziminazoles may be interpreted as evidence in support of Hawking's thesis (*loc. cit.*), in that, by reason of its more condensed structure, the compound (II; R = $CHMe_2$, X = Cl), unlike paludrine, might not be able to undergo the *in vivo* chemical change necessary to convert it into an active metabolite.

Experimental.

2-Guanidinobenziminazole.—A mixture of *o*-phenylenediamine (2·16 g., 1 mol.), dicyandiamide (1·68 g., 1 mol.), concentrated hydrochloric acid (4 c.c., 2 mols.) and water (15 c.c.) was heated under reflux for 1 hour; on basifying the cooled solution, 2-guanidinobenziminazole (2·3 g., 66%) was obtained, crystallising in pale buff-coloured plates or colourless needles, m. p. 245° (decomp.). The benziminazole nitrate separated from water in small colourless needles, m. p. 228° (decomp.) (Found : C, 40·2; H, 4·2. Calc. for $C_8H_9N_5,HNO_3$: C, 40·3; H, 4·2%) [Pellizarri (*loc. cit.*) gives m. p. 216° (decomp.)]; the picrate crystallised from a large volume of water in fine yellow needles, m. p. 264—265° (decomp.) (Found : C, 41·4; H, 2·9. Calc. for $C_8H_9N_5,C_6H_3O_7N_3$: C, 41·2; H, 3·0%); and the *dihydrochloride monohydrate* was precipitated from alcohol–ether containing a little concentrated hydrochloric acid in minute fine needles rapidly changing to bipyramids, m. p. 237° (decomp.) (Found : C, 36·7; H, 4·8; Cl, 26·6. $C_8H_9N_5,2HCl,H_2O$ requires C, 36·1; H, 4·9; Cl, 26·7%).

5-Chloro-2-guanidinobenziminazole (II; R = H, X = Cl).—4-Chloro-*o*-phenylenediamine dihydrochloride (13·5 g.) was condensed with dicyandiamide (5·38 g.) in boiling water (75 c.c.), a coal-gas atmosphere being used to prevent oxidation of the diamine. Addition of alkali liberated the *benziminazole* (II; R = H, X = Cl) (5·0 g.), which crystallised from water in pale yellow cubes, m. p. after drying at 140°, 207° (decomp.) (Found, in the dried material : C, 45·9; H, 3·9; Cl, 16·9. $C_8H_8N_5Cl$ requires C, 45·8; H, 3·8; Cl, 16·9%). The *dihydrochloride* was obtained from *n*-propyl-alcoholic hydrogen chloride in microscopic colourless prisms, m. p. 211° (decomp.) (Found : C, 33·5; H, 3·8. $C_8H_8N_5Cl,2HCl$ requires C, 34·0; H, 3·5%). The *picrate* separated from a large volume of water in microscopic yellow needles, m. p. 260—261° (decomp.) (Found : C, 38·5; H, 2·5. $C_8H_8N_5Cl,C_6H_3O_7N_3$ requires C, 38·3; H, 2·5%).

2-Guanidino-5-methoxybenziminazole (II; R = H, X = OMe).—Prepared in aqueous solution, from 4-methoxy-*o*-phenylenediamine dihydrochloride (7·0 g.) and dicyandiamide (2·8 g.), the *base* (3·5 g., 50%) separated from water in pale buff prisms, m. p. 203° (decomp.) (Found : C, 52·6; H, 5·3. $C_9H_{11}ON_5$ requires C, 52·7; H, 5·4%). The *dihydrochloride* crystallised from *n*-propanol containing hydrogen chloride in colourless microscopic needles, m. p. 219—220° (decomp.) (Found : N, 25·4; Cl, 26·0. $C_9H_{11}ON_5,2HCl$ requires N, 25·2; Cl, 25·5%). The *picrate* separated from water as a microcrystalline orange-yellow powder, m. p. 258—259° (decomp.) with sintering at 254° (Found : C, 41·2; H, 3·2. $C_9H_{11}ON_5,C_6H_3O_7N_3$ requires C, 41·5; H, 3·2%).

2-Guanidino-5-methylbenziminazole (II; R = H, X = Me).—3-Nitro-4-aminotoluene (3·8 g.) was hydrogenated over Raney nickel in methanol, and the solution of amine filtered into concentrated hydrochloric acid (5 c.c.). The dihydrochloride (obtained on evaporation under reduced pressure), dicyandiamide (2·1 g.), and water (15 c.c.) were heated under reflux for 45 minutes, and the gummy product liberated by alkali was treated with alcoholic picric acid. The precipitated *picrate* (6·0 g., 58%), m. p. 240° (decomp.), on recrystallisation from aqueous ethanol formed orange needles, m. p. 264° (decomp.) after discolouring at 240° (Found : C, 43·4; H, 3·6; N, 26·7. $C_9H_{11}N_5,C_6H_3O_7N_3$ requires C, 43·1; H, 3·3; N, 26·8%). The *dihydrochloride* obtained from the purified picrate separated from *n*-propanol containing hydrogen chloride in colourless prisms, m. p. 228—229° (decomp.) (Found : C, 41·0; H, 5·1. $C_9H_{11}N_5,2HCl$ requires C, 41·2; H, 5·0%).

2-Guanidino-5 : 6-dimethoxybenziminazole.—The deep red solution obtained by heating 4 : 5-dimethoxy-*o*-phenylenediamine dihydrochloride (3·38 g.) and dicyandiamide (1·2 g.) with water (10 c.c.) under reflux for 1 hour was decolourised with charcoal. The *hydrochloride monohydrate* (2·7 g., 66%) which separated on cooling crystallised from water in colourless prisms, m. p. 285° (decomp.) (Found : C, 41·3; H, 5·6; N, 23·6; Cl, 12·3. $C_{10}H_{13}O_2N_5,HCl,H_2O$ requires C, 41·4; H, 5·5; N, 24·2; Cl, 12·3%. Found, on a sample dried at 120° in a vacuum : C, 42·4; H, 5·6; loss 3·2. $C_{10}H_{13}O_2N_5,HCl,\frac{1}{2}H_2O$ requires C, 42·8; H, 5·3; loss, 3·1%). *2-Guanidino-5 : 6-dimethoxybenziminazole* separated from water in irregular colourless prisms, m. p. 163° (decomp.) (Found, after drying at room temperature over phosphoric anhydride : C, 49·1; H, 5·8; N, 29·4. $C_{10}H_{13}O_2N_5,\frac{1}{2}H_2O$ requires C, 49·2; H, 5·7; N, 28·7%. Found, after drying at 120° in a vacuum : C, 50·9; H, 5·6. $C_{10}H_{13}O_2N_5$ requires C, 51·1; H, 5·6%). The hydrated *picrate* crystallised from aqueous ethanol in slender orange needles, m. p. 280° (decomp.) (Found, after drying at 100° in a vacuum : C, 39·5; H, 3·6; N, 23·8.

$C_{10}H_{13}O_2N_5,C_6H_3O_7N_3,H_2O$ requires C, 39·8; H, 3·7; N, 23·2%. Found, in a sample dried at 120° in a vacuum: C, 40·4; H, 4·0. $C_{10}H_{13}O_2N_5,C_6H_3O_7N_3,\frac{1}{2}H_2O$ requires C, 40·6; H, 3·6%).

5 : 6-*Dichloro*-2-*guanidinobenziminazole*.—1 : 2-Dichloro-4 : 5-dinitrobenzene (Turner and LeFevre, *J.*, 1927, 1113) (4·75 g.) was hydrogenated in methanol (20 c.c.) over Raney nickel at room temperature/2—3 atm., and the filtered solution poured into concentrated hydrochloric acid (4·4 c.c.). After rapid evaporation under reduced pressure, dicyandiamide (1·68 g.) and water (12 c.c.) were added, and the thick grey sludge produced by boiling for 10 minutes was heated on a steam-bath for a further 50 minutes. When cold, the hydrated 5 : 6-*dichloro*-2-*guanidinobenziminazole hydrochloride* (3·9 g., 66%), m. p. 285° (decomp.), was crystallised from water (charcoal), giving fine colourless needles, m. p. 287—290° (decomp.) (Found: C, 32·3; H, 3·6; Cl, 35·0. $C_8H_7N_5Cl_2,HCl,H_2O$ requires C, 32·2; H, 3·4; Cl, 35·6%). The *benziminazole* separated from water in slender pale brown needles, m. p. 244° (decomp.) (Found, after drying at 100° in a vacuum: C, 39·2; H, 3·0. $C_8H_7N_5Cl_2$ requires C, 39·4; H, 2·9%). The *picrate*, thin yellow prisms from aqueous ethanol, had m. p. 319° (decomp.) (Found: Cl, 14·8; N, 24·1. $C_8H_7N_5Cl_2,C_6H_3O_7N_3$ requires Cl, 15·0; N, 23·7%).

2-*Guanidino*-5 : 6-*dimethylbenziminazole*.—The diamine prepared from 5-nitro-4-amino-*o*-xylene (Noelting, Braun, and Thesmar, *Ber.*, 1901, **34**, 2248) (2·8 g.), heated with hydrochloric acid and dicyandiamide (1·42 g.), gave the hydrated benziminazole *hydrochloride* (3·0 g.) on cooling, and this crystallised from water (charcoal) in very light brown prisms, m. p. 265° (decomp.) (Found: C, 45·3; H, 6·4. $C_{10}H_{13}N_5,HCl,1\frac{1}{2}H_2O$ requires C, 45·0; H, 6·4%). 2-*Guanidino*-5 : 6-*dimethylbenziminazole* crystallised from aqueous ethanol as a hemihydrate in long fawn-coloured needles, m. p. 191° (Found, after drying at 100° in a vacuum: C, 56·4; H, 6·4. $C_{10}H_{13}N_5,\frac{1}{2}H_2O$ requires C, 56·6; H, 6·6%), and the *picrate* from aqueous ethanol in brick-red prisms, m. p. 258—259° (decomp.) (Found: C, 44·7; H, 3·8. $C_{10}H_{13}N_5,C_6H_3O_7N_3$ requires C, 44·4; H, 3·7%).

Guanylurea Formate.—A vigorous reaction occurred when dicyandiamide (4·2 g. 1 mol.) and formic acid (4 c.c. of 98—100%, 2 mols.) were heated on a steam-bath, and the solid dissolved with evolution of carbon monoxide. A few minutes later the liquid set to a hard white mass of *guanylurea formate*, which crystallised from water (5 c.c.) in colourless rectangular prisms (4 g.)., m. p. 170° (decomp.) (Found: N, 37·8. $C_2H_6ON_4,H{\cdot}CO_2H$ requires N, 37·8%). Treatment with aqueous picric acid gave guanylurea picrate, crystallising from water in yellow prisms decomposing above 250° (Found: C, 28·8; H, 2·9; N, 29·2. Calc. for $C_2H_6ON_4,C_6H_3O_7N_3$: C, 29·0; H, 2·7; N, 29·6%).

iso*Propyldicyandiamide*.—Sodium dicyanimide (5·0 g., 1·12 mol.) and *iso*propylamine hydrochloride (4·8 g., 1 mol.) were refluxed in *n*-butanol (50 c.c.) for 20 hours, after which the solution was filtered and evaporated to dryness under reduced pressure. The residue was redissolved in butanol, and the solution again filtered and evaporated, whereupon the iso*propyldicyandiamide* was obtained as a colourless glass (theoretical yield), in which form it was used for the synthesis of *iso*propylguanidinobenziminazoles. After very long standing the glass solidified to a waxy solid, m. p. 84—86° (Found, in a sample dried over phosphoric anhydride at 115°/0·06 mm.: N, 44·8. $C_5H_{10}N_4$ requires N, 44·4%). The alkyldicyandiamide is soluble in water and polar solvents, insoluble in light petroleum and benzene. It does not form a compound with picric acid. A portion of the substance (5·9 g.) was heated to boiling with acetic anhydride (12 g.); a reaction then set in which kept the mixture boiling for 10 minutes. After refluxing for 30 minutes, the solution was set aside for 3 days. A solid had then separated, which was collected and washed with a little acetic acid and then with ether. Further quantities were obtained by the addition of a large volume of ether to the filtrate. It crystallised from ethanol in very pale yellow prisms, m. p. 271° (slight decomp.), and consisted of 2-*isopropylamino*-6-*hydroxy*-4-*methyltriazine* (Found: C, 49·6; H, 7·2; N, 33·9. $C_7H_{12}ON_4$ requires C, 50·0; H, 7·1; N, 33·3%).

2-(N^3-iso*Propylguanidino*)*benziminazole* (II; R = $CHMe_2$, X = H).—*o*-Phenylenediamine (5·4 g., 1 mol.), concentrated hydrochloric acid (10 c.c., 2 mols.), and *iso*propyldicyandiamide (6·3 g., 1 mol.) were refluxed in aqueous solution (20 c.c.) for 1 hour. The addition of alkali gave a sticky yellow oil, which was dissolved in ethanol and treated with an aqueous solution of copper sulphate pentahydrate (12·6 g., 1 mol.). The pale green copper derivative was collected, washed with ethanol, dried, and dissolved in concentrated hydrochloric acid (20 c.c.), forming a deep red solution. To this, sodium sulphide (14 g.) in saturated aqueous solution was added, the copper sulphide removed, and the filtrate strongly basified. The resulting yellow gum slowly solidified, and separated from its solution in aqueous ethanol in long colourless prisms, m. p. 168°, consisting of iso*propylguanidinobenziminazole* (Found: C, 60·4; H, 6·8; N, 32·6. $C_{11}H_{15}N_5$ requires C, 60·8; H, 6·9; N, 32·3%). The *picrate* crystallised from aqueous ethanol in fine yellow needles, m. p. 263—264° (decomp.) after sintering at *ca.* 260° (Found: C, 45·8; H, 4·0; N, 25·4. $C_{11}H_{15}N_5,C_6H_3O_7N_3$ requires C, 45·7; H, 4·0; N, 25·1%). The *dihydrochloride* separated in colourless prisms, m. p. 230—232° (decomp.), from ethanol containing a trace of hydrogen chloride (Found: C, 45·8; H, 6·0; N, 24·0. $C_{11}H_{15}N_5,2HCl$ requires C, 45·5; H, 5·9; N, 24·1%).

5-*Chloro*-2-(N^3-iso*propylguanidino*)*benziminazole* (II; R = $CHMe_2$, X = Cl).—4-Chloro-*o*-phenylenediamine dihydrochloride, prepared from 4-chloro-2-nitroaniline (8·65 g., 1 mol.) by hydrogenation in the usual way, was condensed with *iso*propyldicyandiamide (1 mol.) by refluxing in water (20 c.c.) for 45 minutes, and the product isolated as a gummy red-green copper salt. The free base, which remained a yellow gum, was converted with ethanolic hydrogen chloride into the *dihydrochloride*, which crystallised from *n*-propanol containing a little hydrogen chloride in colourless prisms, m. p. 215—217° (decomp.) (Found: C, 41·1; H, 4·8; Cl, 32·2. $C_{11}H_{14}N_5Cl,2HCl$ requires C, 40·7; H, 4·9; Cl, 32·8%). The *picrate*, yellow needles from aqueous ethanol, had m. p. 248° (decomp.) (Found: C, 42·5; H, 3·2; N, 23·0. $C_{11}H_{14}N_5Cl,C_6H_3O_7N_3$ requires C, 42·5; H, 3·5; N, 23·3%). A solution of the benziminazole dihydrochloride (1 g.) in hot water (5 c.c.), added to cupric nitrate hexahydrate (0·49 g.) in aqueous ammonia (2·5 c.c., *d* 0·880, in 2·5 c.c. of water) (cf. Dubsky, Langer, and Strnad, *Coll. Czech. Chem. Comm.*, 1938, **10**, 103), precipitated the *copper* derivative, which crystallised from aqueous ethanol in red prisms, m. p. 285° (decomp.), easily soluble in chloroform [Found: C, 47·0; H, 4·9; Cl, 12·4. $(C_{11}H_{13}N_5Cl)_2Cu$ requires C, 46·8; H, 4·6; Cl, 12·6%].

2-(N³-iso*Propylguanidino*)-5-*methoxybenziminazole* (II; R = $CHMe_2$, X = OMe).—Starting from 2-nitro-4-methoxyaniline (8·4 g., 1 mol.) the amine (II; R = $CHMe_2$, X = OMe) was obtained as a yellow-brown gum on basifying the deep blue reaction mixture. Purification through the copper salt being unsatisfactory, the crude product was dissolved in a little hot ethanol, and after filtration, a solution of picric acid (11·5 g., 1 mol.) in hot ethanol (50 c.c.) was added. The *picrate* (10·7 g., 45%) was rapidly precipitated, and was washed with ethanol and ether and crystallised from a large volume of alcohol, forming minute orange prisms, m. p. 224—225° (decomp.) (Found: C, 45·2; H, 4·1; N, 23·5. $C_{12}H_{17}ON_5,C_6H_3O_7N_3$ requires C, 45·3; H, 4·2; N, 23·5%). The finely ground salt (8 g., 1 mol.) was shaken with concentrated hydrochloric acid (5·1 c.c., 3 mols.) and water (70 c.c.), and the mixture extracted with ether until free from picric acid. The filtered aqueous solution was basified, and the solid crystallised from aqueous ethanol, whereupon the benziminazole *monohydrate* separated in colourless prisms, m. p. 117—122° (decomp.) (Found: C, 54·2; H, 7·0; N, 26·8. $C_{12}H_{17}ON_5,H_2O$ requires C, 54·3; H, 7·2; N, 26·4%). The anhydrous *compound*, m. p. 97°, was obtained as a pale brown glass on drying at 100° in a vacuum (Found: C, 58·0; H, 7·0. $C_{12}H_{17}ON_5$ requires C, 58·3; H, 6·9%). The *dihydrochloride*, purified by dissolving it in methanolic hydrogen chloride and precipitating it by slow addition of ether, was obtained as a white powder, m. p. 207° (decomp.) (Found: C, 45·0; H, 5·9; Cl, 21·7. $C_{12}H_{17}ON_5,2HCl$ requires C, 45·0; H, 5·9; Cl, 22·2%).

2-(N³-iso*Propylguanidino*)-5-*methylbenziminazole* (II; R = $CHMe_2$, X = Me).—Similarly prepared from 3-nitro-*p*-toluidine (7·6 g., 1 mol.), this amine was isolated as the *picrate* (11 g., 48%), m. p. 212° (decomp.). When recrystallised from aqueous ethanol, it formed orange prisms, m. p. 217° (Found, after drying at 100° in a vacuum: C, 47·2; H, 4·4; N, 23·6. $C_{12}H_{17}N_5,C_6H_3O_7N_3$ requires C, 46·9; H, 4·3; N, 24·3%). It was decomposed by hydrogen chloride in 2-ethoxyethanol to give a *hydrochloride* (5·5 g.), which separated from *n*-propanol containing hydrogen chloride on the addition of ether as a white microcrystalline powder, m. p. 214—217° (decomp.), but the product was not obtained analytically pure (Found: C, 48·8; H, 6·2. $C_{12}H_{17}N_5,2HCl$ requires C, 47·4; H, 6·2%).

2-(N³-iso*Propylguanidino*)-5 : 6-*dimethoxybenziminazole*.—The benziminazole was prepared from 4 : 5-dinitroveratrole (10·8 g.) and isolated as the *picrate* (16·5 g., 63%), which crystallised from aqueous *n*-propanol in orange-brown needles, m. p. 278° (decomp.) (Found, in a sample dried at 100° in a vacuum C, 44·9; H, 4·3; N, 21·7. $C_{13}H_{19}O_2N_5,C_6H_3O_7N_3$ requires C, 45·1; H, 4·3; N, 22·1%). Decomposition of the picrate with aqueous hydrochloric acid being unsatisfactory owing to its insolubility, a suspension of the crude salt (1 g., 1 mol.) in boiling 2-ethoxyethanol (10 c.c.) was treated with hydrogen chloride (0·25 g., 3·5 mols.) in *n*-propanol (3 c.c.). After 10 minutes on a steam-bath, picric acid was removed from the cooled crystalline sludge by ether, and the crude *dihydrochloride* collected. When well washed with dry ether, the product (0·65 g., 94%) was crystallised from *n*-propanol containing a little hydrogen chloride, the pure derivative separating in brushlike bunches of colourless needles, m. p. 244—246° (decomp.) (Found: C, 44·3; H, 6·3; N, 19·9; Cl, 20·5. $C_{13}H_{19}O_2N_5,2HCl$ requires C, 44·6; H, 6·0; N, 20·0; Cl, 20·3%). Addition of alkali gave the crystalline *benziminazole*, separating from aqueous ethanol in very pale brown stout square prisms, m. p. 215° (decomp.) (Found, in a sample dried at 120° in a vacuum: C, 56·4; H, 6·8; N, 25·9. $C_{13}H_{19}O_2N_5$ requires C, 56·3; H 6·9; N, 25·3%). The *copper* derivative, prepared as described for the copper compound of (II; R = $CHMe_2$, X = Cl), was slightly soluble in benzene, moderately soluble in ethyl acetate, and dissolved easily in ethanol and chloroform. It crystallised from aqueous ethanol as a hemihydrate in purple-red prisms, m. p. 227—228° (decomp.) [Found: C, 49·7; H, 6·1; N, 22·2. $(C_{13}H_{18}O_2N_5)_2Cu,\frac{1}{2}H_2O$ requires C, 49·9; H, 5·9; N, 22·4%].

5 : 6-*Dichloro*-2-(N³-iso*propylguanidino*)*benziminazole*.—Prepared from 1 : 2-dichloro-4 : 5-dinitrobenzene (11·85 g., 1 mol.) in the usual way, the benziminazole (11 g., 43%), m. p. 298° (decomp.), after being washed with a little ethanol, was dissolved in 2-ethoxyethanol and converted into the *dihydrochloride*, m. p. 222° (decomp.), with 98% recovery. This separated from *n*-propanolic hydrogen chloride in microscopic colourless prisms, m. p. 224—225° (decomp.) (Found: C, 37·1; H, 4·4; Cl, 39·1. $C_{11}H_{13}N_5Cl_2,2HCl$ requires C, 36·7; H, 4·2; Cl, 39·6%). The *picrate* crystallised from a large volume of aqueous propanol in yellow prisms, m. p. 296° (decomp.) (Found: C, 39·9; H, 3·1; Cl, 13·6. $C_{11}H_{13}N_5Cl_2,C_6H_3O_7N_3$ requires C, 39·6; H, 3·1; Cl, 13·8%). The dihydrochloride was decomposed by water to give the *hydrochloride monohydrate*, slender colourless needles, m. p. 157—160° (decomp.) with sintering *ca.* 145° (Found: C, 38·5; H, 4·7; N, 20·6; Cl, 31·5. $C_{11}H_{13}N_5Cl_2,HCl,H_2O$ requires C, 38·7; H, 4·7; N, 20·6; Cl, 31·3%). The *base* crystallised from aqueous ethanol in very pale brown prisms, m. p. 204° (Found, in a sample dried 100° in a vacuum: C, 46·2; H, 4·6. $C_{11}H_{13}N_5Cl_2$ requires C, 46·2; H, 4·5%). Attempts to form a copper derivative by the action of hot aqueous cupric chloride and sulphate on a boiling aqueous solution of the benziminazole dihydrochloride gave, respectively, the hydrate hydrochloride and the hydrated *sulphate*. The latter separated in large buff prisms, m. p. 248—249° (decomp.) (Found: C, 38·4; H, 4·4; S, 4·9; Cl, 20·1. $C_{11}H_{13}N_5Cl_2,\frac{1}{2}H_2SO_4,\frac{1}{2}H_2O$ requires C, 38·4; H, 4·4; S, 4·6; Cl, 20·6%).

2-(N³-iso*Propylguanidino*)-5 : 6-*dimethylbenziminazole*.—5-Nitro-4-amino-*o*-xylene was converted into the diamine dihydrochloride and condensed with the *iso*propyldicyandiamide by refluxing for 45 minutes in aqueous solution (20 c.c.). On cooling, the *hydrochloride monohydrate* separated as a brown solid (5·8 g., 53%), m. p. 137° (decomp.), which crystallised from water (charcoal) in almost colourless prisms, m. p. 138—141° (decomp.) (Found: C, 52·2; H, 7·4; Cl, 11·6. $C_{13}H_{19}N_5,HCl,H_2O$ requires C, 52·1; H, 7·3; Cl, 11·9%). The *picrate*, brushlike bunches of fine yellow needles from aqueous ethanol, had m. p. 245° (decomp.) (Found: C, 47·8; H, 4·5. $C_{13}H_{29}N_5,C_6H_3O_7N_3$ requires C, 48·1; H, 4·6%).

2-(N³-n-*Butylguanidino*)-5 : 6-*dimethoxybenziminazole*.—*n*-Butylamine hydrochloride (7·7 g., 1 mol.) was refluxed with sodium dicyanimide (7·0 g., 1·12 mols.) in *n*-butanol (50 c.c.) for 24 hours. Of the filtered solution and washings (total 54 c.c.), a portion (15 c.c.) was evaporated to dryness and condensed with the amine dihydrochloride prepared from 4 : 5-dinitroveratrole (4·4 g.). The product was isolated as the *picrate* (4·3 g., 43%), which separated from a large volume of aqueous *n*-propanol in very fine red needles, m. p. 256° (decomp.) (Found, in a sample dried at 100° in a vacuum: C, 46·5; H, 4·6; N, 21·5.

$C_{14}H_{21}O_2N_5,C_6H_3O_7N_3$ requires C, 46·2; H, 4·6; N, 21·5%). Decomposition with hydrogen chloride in 2-ethoxyethanol gave the *dihydrochloride*, which crystallised from alcoholic hydrogen chloride in slender colourless needles, m. p. 232° (decomp.) (Found: C, 46·1; H, 6·2. $C_{14}H_{21}O_2N_5,2HCl$ requires C, 45·2; H, 6·3%). The benziminazole separated from aqueous ethanol as a *sesquihydrate* in stellate clusters of colourless prisms, m. p. 115—120° (decomp.) (Found: C, 52·9; H, 7·0. $C_{14}H_{21}O_2N_5,1\frac{1}{2}H_2O$ requires C, 52·8; H, 7·5%. Found, in a sample dried at 110° in a vacuum: C, 55·9; H, 7·0. $C_{14}H_{21}O_2N_5,\frac{1}{2}H_2O$ requires C, 56·0; H, 7·3%).

2 : 4-*Diaminobenzo*-1 : 3 : 5-*triazepine* (III).—*o*-Phenylenediamine (1·08 g., 1 mol.), sodium dicyanimide (0·89 g., 1 mol.), and water (10 c.c.) containing concentrated hydrochloric acid (1 c.c., 1 mol.) were heated to boiling and kept at 100° for 5 minutes. After cooling, nitric acid (0·9 c.c., *d* 1·42, 1·04 mols.) was added, and the precipitate crystallised from water, giving the *triazepine nitrate* (1·4 g.) as colourless hair-like needles, m. p. 269° (decomp.) (Found: C, 40·3; H, 4·5; N, 35·1. $C_8H_9N_5,HNO_3$ requires C, 40·3; H, 4·2; N, 35·3%). Increasing the amount of hydrochloric acid or of diamine to 2 mols. in this preparation did not affect the nature of the product. Sodium picrate and the nitrate in water gave a *picrate*, which separated in fine yellow needles from aqueous ethanol, m. p. 268° (decomp.) (Found: C, 41·8; H, 3·3; N, 27·0. $C_8H_9N_5,C_6H_3O_7N_3$ requires C, 41·6; H, 3·0; N, 27·7%). The *base* crystallised from aqueous ethanol in pale brown prisms, m. p. 191° (decomp.), difficult to dehydrate (Found, in a sample dried at 120° in a vacuum: C, 53·7; H, 5·5; N, 38·2. $C_8H_9N_5,\frac{1}{4}H_2O$ requires C, 53·5; H, 5·3; N, 39·0%).

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