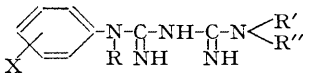
332. *Synthetic Antimalarials. Part XXVIII. An Alternative Route to* N^1-*Aryl*-N^5-*alkyldiguanides.*

By F. H. S. Curd, J. A. Hendry, T. S. Kenny, A. G. Murray, and F. L. Rose.

Part X (*J.*, 1946, 729) of this series described the preparation of N^1-aryl-N^5-alkyl- and -dialkyl-diguanides, for examination as antimalarial agents, by the interaction of alkyl- or dialkyl-amines with aryldicyandiamides. The latter were prepared from the triazenes resulting from the coupling of diazonium salts with dicyandiamide. Their preparation is now described from arylamines and dicyanimide. Alkylamines or dialkylamines with dicyanimide analogously give alkyl- or dialkyl-dicyandiamides which react with arylamines to yield the N^1 : N^5-substituted diguanides of the same type. Alkyldicyandiamides have also been prepared by amination of the *S*-alkyl*iso*thioureas resulting from alkylation of the *N*-cyano-thioureas obtained by reaction of alkyl *iso*thiocyanates with cyanamide.

In Part X of this series (*J.*, 1946, 729) there was reported the preparation of a number of N^1-aryl-N^5-alkyldiguanides of type (I; R = H or Me) possessing antimalarial activity, and the selection of one member of the series (I; X = *p*-Cl, R = R′ = H, R″ = Pr$^\beta$) ("Paludrine") for use in the clinical treatment of human malaria was noted. These substances were all made by the reaction of an aryldicyandiamide (II) with an amine either as a salt of a mineral acid or in the presence of an agent such as copper sulphate, in which case the copper complex of the diguanide was formed. The aryldicyandiamides were themselves prepared through the intermediate triazenes (III) obtained by coupling the appropriate diazonium salt with

dicyandiamide. To obtain the diguanides (I; R = Me) the intermediate aryldicyandiamide was treated in alkaline solution with methyl sulphate. This reaction series often gave



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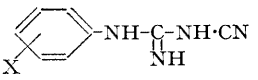

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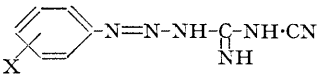
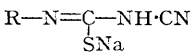


(III.)

satisfactory yields of the products required, but the route had too many limitations for convenient use in the extensive exploration of the relationship between antimalarial activity and the many chemical modifications of which the diguanides should be capable. For example, not all primary aromatic amines could be diazotised and coupled with dicyandiamide, and the resultant triazenes converted into aryldicyandiamides in good yield, and furthermore the method either did not allow or appeared unsuitable for the preparation of derivatives carrying substituents, such as further aryl and alkyl groups, on N^2, N^3, and N^4. For this reason many alternative preparative procedures have been examined which it is proposed to report in later papers of this series. In this, the second communication on diguanides, only those routes based on N^1-substituted dicyandiamide derivatives (VI) are discussed.

The first alternative route investigated was the converse of that described in Part X (*loc. cit.*), namely, the preparation of alkyldicyandiamides and their reaction with arylamines. This method appeared to be particularly suitable for the synthesis of N^1-aryl-N^5-alkyldiguanides variously substituted in the aromatic ring, since it was independent of the capacity of the aniline to diazotise and couple with dicyandiamide. No monoalkyldicyandiamides had been recorded in the literature, but it was thought that they should be accessible by a route analogous to that first employed by Wheeler and Jamieson (*J. Amer. Chem. Soc.*, 1903, **25**, 719) for the preparation of phenyldicyandiamide. In this synthesis, phenyl *iso*thiocyanate was condensed with sodium cyanamide to give (IV; R = Ph) which on successive methylation and reaction with ammonia



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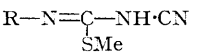

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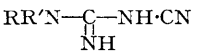


(VI.)

gave (V; R = Ph) and then (II; X = H). The condensation of sodium cyanamide with mustard oils to give (IV; R = alkyl) was first described by Wunderlich (*Ber.*, 1886, **19**, 448), and the same worker brought the products into reaction with alkyl halides to give the corresponding compounds of type (V; R = alkyl), although, as pointed out by Wheeler and Jamieson (*loc. cit.*), an incorrect structure was initially assigned to these dialkyl derivatives. Later, Hecht (*Ber.*, 1890, **23**, 1658) prepared a large number of homologues. By treatment of these compounds with ammonia, for example in alcohol at 120°, we have shown that an alkylthiol is eliminated, and in this way have prepared the *methyl-*, *ethyl-*, n- and iso-*propyl-*, and n- and iso-*butyl-dicyandiamides* (VI; R = H, R′ = alkyl). While this paper was being written May (*J. Org. Chem.*, 1947, **12**, 437) described the preparation, by a similar reaction, of (VI; R = H, R′ = Me) and (VI; R = H, R′ = Pr^{β}), although the latter was not isolated or characterised.

A more satisfactory route to the same alkyldicyandiamides was that using dicyanimide. Slotta and Tschesche (*Ber.*, 1929, **62**, 1394) caused this substance to react with two molecular proportions of alkylamines at 120—130°, and obtained the symmetrical N^1 : N^5-dialkyldiguanides. They do not record the intermediate production of alkyldicyandiamides. In a similar way we have prepared N^1 : N^5-di*iso*propyldiguanide, but we have also found that by the use of one molecular proportion of an alkylamine alkyldicyandiamides can be prepared in good yield. This route is not only simple, but makes it possible to obtain dialkyl dervatives of type (VI; R = R′ = Me, Et; R = Me, R′ = Pr^{β}; RR′ = $[CH_2]_5$) which are not available through the alkyl*iso*thioureas (V). The reaction can be effected in several ways. Thus sodium dicyanimide and *iso*propylamine hydrochloride have been condensed by heating them either in a solvent such as butanol or in an aqueous solution of such concentration that a temperature of 116—120° was achieved. Alternatively, the *iso*propylamine salt of dicyanimide was prepared by double decomposition in water of *iso*propylamine and zinc dicyanimide (U.S.P. 2,418,476), and removal of the hydrated zinc oxide. Evaporation to dryness and fusion of the resultant hygroscopic salt at 85° gave a high yield of *iso*propyldicyandiamide.

Dicyanimide has been made in a number of ways. Madelung and Kern (*Annalen*, 1922, **427**, 1) described its preparation from cyanogen bromide and disodium cyanamide, and Biechler (*Chem. Zentr.*, 1935, II, 1163) from cyanogen bromide and sodamide. The former reaction was

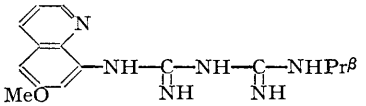
effected in aqueous solution, and the dry sodium salt obtained by evaporation. This has been used although for some purposes the aqueous reaction mixture was suitable. A convenient alternative was by adding cyanogen bromide to or passing gaseous cyanogen chloride into a solution of commercial calcium cyanamide, making the mixture slightly acid, heating it to destroy cyanate produced from a side reaction, and then using the total liquor in subsequent condensations.

Many diguanides were made by boiling alkyldicyandiamides with arylamine salts, usually the hydrochlorides, for a few hours, and isolated as the hydrochlorides which crystallised from the mixture on cooling. This method has been applied to *p*-chloroaniline, which with *iso*propyldicyandiamide gave N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide (" Paludrine ") identical with the product prepared as described in Part X. β-Ethoxyethanol with or without the addition of water was a convenient alternative solvent, particularly when the arylamine salts were sparingly water-soluble.

The dicyanimide route has been applied in a similar manner to the preparation of the aryldicyandiamides (II). This substance reacted more easily with arylamines than with alkylamines. Thus with *p*-chloroaniline hydrochloride in water, the reaction was approximately 80% complete after 24 hours at room temperature, or after 7 hours at 50—60°. For the preparation of the *α-naphthyl-* and NN-*diphenyl-dicyandiamides* (VI; R = H, R′ = α-$C_{10}H_7$; R = R′ = Ph) the reaction was carried out in aqueous ethanol. Several of the aryldicyandiamides described in Part X have been made by the new method, and the identity of the specimens established. In addition, the aryldicyandiamides have been condensed with alkylamines, the latter being used as salts such as the hydrochlorides, by a method which is less tedious than those described in Part X. Previous experience was that refluxing the components together in aqueous solution gave, in general, poor yields of the diguanides. Good yields are obtained, however, when water is replaced by an organic solvent which permits the reaction to be effected at a higher temperature. Typical reaction conditions are described in the experimental section for the preparation of N¹-p-*fluorophenyl*-N⁵-iso*propyldiguanide* (I; X = *p*-F, R = R′ = H, R″ = Pr^{β}) from *p*-fluorophenyldicyandiamide and *iso*propylamine hydrochloride in nitrobenzene at 130—135°.

Development of the above synthetic methods has enabled us to prepare a large number of N^1-substituted phenyl-N^5-alkyl-(and dialkyl-) diguanides and N¹-(6-*bromo*-2-*naphthyl*)-N⁵-iso*propyldiguanide* carrying the bromonaphthyl residue which conferred high antimalarial activity in the anilinopyrimidines (see Part V, *J.*, 1946, 366). We have also been enabled to prepare diguanides such as N¹-(6-*quinolyl*)-N⁵-iso*propyldiguanide hydrochloride* and N¹-(8-*chloro*-6-*quinolyl*)-N⁵-iso*propyldiguanide hydrochloride* which contain a quinoline residue in place of the substituted phenyl group of type (I), a variation that was suggested by the work described in Part XXII (*J.*, 1947, 1613) where an analogous alteration of the earlier pyrimidine type is reported.

Spinks (*Ann. Trop. Med. Parasit.*, 1947, **41**, 30) has shown that Paludrine exhibits absorption and distribution characteristics qualitatively similar to those of mepacrine and quinine. On the assumption that the basic side chain of the older antimarial compounds is primarily responsible for these properties (see Magidson *et al.*, *Arch. Pharm.*, 1934, **274**, 74; Magidson and Grigorowsky, *Ber.*, 1936, **69**, 396), this suggested that the *iso*propyldiguanide residue of Paludrine, besides being concerned with the intrinsic antimalarial activity, also simulated the dialkylaminoalkylamino-group in its effect on absorption, etc. Accordingly we have prepared N^1-(6-methoxy-8-quinolyl)-N^5-*iso*propyldiguanide (VII) (*hydrochloride*) in which the place of the basic side chain in pamaquin (VIII) is taken by an *iso*propyldiguanide residue.



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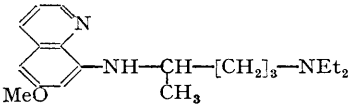

(VIII.)

In previous papers of this series it has been customary to include brief notes recording the results obtained by our colleague, Dr. D. G. Davey, with the compounds described, in tests against avian malaria. The diguanide type of antimalarial has been the subject of very extensive biological as well as chemical researches. It is more convenient to record the preparative work here and to reserve the biological results for discussion elsewhere when they can be dealt with in a more logical manner.

Experimental.

Alkyldicyandiamides. (a) *From Dicyanimide.*

Methyldicyandiamide (VI; R = H, R′ = Me).—Methylamine hydrochloride (6·8 g.), sodium dicyanimide (8·9 g.), and butanol (50 c.c.) were refluxed with stirring for 3 hours. The cooled suspension was filtered and the filtrate evaporated. The residual syrup solidified on treatment with dioxan and the compound recrystallised from the same solvent in colourless prisms (5·5 g.), m. p. 83° (Found: C, 33·2; H, 6·5; N, 52·6. Calc. for $C_3H_6N_4,\frac{1}{2}H_2O$: C, 33·65; H, 6·55; N, 52·35%). After being dried for 48 hours over sodium hydroxide and paraffin wax in a vacuum it had m. p. 93—94° (Found: C, 36·2; H, 6·15. Calc. for $C_3H_6N_4$: C, 36·8; H, 6·1%). May (*loc. cit.*) gives m. p. 91—92°.

Ethyldicyandiamide (VI; R = H, R′ = Et).—Similarly prepared from ethylamine hydrochloride (8·2 g.), the *compound* (5·4 g.), m. p. 108—109°, retained dioxan after recrystallisation from water (Found: C, 45·45; H, 7·3; N, 36·9. $C_4H_8N_4,\frac{1}{2}C_4H_8O_2$ requires C, 46·2; H, 7·7; N, 36·0%). Prolonged drying as for the methyl homologue followed by recrystallisation from ethyl acetate–petroleum gave colourless prisms, m. p. 71—72° (Found: C, 42·85; H, 7·3; N, 49·8. $C_4H_8N_4$ requires C, 42·8; H, 7·1; N, 50·0%).

n-*Propyldicyandiamide* (VI; R = H, R′ = Pr^n).—Similarly prepared from *n*-propylamine hydrochloride, itself obtained solid in the reaction flask by neutralising 4N-hydrochloric acid (25 c.c.) with *n*-propylamine and evaporating to dryness, the *compound* successively recrystallised from dioxan and water formed colourless prisms, m. p. 92—93° (Found: C, 47·75; H, 7·7; N, 44·1. $C_5H_{10}N_4$ requires C, 47·6; H, 7·95; N, 44·45%).

iso*Propyldicyandiamide* (VI; R = H, R′ = Pr$^\beta$).—Similarly prepared using *iso*propylamine hydrochloride (72 g.), sodium dicyanimide (67 g.), and butanol (185 c.c.), the *compound*, recrystallised from dioxan and dried at 40—45°, formed colourless rods, m. p. 111—113° (Found: C, 49·6; H, 8·1; N, 31·65. $C_5H_{10}N_4,\frac{1}{2}C_4H_8O_2$ requires C, 49·5; H, 8·25; N, 32·95%). Dried in a vacuum at 70—75° it had m. p. 101° (Found: C, 47·35; H, 7·45; N, 44·35. $C_5H_{10}N_4$ requires C, 47·6; H, 7·95; N, 44·45%).

iso*Butyldicyandiamide* (VI; R = H, R′ = Bu$^\beta$).—Similarly prepared using *iso*butylamine hydrochloride (37·5 g.), sodium dicyanimide (30 g.), and butanol (120 c.c.), the *compound*, recrystallised from water, formed flat colourless prisms, m. p. 112° (Found: C, 51·8; H, 8·5; N, 39·6. $C_6H_{12}N_4$ requires C, 51·4; H, 8·6; N, 40·0%).

cyclo*Hexyldicyandiamide* (VI; R = H, R′ = C_6H_{11}).—Similarly prepared using *cyclo*hexylamine hydrochloride (27 g.), sodium dicyanimide (18 g.), and butanol (50 c.c.), the *compound*, recrystallised from water, formed flat colourless prisms, m. p. 166° (Found: C, 58·1; H, 8·2; N, 33·6. $C_8H_{14}N_4$ requires C, 57·8; H, 8·4; N, 33·7%).

n-*Amyldicyandiamide* (VI; R = H, R′ = Am^n).—Similarly prepared using *n*-amylamine hydrochloride (23·9 g.), sodium dicyanimide (18 g.), and butanol (50 c.c.), the *compound*, recrystallised first from a little chlorobenzene and then from water, formed long colourless prisms, m. p. 113—115° (Found: C, 54·5; H, 8·8; N, 36·1. $C_7H_{14}N_4$ requires C, 54·6; H, 9·1; N, 36·4%).

n-*Butyldicyandiamide* (VI; R = H, R′ = Bu^n).—*n*-Butylamine hydrochloride (9·9 g.), sodium dicyanimide (9 g.), and water (2·5 c.c.) were heated at 95—100° for 4 hours, diluted with cold water (75 c.c.), and extracted with chloroform. The chloroform solution was dried (Na_2SO_4) and evaporated. The solid obtained after expressing the oil from the residue gave the *compound* as colourless prisms after crystallisation from water, m. p. 76—78° (Found: C, 51·4; H, 8·5; N, 40·0. $C_6H_{12}N_4$ requires C, 51·4; H, 8·6; N, 40·0%).

Dimethyldicyandiamide (VI; R = R′ = Me).—Prepared as described for the monomethyl homologue from dimethylamine hydrochloride (46 g.), sodium dicyanimide (37 g.), and butanol (120 c.c.), the *compound* crystallised on cooling (18 g., and a further 14 g. from evaporation of the mother liquor). It gave colourless crystals from water, m. p. 176—177° (Found: C, 42·9; H, 7·0; N, 50·0. $C_4H_8N_4$ requires C, 42·8; H, 7·1; N, 50·1%).

Diethyldicyandiamide (VI; R = R′ = Et).—Similarly prepared, the *compound* gave colourless needles from toluene, m. p. 150—151° (Found: C, 51·35; H, 8·55; N, 40·1. $C_6H_{12}N_4$ requires C, 51·4; H, 8·6; N, 40·0%).

*Methyl*iso*propyldicyandiamide* (VI; R = Me, R′ = Pr$^\beta$).—Prepared as described for the *n*-propyl homologue, the *compound* was obtained solid after distilling off the butanol, digesting the residue with hot water, treating it with charcoal, and cooling. It formed colourless leaflets, m. p. 64—65° (Found: C, 48·25; H, 8·85; N, 37·35. $C_6H_{12}N_4,\frac{1}{2}H_2O$ requires C, 48·3; H, 8·75; N, 37·6%).

cyclo*Pentamethylenedicyandiamide* (VI; RR′ = $[CH_2]_5$).—Piperidine (30 c.c.), 2N-hydrochloric acid (150 c.c.), and sodium dicyanimide (30 g.) were refluxed for 8 hours. The dark precipitate of the *compound* obtained on cooling when recrystallised from water with charcoal treatment formed colourless prisms, m. p. 153—155° (Found: C, 55·6; H, 7·35; N, 36·45. $C_7H_{12}N_4$ requires C, 55·3; H, 7·9; N, 36·8%).

Alkyldicyandiamides. (b) *From* N-*Cyano*-S-*methyl*iso*thiourea Derivatives.*

N-*Cyano*-N′S-*dimethyl*iso*thiourea* (V; R = Me).—A mixture of methyl *iso*thiocyanate (7·3 g.) and sodium cyanamide (6·4 g.) in ethanol (150 c.c.) was stirred for 18 hours at laboratory temperature and then filtered from a little insoluble solid. Methyl iodide (28 g.) was added to the filtrate, and after ½ hour the crystalline suspension which formed was refluxed for ½ hour and cooled, and the product collected and washed with water and ethanol. After several recrystallisations from ethanol it had m. p. 196° (decomp.) (Found: C, 37·25; H, 5·7; N, 33·0; S, 24·8. Calc. for $C_4H_7N_3S$: C, 37·2; H, 5·45; N, 32·6; S, 24·8%). Hecht (*loc. cit.*) gave m. p. 194—195° for the same product. Similarly prepared were the homologues: N′-*ethyl*-, m. p. 161—163° (Found: C, 42·0; H, 5·95; N, 29·55; S, 22·4. $C_5H_9N_3S$ requires C, 41·95; H, 6·3; N, 29·35; S, 22·4%); N′-n-*propyl*-, m. p. 113° (Found: C, 45·9; H, 7·05; N, 27·15. $C_6H_{11}N_3S$ requires C, 45·85; H, 7·0; N, 26·75%); N′-iso*propyl*-, m. p. 117—119° (Found: C, 45·95; H, 6·9; N, 26·15; S, 20·9. $C_6H_{11}N_3S$ requires C, 45·85; H, 7·0; N, 26·75; S, 20·4%); N′-n-*butyl*-, m. p. 120° (Found: C, 48·75; H, 7·35; N, 24·75. $C_7H_{13}N_3S$ requires C, 49·1; H, 7·6; N, 24·55%); and N′-iso*butyl*-, m. p. 119—120° (Found: C, 49·4; H, 7·7; N, 24·75%).

The above *N*-cyano-*S*-methyl-*N'*-alkyl*iso*thioureas were converted into the corresponding *N*-alkyldicyandiamides by treatment with ammonia. The products in some experiments were viscous water-soluble oils which, however, were shown to consist mainly of the required substances by reaction with arylamine salts to give the expected N^1-aryl-N^5-alkyldiguanides in good yield. A typical experiment for the production of *iso*propyldicyandiamide was as follows. *N*-Cyano-*S*-methyl-*N'-iso*propyl*iso*thiourea (3 g.) and saturated alcoholic ammonia (50 c.c.) were heated in a sealed tube at 120° for 6 hours. The alcohol, excess of ammonia, and methylthiol were distilled off and the residual oil was dissolved in chloroform and filtered, and the solvent evaporated. Treatment of the residue with dioxan gave a solid which when recrystallised from the same solvent and dried in a vacuum at 70—75° had m. p. 101° and was identical with the product obtained by the dicyanimide route.

Aryldicyandiamides.

p-*Chlorophenyldicyandiamide* (II; X = *p*-Cl).—Cyanogen chloride was passed into calcium cyanamide (commercial fertiliser, 250 g.) and water (1 l.) cooled in ice–water, until the mixture was only faintly alkaline to litmus. The suspension was left overnight and filtered. A solution of *p*-chloroaniline (180 g.) in 3·5N-hydrochloric acid (410 c.c.) at 40° was added, and the mixture stirred for 24 hours at laboratory temperature. The precipitate which formed was collected, dissolved in 2N-sodium hydroxide (3 l.) at 60°, treated with charcoal, and filtered, and the filtrate made acid with hydrochloric acid. The pale cream crystalline precipitate of *p*-chlorophenyldicyandiamide when filtered off, washed with water, and dried (116 g.) had m. p. 197—200°. When recrystallised from ethanol it had m. p. 204—205° undepressed in admixture with material made as described in Part X (*loc. cit.*). Higher yields (*ca.* 80%) were obtained by interaction of sodium dicyanimide and *p*-chloroaniline hydrochloride either as above, at 60—70° for 6 hours, or at 85—90° for 2 hours.

p-*Iodophenyldicyandiamide* (II; X = *p*-I).—*p*-Iodoaniline hydrochloride (5·1 g.), sodium dicyanimide (1·8 g.), dioxan (30 c.c.), and water (100 c.c.) were stirred for 8 hours at 50—55°. The precipitate which formed was collected, washed with water, and dissolved in 2N-sodium hydroxide (60 c.c.) at 70—75°, the solution filtered, and the filtrate made acid with hydrochloric acid. The *product* recrystallised from wet ethanol, m. p. 222° (Found: C, 33·5; H, 2·7; N, 19·3. $C_8H_7N_4I$ requires C, 33·55; H, 2·45; N, 19·6%). Similar methods were used for the preparation of the corresponding phenyl- (m. p. 198—199°) and *p*-methoxyphenyl (m. p. 192°) dicyandiamides, and the identity of the products with those described in Part X established. For the preparation of *α-naphthyldicyandiamide* (VI; R = H, R' = α $C_{10}H_7$), naphthylamine (7·25 g.) in 2N-hydrochloric acid (25 c.c.) and ethanol (50 c.c.) was kept at 40° with sodium dicyanimide (5·5 g.) in water (20 c.c.). The insoluble oil that formed solidified on standing and when recrystallised from ethanol had m. p. 160—161° (Found: C, 68·4; H, 5·1; N, 26·1. $C_{12}H_{10}N_4$ requires C, 68·6; H, 4·8; N, 26·6%). NN-*Diphenyldicyandiamide* (VI; R = R' = Ph) was prepared in the same manner, using aqueous ethanol as solvent. The crude *product* obtained on adding water to the reaction mixture was freed from unchanged amine by treatment with toluene, and reprecipitated by addition of water to a filtered solution in acetone, and then gave colourless prisms from ethanol, m. p. 204—205° (Found: C, 70·8; H, 5·2; N, 24·2. $C_{14}H_{12}N_4$ requires C, 71·2; H, 5·1; N, 23·7%).

o-*Tolyldicyandiamide* (VI; R = H, R' = *o*-C_6H_4Me), colourless rhombs from ethanol, m. p. 131—132° (Found: C, 62·2; H, 6·05; N, 31·5. $C_9H_{10}N_4$ requires C, 62·2; H, 5·7; N, 32·2%), and *β-naphthyldicyandiamide* (VI; R = H, R' = β-$C_{10}H_7$), m. p. 248—249° (Found: C, 68·15; H, 4·5; N, 27·1. $C_{12}H_{10}N_4$ requires C, 68·6; H, 4·8; N, 26·6%), were prepared in the same way but using water only as the solvent. *N*-Methylaniline hydrochloride similarly gave N^1-*phenyl*-N^1-*methyldicyandiamide* (VI; R = Me, R' = Ph) which crystallised from toluene and had m. p. 135—136° (Found: C, 61·85; H, 6·0; N, 32·0. $C_9H_{10}N_4$ requires C, 62·2; H, 5·7; N, 32·2%). The preparation of the corresponding *p*-chlorophenyl derivative by methylation of *p*-chlorophenyldicyandiamide was described in Part X. Both substances are insoluble in dilute sodium hydroxide.

Diguanides.

N^1-p-*Chlorophenyl*-N^5-iso*propyldiguanide* (I; X = *p*-Cl, R = R' = H, R'' = Pr$^\beta$) ("*Paludrine*").—*p*-Chloroaniline hydrochloride (16·4 g.), *iso*propyldicyandiamide (12·9 g.), and water (50 c.c.) were refluxed for 4 hours. The cooled suspension was filtered, and the colourless crystals (yield, 22 g., 80%) when recrystallised from aqueous ethanol gave the diguanide hydrochloride, m. p. 243—244° undepressed in admixture with the hydrochloride made as described in Part X. The free base liberated by addition of sodium hydroxide to an aqueous-ethanolic suspension of the hydrochloride when crystallised from aqueous ethanol and air-dried at laboratory temperature formed colourless needles of the *monohydrate* and had m. p. 94—95° (Found: C, 48·75; H, 6·2; N, 25·4; Cl, 13·1. $C_{11}H_{16}N_5Cl,H_2O$ requires C, 48·6; H, 6·6; N, 25·8; Cl, 13·1%). Continued drying at 90—100° gave anhydrous material, m. p. 129°, identical with that obtained by recrystallisation from toluene (see Part X), but until dehydration was complete sintering at 104—106° gave evidence of an intermediate hydrate.

(a) N^1-p-*Substituted-phenyl*-N^5-iso*propyldiguanides*.—N^1-p-*Fluorophenyl*-N^5-iso*propyldiguanide* (I; X = *p*-F, R = R' = H, R'' = Pr$^\beta$). *p*-Fluoroaniline hydrochloride (6·7 g.), *iso*propyldicyandiamide (6·3 g.), and β-ethoxyethanol (40 c.c.) were refluxed for 5 minutes, the bulky precipitate which formed being broken up by shaking the mixture. After cooling, ethyl acetate (30 c.c.) was added and the suspension was filtered. The *hydrochloride* crystallised from water in colourless plates, m. p. 250—251° (Found: C, 48·7; H, 5·95; N, 24·9. $C_{11}H_{16}N_5F,HCl$ requires C, 48·25; H, 6·2; N, 25·6%) (5639) The product was identical with that made by the general method described in Part X (*loc. cit.*) by heating p-*fluorophenyldicyandiamide* (1·2 g.) [colourless prisms from water, m. p. 204—205° (Found: C, 53·9; H, 3·7; N, 32·2. $C_8H_7N_4F$ requires C, 53·9; H, 3·9; N, 31·5%)] and *iso*propylamine hydrochloride (1 g.) in nitrobenzene at 130—135° for 16 hours, extracting the resultant suspension with hot water, and crystallising the hydrochloride from the aqueous layer by chilling.

The following N^1-*p*-substituted-phenyl-N^5-*iso*propyldiguanide hydrochlorides were made similarly using the same solvent: N^1-p-*iodophenyl*- (I; X = *p*-I, R = R' = H, R'' = Pr$^\beta$), colourless needles

from water, m. p. 237—239° (Found: C, 34·9; H, 4·5; N, 18·1. $C_{11}H_{16}N_5I$,HCl requires C, 34·6; H, 4·45; N, 18·35%) (5744); N¹-p-*nitrophenyl*- (I; X = *p*-NO_2, R = R′ = H, R″ = Pr$^\beta$), yellow prismatic needles from water, m. p. 254° (decomp.) (Found: C, 44·35; H, 5·8; N, 27·8. $C_{11}H_{16}O_2N_6$,HCl requires C, 43·95; H, 5·65; N, 27·95%) (5858); N¹-p-*cyanophenyl*- (I; X = *p*-CN, R = R′ = H, R″ = Pr$^\beta$), colourless prisms from water, m. p. 239—241° (Found: C, 50·9; H, 5·85; N, 29·0. $C_{12}H_{16}N_6$,HCl requires C, 51·35; H, 6·05; N, 29·95%) (5859); and N¹-p-*tolyl*- (I; X = *p*-Me, R = R′ = H, R″ = Pr$^\beta$), colourless prisms from water, m. p. 240° (Found: C, 53·2; H, 7·45; N, 25·95. $C_{12}H_{19}N_5$,HCl requires C, 53·35; H, 7·4; N, 25·95%) (5909).

N¹-p-*Diphenylyl*-N⁵-iso*propyldiguanide* (I; X = *p*-Ph, R = R′ = H, R″ = Pr$^\beta$). *p*-Aminodiphenyl hydrochloride (5·5 g.), *iso*propyldicyandiamide (2·8 g.), and water (30 c.c.) were refluxed for 3 hours. The *hydrochloride* precipitated on cooling and recrystallised from aqueous ethanol in colourless needles, m. p. 253—254° (Found: C, 61·2; H, 6·2; N, 21·1. $C_{17}H_{21}N_5$,HCl requires C, 61·55; H, 6·55; N, 21·1%) (5983).

The following *N*¹-*p*-substituted-phenyl-*N*⁵-*iso*propyldiguanide hydrochlorides were made in a similar manner: N¹-p-*bromophenyl*- (I; X = *p*-Br, R = R′ = H, R″ = Pr$^\beta$), colourless prisms from water, m. p. 246° (Found: C, 39·55; H, 4·85; N, 20·2; Cl′, 10·8. $C_{11}H_{16}N_5Br$,HCl requires C, 39·45; H, 5·1; N, 20·95; Cl′, 10·6%) (5382); N¹-p-*ethoxyphenyl*- (I; X = *p*-OEt, R = R′ = H, R″ = Pr$^\beta$), colourless needles from water, m. p. 240° (Found: C, 51·85; H, 7·05; N, 23·55. $C_{13}H_{21}ON_5$,HCl requires C, 52·05; H, 7·35; N, 23·4%) (5568); N¹-p-*methylthiophenyl* (I; X = *p*-SMe, R = R′ = H, R″ = Pr$^\beta$), colourless needles from water, m. p. 242—244° (Found: C, 47·85; H, 6·5; N, 23·6. $C_{12}H_{19}N_5S$,HCl requires C, 47·75; H, 6·65; N, 23·2%) (5739); and N¹-*phenyl*- (I; X = R = R′ = H, R″ = Pr$^\beta$), colourless plates from water, m. p. 235—236° (Found: C, 51·85; H, 6·95; N, 27·55. $C_{11}H_{17}N_5$,HCl requires C, 51·65; H, 7·0; N, 27·4%) (5771).

(b) N¹-o- *or* -m-*Substituted-phenyl*-N⁵-iso*propyldiguanides*.—The following hydrochlorides of this type were made by the methods described in (a). Reaction in water: N¹-o-*chlorophenyl*- (I; X = *o*-Cl, R = R′ = H, R″ = Pr$^\beta$), colourless prisms from water, m. p. 234—235° (Found: C, 45·6; H, 5·8; N, 24·3. $C_{11}H_{16}N_5Cl$,HCl requires C, 45·5; H, 5·85; N, 24·15%) (5741), and N¹-m-*chlorophenyl*- (I; X = *m*-Cl, R = R′ = H, R″ = Pr$^\beta$), colourless prisms from water, m. p. 232° (Found: C, 46·1; H, 6·15; N, 23·45. $C_{11}H_{16}N_5Cl$,HCl requires C, 45·5; H, 5·85; N, 24·15%) (5383). Reaction in β-ethoxyethanol: N¹-o-*tolyl*- (I; X = *o*-Me, R = R′ = H, R″ = Pr$^\beta$), colourless needles from water, m. p. 237° (Found: C, 53·15; H, 7·35; N, 25·6. $C_{12}H_{19}N_5$,HCl requires C, 53·45; H, 7·4; N, 25·95%) (5908); N¹-m-*tolyl*- (I; X = *m*-Me, R = R′ = H, R″ = Pr$^\beta$), colourless prisms from water, m. p. 216—217° (Found: C, 53·2; H, 7·6; N, 25·9. $C_{12}H_{19}N_5$,HCl requires C, 53·45; H, 7·4; N, 25·95%) (5910); and N¹-m-*cyanophenyl*- (I; X = *m*-CN, R = R′ = H, R″ = Pr$^\beta$), colourless prisms from water, m. p. 220—221° (Found: C, 51·5; H, 6·0; N, 29·8. $C_{12}H_{16}N_6$,HCl requires C, 51·35; H, 6·05; N, 29·95%) (5906); N¹-m-*carboxyphenyl*- (I; X = *m*-CO_2H, R = R′ = H, R″ = Pr$^\beta$), colourless prisms from water, m. p. 202—204° (Found: C, 48·65; H, 6·05; N, 22·9. $C_{12}H_{17}O_2N_5$,HCl requires C, 48·25, H, 5·7; N, 23·45%) (6655).

(c) N¹-*Substituted-phenyl*-N⁵ : N⁵-*dialkyldiguanides*.—The following were obtained by the methods described in (a) above, using methyl*iso*propyldicyandiamide (VI; R = Me, R′ = Pr$^\beta$) and in one instance diethyldicyandiamide (VI; R = R′ = Et). Reaction in water: N¹-o-*chlorophenyl*-N⁵-*methyl*-N⁵-iso*propyldiguanide hydrochloride* (I; X = *o*-Cl, R = H, R′ = Me, R″ = Pr$^\beta$), colourless prisms from water, m. p. 227° (Found: C, 47·15; H, 6·1; N, 22·3. $C_{12}H_{18}N_5Cl$,HCl requires C, 47·35; H, 6·25; N, 23·0%) (5985); N¹-m-*chlorophenyl*-N⁵-*methyl*-N⁵-iso*propyldiguanide hydrochloride* (I; X = *m*-Cl, R = H, R′ = Me, R″ = Pr$^\beta$), colourless needles from water, m. p. 234° (Found: C, 47·15; H, 6·0; N, 23·0. $C_{12}H_{18}N_5Cl$,HCl requires C, 47·35; H, 6·25; N, 23·0%) (5984); N¹-p-*nitrophenyl*-N⁵-*methyl*-N⁵-iso*propyldiguanide hydrochloride* (I; X = *p*-NO_2, R = H, R′ = Me, R″ = Pr$^\beta$), yellow needles from water, m. p. 249° (Found: C, 45·75; H, 6·15; N, 26·75. $C_{12}H_{18}O_2N_6$,HCl requires C, 45·8; H, 6·05; N, 26·7%) (6001); and N¹-p-*cyanophenyl*-N⁵-*methyl*-N⁵-iso*propyldiguanide hydrochloride* (I; X = *p*-CN, R = H, R′ = Me, R″ = Pr$^\beta$), colourless needles from water, m. p. 252—253° (Found: C, 52·9; H, 6·25; N, 28·15. $C_{13}H_{18}N_6$,HCl requires C, 52·95; H, 6·45; N, 28·55%) (6002). Reaction in β-ethoxyethanol: *N*¹-*m*-chlorophenyl-*N*⁵ : N⁵-diethyldiguanide (I; X = *m*-Cl, R = H, R′ = R″ = Et), colourless prisms from water, m. p. 226—227°; *hydriodide*, m. p. 218—219° (Found: C, 36·4; H, 4·9; N, 17·4. $C_{12}H_{18}N_5Cl$,HI requires C, 36·4; H, 4·8; N, 17·7%) (5944); and N¹-p-*iodophenyl*-N⁵-*methyl*-N⁵-iso*propyldiguanide hydrochloride* (I; X = *p*-I, R = H, R′ = Me, R″ = Pr$^\beta$), colourless needles from water, m. p. 236—237° (Found: C, 36·9; H, 4·9; N, 17·9. $C_{12}H_{18}N_5I$,HCl requires C, 36·5; H, 4·8; N, 17·7%) (6004).

(d) *Miscellaneous Diguanides*.—N¹-(6-*Bromo*-2-*naphthyl*)-N⁵-iso*propyldiguanide*. Prepared by method (a) above from 6-bromo-2-naphthylamine hydrochloride and *iso*propyldicyandiamide in β-ethoxyethanol, the *base* was isolated by warming the crude reaction precipitate in aqueous ethanolic sodium hydroxide, and formed colourless prisms from alcohol, m. p. 183° (Found: C, 52·0; H, 5·25; N, 19·9. $C_{15}H_{18}N_5Br$ requires C, 51·7; H, 5·15; N, 20·1%) (5437).

N¹-4-3′ : 5′-*Dimethylphenoxyphenyl*-N⁵-iso*propyldiguanide* (I; X = -C_6H_4·O·$C_6H_3Me_2$-3 : 5, R = R′ = H, R″ = Pr$^\beta$). Prepared by refluxing 4-3′ : 5′-dimethylphenoxyaniline hydrochloride and *iso*propyldicyandiamide in water, the *hydrochloride* formed colourless needles from water, m. p. 236—238° (Found: C, 60·6; H, 6·9; N, 18·7. $C_{19}H_{25}ON_5$,HCl requires C, 61·05; H, 6·95; N, 18·75%) (6101).

N¹-p-*Tolyl*-N⁵-*ethyldiguanide* (I; X = *p*-Me, R′ = H, R″ = Et). The *hydrochloride*, prepared from *p*-toluidine hydrochloride and ethyl dicyandiamide, crystallised from alcohol and had m. p. 222—223° (Found: C, 51·85; H, 7·0; N, 27·5. $C_{11}H_{17}N_5$,HCl requires C, 51·65; H, 7·05; N, 27·4%) (5567).

N¹-(6-*Quinolyl*)-N⁵-iso*propyldiguanide*. The *hydrochloride*, prepared from 6-aminoquinoline hydrochloride and *iso*propyldicyandiamide in boiling β-ethoxyethanol, crystallised from water, m. p. 241—242° (Found: C, 54·8; H, 6·1; N, 27·5. $C_{14}H_{18}N_6$,HCl requires C, 54·8; H, 6·2; N, 27·4%) (5738).

N¹-(8-*Chloro*-6-*quinolyl*)-N⁵-iso*propyldiguanide*. Prepared similarly from 8-chloro-6-aminoquinoline hydrochloride and *iso*propyldicyandiamide, the *hydrochloride* separated from water, m. p. 264—265° (Found: C, 49·1; H, 5·3; N, 24·2. $C_{14}H_{17}N_6Cl$,HCl requires C, 49·25; H, 5·3; N, 24·65%) (5907)

N^1-(6-*Methoxy*-8-*quinolyl*)-N^5-iso*propyldiguanide* (VII). Prepared similarly from *iso*propyldicyandiamide and 8-amino-6-methoxyquinoline hydrochloride in boiling β-ethoxyethanol, the *hydrochloride* crystallised from water and then had m. p. 237° (Found : C, 50·5; H, 6·6; N, 24·0. $C_{15}H_{20}ON_6,HCl,H_2O$ requires C, 50·8; H, 6·5; N, 23·7%) (5742).

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