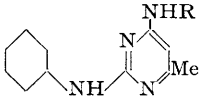
149. *Synthetic Antimalarials. Part X. Some Aryl-diguanide* (" *-biguanide* ") *Derivatives.*

By F. H. S. Curd and F. L. Rose.

The relation between antimalarial activity and the chemical constitution of the pyrimidine compounds described in earlier papers in this series has been studied and a working hypothesis has been advanced which led to the synthesis of and discovery of activity in a series of diguanides (" biguanides "). One derivative, N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide (" Paludrine ") has been examined extensively in human malaria.

In Part I (Curd and Rose, this vol., p. 343) the discovery was recorded of a new class of antimalarial drugs typified by structure [I; R = alkylene·N(alkyl)$_2$]. The phenyl nucleus carried a variety of substituents.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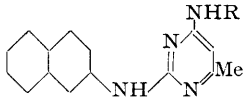
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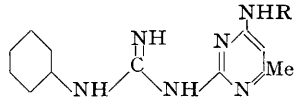
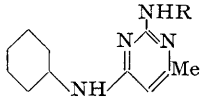

(III.)

In subsequent papers it was shown how this type had been elaborated to provide yet other active structures, as (II), (III) and (IV), again with the nucleus variously substituted. The suggestion was made, supported in part by the work of our colleague Dr. Madinaveitia (*Biochem. J.*, in press), that these substances might be func-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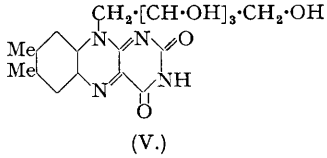
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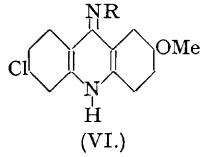
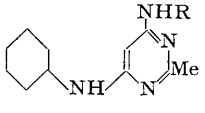
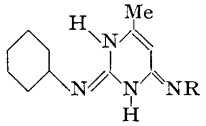

(VI.)

tioning as plasmodicidal agents by virtue of their antagonism for riboflavin (V) to which they could be shown to bear some formal structural resemblance. Attempts have been made to enhance the antimalarial activity by introducing substituents into (I), *e.g.*, 3 : 4-dimethyl into the benzene ring (Part II, this vol., p. 351) and 5-methyl into the pyrimidine nucleus (Part VII, this vol., p. 378), with the object of still further increasing the similarity to riboflavin. The results obtained have been inconclusive and, while we do not dismiss the possible validity of the antagonism hypothesis, we have returned as a means of extending our researches to one of the early arguments on which the new antimalarial drugs were in part based, namely, consideration of the tautomeric possibilities existing within certain known active drug molecules. This line of thought also provided a rational means for further simplifying drug structure and thus facilitating the elucidation of the ultimate relation between chemical constitution and biological activity. In earlier papers we have referred to the hypothesis presented by Schönhöfer (*Z. physiol. Chem.*, 1942, **274**, 1) which seeks to relate antimalarial activity in the mepacrine molecule to the possible formation of a *p*-quinonoid tautomer involving the ring nitrogen atom and the 5-alkylamino group in the manner shown in (VI). Reference to types (I) and (IV) shows that a similar *p*-quinonoid structure is only possible in the former, yet both provide active substances. We therefore tentatively modified the Schönhöfer hypothesis to embrace tautomerism leading to an *o*-quinonoid structure and concluded that, in the pyrimidine series, antimalarial activity might be expected when both arylamino and alkylamino substituents were present each of which permitted the formulation of either *o*- or *p*-quinonoid-like tautomers. The inactivity of the isomeric type (VII) (see Part VIII, this vol., p. 717) called for some modification of this


(VII.)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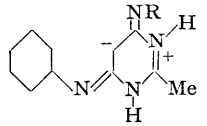
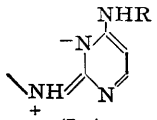
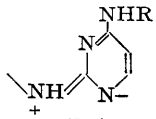

(IX.)

generalisation, and it was further postulated that the tautomeric systems associated with the substituent arylamino and alkylamino groups should be capable of independent function. In (VII) the tautomeric systems

are interdependent in that, for example, positioning of the bonds in the RNH—C═N— system in the manner formulated prevents tautomerism elsewhere in the molecule. Without listing all the possibilities inherent in types (I), (IV), and (VII), this point can be further illustrated by referring to tautomer (VIII) which has no equivalent amongst the variants of (VII), except the unlikely (IX). The guanidine (III) is similar to (I) and in fact introduces still another system, that of the guanidine linkage, capable of tautomeric modification. In addition to the prototropic changes inherent in the molecules now being considered, a like number of resonance possibilities are conceivable. Thus, the pyrimidine moiety of (I) may be a hybrid between the several zwitterion forms (IA)—(IE) and the " Kékulé " forms. Here again there are limitations in type (VII) not to be found in types (I), (III), or (IV). To what extent prototropy or resonance, or both, are associated with antimalarial


(IA.)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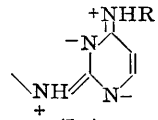
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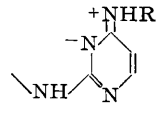
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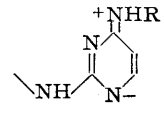
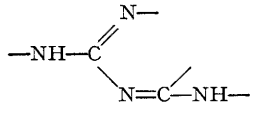
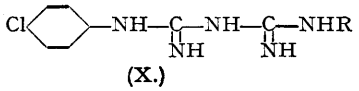

(IE.)

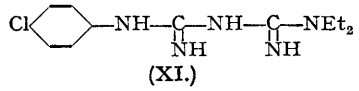
activity, it was not at this stage possible to indicate. These properties would be influenced by changes in the molecule, such as the introduction of substituents into the benzene ring, or replacement of amino hydrogen by alkyl. Much of the work subsequent to that described here has been devoted to a study of these aspects and will be discussed in detail at a later date. For the moment we accepted the principles enunciated above as the basis for a working hypothesis. Further consideration suggested that while a pyrimidine ring provided a convenient means for the synthesis of structures containing the salient features, a ring system *per se* need not be essential, and any heteroenoid system of the type



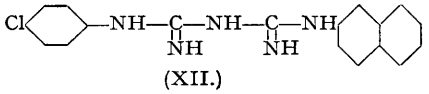
might be expected to function in the same manner.

The diguanide (" biguanide ") molecule, in which we had previously been interested for the synthesis of compounds of type (III) (see Part IV, this vol., p. 362), provided the necessary structural features around which we might expect to build up active drugs. Initial research was therefore directed towards the preparation of compounds of type (X) in which R=$[CH_2]_2$·NEt_2, $[CH_2]_3$·NEt_2, and CHMe·$[CH_2]_3$·NEt_2. The preparative methods employed are discussed below. Only the first of these compounds was examined in detail; it proved quite inactive. We have been unable to explain this result, but at the time it was attributed to the highly basic character of the molecule, and the possible influence on tautomerism and resonance of the ionic charges that it would carry under physiological conditions. To minimise any such effect, one of the basic groups was omitted and simpler molecules typified by (XI) were synthesised. These proved markedly active and the research


(X.)


(XI.)

then became an investigation of the effect of variation in the aryl substituents and the terminal alkyl groups. Constitutions and antimalarial activities are given in the table on p. 733. It was found that a wide range of mono- and di-alkyl derivatives corresponding to (X) and (XI) were active, highest activity occurring with a total of 3 or 4 carbon atoms in the alkyl groups with a maximum at mono-*iso*propyl (X; R = Pr^{β}). The parent *p*-chlorophenyldiguanide and its monomethyl derivative were ineffective. An important feature of these compounds was that their biological activity was not confined to the erythrocytic forms of the malarial parasite. This point is discussed elsewhere in detail (Curd, Davey, and Rose, *Ann. Trop. Med. Parasit.*, 1945, **39**, 208), but briefly it has been found by Dr. Davey that many of these substances act on a parasite phase preceding the blood-invasive form, that is, in experimental species at least, they function as true causal prophylactic agents. Replacement of the alkyl group by a further aryl residue to give, *e.g.*, (XII) greatly reduces the antimalarial effect, as does also the introduction of a methyl group as in (XIII). The influence of the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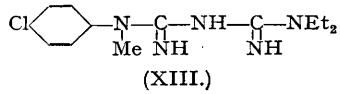
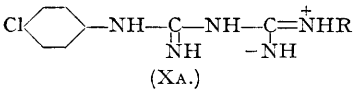
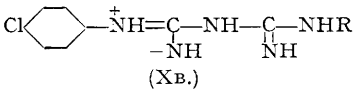
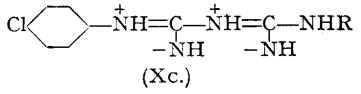

(XIII.)

substituent in the benzene ring appeared to be similar to that observed in the earlier pyrimidine drugs, chlorine in the *para* position being the most effective of the few variants examined. Reviewing, in the light of these results, the premises relating to resonance and tautomerism which led to the preparation and examination of the diguanide drugs, it is apparent that some differentiation of the two effects may

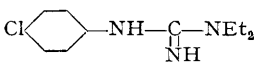
become possible. Structure (X) can be formulated in seven " zwitterion " modifications [compare (IA)—(IE)] of which (XA), (XB), and (XC) are examples and the same number of possibilities exists for the di- and


(XA.)


(XB.)


(XC.)

tri-alkyl derivatives such as (XI) and (XIII), active and almost inactive respectively. The number of possible tautomerides available through prototropy is dependent, however, on the degree of alkylation of the diguanide chain, and it may be significant that in the feebly active (XIII) the positioning of the alkyl groups does not permit the existence of the molecule of the two independent tautomeric systems originally postulated as essential for antimalarial activity. Similar limitations apply to the simple guanidine (XIV) which is inactive. A further feature of the diguanide structure which has to be considered is the possibility that the molecule may be modified by hydrogen bonding, leading to cyclic structures such as (XV), the existence of which may profoundly influence biological properties.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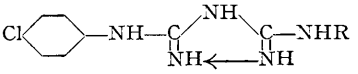
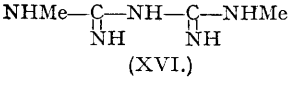
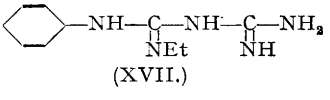

(XV.)

Several of the compounds described in this paper have been examined in human malaria. Clinical details will be published elsewhere by the workers concerned, but it may be said here that (X; R = Pr^{β}), for example, for which the name " Paludrine " has been registered, has proved highly effective at doses lower than those customary with mepacrine and quinine.

The synthesis of diguanide and its simple alkyl and aryl derivatives has been fairly extensively studied by other workers. The most convenient starting material has been dicyandiamide. This substance by interaction with ammonium chloride yields diguanide hydrochloride (Bamberger and Dieckmann, *Ber.*, 1892, **25**, 545; Smolka and Friedreich, *Montash.*, 1888, **9**, 228) and Smolka and Friedreich have extended the reaction to arylamines and alkylamines. The use of ammoniacal copper sulphate solution appears to facilitate the reaction with ammonia and allows diguanide to be isolated as its sparingly soluble copper complex (Rathke, *Ber.*, 1879, **12**, 780; Herth, *Ber.*, 1880, **13**, 1358; Rackmann, *Annalen*, 1910, **376**, 170). Slotta and Tschesche (*Ber.*, 1929, **62**, 1394) showed that dicyanimide could be made to react with two molecules of an alkylamine hydrochloride, *e.g.*, methylamine hydrochloride, to give (XVI), but, so far as we are aware, the only example of a disubstituted diguanide bearing an aryl group and an alkyl group on different nitrogen atoms has been provided by Cramer (*Ber.*, 1901, **34**, 2602) who caused *N*-phenyl-*N'*-ethylthiourea to react with guanidine in the presence of mercuric oxide to yield (XVII). An aryldiguanide (XVIII; R = NH·$[CH_2]_2$·NEt_2) has been described by I.G. Farbenind. (D.R.-P. 632,572/1933) and said *inter alia* to exhibit plasmodicidal and antibacterial


(XVI.)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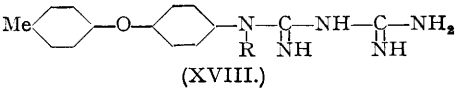
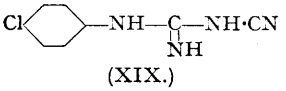
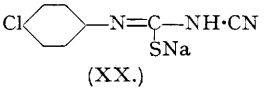

(XVIII.)

properties. The parent *p*-chlorophenyldiguanide corresponding to (X) has been described by us (Part IV, *loc. cit.*) and by Strukov, Sychra, and Smirnov (*J. Chem. Ind.* (U.S.S.R.), 1941, **18**, 22), and was made by reaction of *p*-chloroaniline hydrochloride with dicyandiamide. We considered that an analogous reaction between *p*-chlorophenyldicyandiamide (XIX) and a dialkylaminoalkylamine would provide the most satisfactory route to (X; R = dialkylaminoalkyl). Other routes have subsequently been examined and many have proved successful. These will be recorded in later papers in this series. Phenyldicyandiamide was first prepared by


(XIX.)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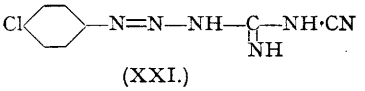
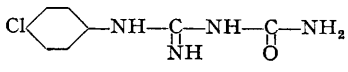

(XXI.)

Wheeler and Jamieson (*J. Amer. Chem. Soc.*, 1903, **25**, 719) from (XXI), the reaction product of phenyl *iso*-thiocyanate and sodium cyanamide, by *S*-methylation and treatment with ammonia, but a more convenient preparation of the same compound and (XIX) was described by Walther and Grieshammer (*J. pr. Chem.*, 1915, **92**, 251) who passed dry hydrogen chloride into an ether suspension of (XXI), and the corresponding phenyl, *m*-tolyl, and *p*-tolyl compounds, and eliminated nitrogen from the products by adding them to hot water. (XXI) is obtained in good yield by coupling diazotised *p*-chloroaniline with dicyandiamide in aqueous sodium carbonate, but we have found it dangerous to handle in bulk when dry, since it is readily detonated by friction. The Walther and Grieshammer method has been modified therefore by employing the method described by Rose and Broadbent (E.P. Appln. 8888/44) in which the more stable wet filter paste from the coupling reaction is decomposed smoothly and cleanly by addition to a mixture of concentrated hydrochloric acid and

a water-miscible solvent, such as β-ethoxyethanol, acetic acid, or acetone. The reaction was effected at temperatures between 20° and 40° and was usually complete in 2 hours. The aryldicyandiamide was then isolated by adding water and purified by reprecipitation from an aqueous solution of the sodium salt. Walther and Grieshammer (*loc. cit.*) record the conversion of (XXI) into (XXII) by heating a solution in ethanol



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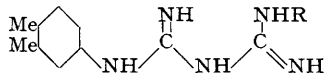


(XXIII.)

and hydrogen chloride (used either as dry gas or as the concentrated aqueous solution), but it is not clear whether hydrolysis of the cyano group preceded or followed elimination of the azo-nitrogen. The modified reaction conditions have been used to prepare, in addition to (XIX), the phenyl, *p*-nitrophenyl, *p*-tolyl, *p*-anisyl, *p*-acetamidophenyl, and 3 : 4-xylyl derivatives. The last named was employed since the resultant diguanides (XXIII), formulated as shown, could still be remotely related to riboflavin (V) although less obviously than (I).

The aryldicyandiamides have been converted into diguanides by interaction with either (*a*) the amine hydrochloride, or (*b*) the amine in the presence of copper sulphate. The first method was used mainly with the aromatic amines, and the reaction, effected in boiling aqueous dioxan or β-ethoxyethanol, was in many cases rapidly completed. Aliphatic amines reacted much more slowly under these conditions and it was found more convenient to employ the second method with excess of free amine dissolved in aqueous ethanol, with addition of one equivalent of copper sulphate calculated on the dicyandiamide used. The diguanide was then obtained as a copper complex which in many cases remained dissolved in the hot reaction mixture. The rate of conversion into diguanide could be judged by the formation of the coloured complex (purple-brown). It was extremely rapid with certain amines, notably dimethylamine, but with the primary amines such as ethylamine a reaction period of 4—24 hours was necessary. In the earliest experiments, the copper compound was precipitated by the addition of water to the cooled reaction mixture. It was then dissolved in dilute hydrochloric acid, the copper removed as the sulphide, and the acid filtrate made alkaline with sodium hydroxide. The use of ammonia in place of sodium hydroxide failed to throw out many of the strongly basic diguanides. In other instances the sparingly soluble hydrochlorides were precipitated. The latter effect could also be obtained with sodium hydroxide if added slowly. Where it was desired to isolate free base with certainty, the acid filtrate was added in a thin stream to an excess of sodium hydroxide solution. In later experiments it was found that, after precipitation of the diguanide copper complex from the initial reaction mixture, a considerable amount of diguanide remained in the aqueous ethanolic filtrate, and the procedure was modified in that either before or after addition of water the excess of ethanol was distilled off, and the resultant suspension was made acid and then worked up without isolation of the copper complex. Copper bronze powder was used in place of copper sulphate in one experiment. The copper complex was found to have been formed as an intermediate and the ultimate yield of diguanide was of the usual order. The exact constitutions of the copper derivatives are now being investigated and they will be characterised in a later paper in this series. Preliminary results suggest that they are chelate compounds with one atom of copper shared by two diguanide molecules. Many are soluble in hydrocarbon solvents, from which they can be extracted, however, by dilute mineral acids.

On the assumption that facile reaction of a cyanamide or dicyandiamide with an amine requires the latter to be present as the ion, the use of the free amine would not be expected to provide good yields of the diguanide. Experience has confirmed this in general, but in certain instances a demonstrable yield of diguanide has been obtained, *e.g.*, with piperidine. This can be attributed to the acidic character of (XIX) which provided the necessary salt formation with the amine for ion production.

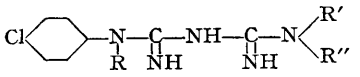
The N^1-methylated diguanides (XIII) were prepared from the corresponding N^1-*p*-chlorophenyl-N^1-methyldicyandiamide. The latter was obtained from (XIX) and methyl sulphate. Reaction was normal with diethylamine and *iso*propylamine in the presence of copper sulphate, but ammonia and ammonium chloride at 150° gave *p*-chloro-*N*-methylaniline, characterised as its acetyl derivative, thus establishing the point of methylation in (XIX).

The arylalkyldiguanides described above were in general low-melting solids, sparingly soluble in cold water, but the lower members were sufficiently soluble to impart a strongly alkaline reaction to their solutions. They have not all been characterised as the free bases since some were not solid at laboratory temperature, and many rapidly absorbed carbon dioxide from the atmosphere. The salts formed with an equivalent of acid, such as the acetates or hydrochlorides, were stable and crystalline and the diguanides were frequently isolated in this form. Physical measurements have indicated the presence of a second basic group in the molecule, but details of this work, together with other results arising from an extensive study of the physical properties of the diguanide drugs, will be recorded in a later communication.

Antimalarial Activities.

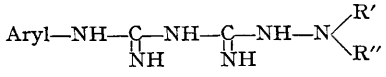
The test method was that described by Curd, Davey, and Rose (*loc. cit.*) using *P. gallinaceum* in chicks. The activity at various doses is indicated either as inactive (−), slight (+), marked (++), or very high (+++). The drugs were administered orally.

(1.)



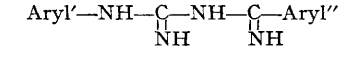
Reference No.	Formula of Diguanide. R.	R′.	R″.	Dose, mg./kg.	Activity.
3374	H	$[CH_2]_2{\cdot}NEt_2$	H	250	—
—	H	$[CH_2]_3{\cdot}NEt_2$	H	—	*
5114	H	$CHMe{\cdot}[CH_2]_3{\cdot}NEt_2$	H	—	*
4172	H	$[CH_2]_2{\cdot}NEt_2$	Et	200	—
3327	H	H	H	125	—
5093	H	Me	H	80	—
4134	H	Me	Me	80	—
4967	H	Et	H	20	++
3926	H	Et	Et	80	++
4094	Me	Et	Et	160	+
4887	H	Pr^{α}	H	20	+++
4888	H	Pr^{β}	H	10	+++
4329	H	Pr^{α}	Me	40	++
4430	H	Pr^{β}	Me	16	+++
5393	Me	Pr^{β}	H	—	*
4968	H	$CH_2{\cdot}CH{:}CH_2$	H	20	++
4565	H	Bu^{α}	H	80	++
4567	H	Bu^{β}	H	320	+
4568	H	Bu^{γ}	H	40	++
4095	H	Bu^{α}	Bu^{α}	200 400	— +
4635	H	$C_5H_{11}{}^{\alpha}$	H	80	++
5596	H	$CH<[CH_2]_4>CH_2$	H	—	*
4204	H	$[CH_2]_4 = R'R''$		80	+
3926	H	$[CH_2]_5 = R'R''$		80	—
5157	H	$[CH_2]_2{\cdot}O{\cdot}[CH_2]_2 = R'R''$		40	—
5234	H	OMe	H	80	—
4171	H	Me	$[CH_2]_2{\cdot}OMe$	160	—

(2.)



Reference No.	Formula of Diguanide. Aryl.	R′.	R″.	Dose, mg./kg.	Activity.
4461	Ph	Me	Pr^{β}	—	*
4210	Ph	Et	Et	160	—
4492	Ph	Bu^{α}	Bu^{α}	160	—
4175	p-C_6H_4Me	Me	Me	200	—
4969	3 : 4-$C_6H_3Me_2$	Et	Et	200 80	+ —
4174	p-$C_6H_4{\cdot}OMe$	Me	Me	200	—
4125	p-$C_6H_4{\cdot}OMe$	Et	Et	120	—
3781	p-$C_6H_4{\cdot}OMe$	$[CH_2]_5 = R'R''$		200	+
—	p-$C_6H_4{\cdot}NO_2$	Me	Me	—	*
4376	p-$C_6H_4{\cdot}NO_2$	Et	Et	80	+
4566	p-$C_6H_4{\cdot}NHAc$	Me	Pr^{β}	80	—

(3.)



Reference No.	Formula of Diguanide. Aryl′.	Aryl″.	Dose, mg./kg.	Activity.
4202	Ph	Ph	80	—
—	p-C_6H_4Cl	Ph	—	*
4123	p-C_6H_4Cl	p-$C_6H_4{\cdot}OMe$	120	—
4970	p-C_6H_4Cl	$C_{10}H_7{}^{\beta}$	80	+
4124	p-$C_6H_4{\cdot}OMe$	p-$C_6H_4{\cdot}OMe$	200	—
—	p-C_6H_4Me	p-C_6H_4Me	—	*

Compounds marked * had not been tested at the time of going to press.

Experimental.

Phenyldicyandiamide derivatives.

Phenyldicyandiamide.—Aniline (23 g.) was diazotised at 5° in 2·5N-hydrochloric acid (250 c.c.) with sodium nitrite (17·5 g. in 100 c.c. of water) and added to dicyandiamide (23 g.) in water (700 c.c.) at 20°. Excess of 10N-sodium hydroxide was added to maintain a strong alkaline reaction, and after ½ hour the golden-yellow solution was acidified with acetic acid. The precipitated triazene was filtered off, washed with water, partly dried by suction on the filter, and added during ¼ hour to a mixture of β-ethoxyethanol (200 c.c.) and 10N-hydrochloric acid (28 c.c.) stirred at 28—30°. After 1

hour no more nitrogen was evolved. Water (500 c.c.) was added and the crude precipitate of phenyldicyandiamide was collected, dissolved in boiling N-sodium hydroxide (250 c.c.), treated with charcoal, and reprecipitated, after filtration, with dilute hydrochloric acid. The dry crystalline solid (20 g.) gave colourless needles from methanol, m. p. 196—197°. Wheeler and Jamieson (*loc. cit.*) give m. p. 190—191°.

p-*Acetamidophenyldicyandiamide*.—Similarly prepared from *p*-aminoacetanilide, the intermediate triazene being decomposed at 34°, mineral acidity neutralised with sodium acetate after dilution of the reaction mixture, and purification *via* the sodium salt omitted. The crude product crystallised from water yielded the *compound* in colourless plates, m. p. 234—235° (decomp.) (Found: N, 29·3. $C_{10}H_{11}ON_5,H_2O$ requires N, 29·8%).

3 : 4-*Xylyldicyandiamide*.—Similarly prepared from 3 : 4-xylidine, but using three times as much β-ethoxyethanol and decomposition of the triazene at 42°. The *compound* formed colourless prisms from β-ethoxyethanol, m. p. 217·5—218° (Found: N, 29·55. $C_{10}H_{12}N_4$ requires N, 29·8%).

p-*Tolyldicyandiamide*.—Similarly prepared from *p*-toluidine. Colourless crystals from methanol, m. p. 211·5—212·5°. Walther and Grieshammer (*loc. cit.*) give m. p. 207—208°.

p-*Anisyldicyandiamide*.—Similarly prepared from *p*-anisidine. The *compound* formed colourless plates from methanol, m. p. 188—189° (Found: N, 29·35. $C_9H_{10}ON_4$ requires N, 29·45%).

p-*Nitrophenyldicyandiamide*.—Sodium nitrite (36 g.) in water (100 c.c.) was added rapidly to the suspension obtained by adding a solution of *p*-nitroaniline (70 g.) in boiling 4N-hydrochloric acid (350 c.c.) to crushed ice (850 g.) and water (400 c.c.). The diazo solution was stirred with dicyandiamide (84 g.) in water (2·2 l.) and ice to maintain it at 0°, 10N-sodium hydroxide being added to give a strong alkaline reaction. After 1 hour, common salt (800 g.) was stirred in and the precipitated sodium salt of the triazene was filtered off, washed with brine, and dried at 40°. It was cautiously crushed and added during 20 minutes to a stirred mixture of β-ethoxyethanol (400 c.c.) and 10N-hydrochloric acid (100 c.c.) kept at 30—34°. Stirring was continued for a further 1½ hours at 25—32° and, after addition of water (300 c.c.) and treatment with charcoal, the mixture was filtered. Nearly pure p-*nitrophenyldicyandiamide* (22 g.) was precipitated on further dilution of the filtrate with water (3 l.); it crystallised from aqueous β-ethoxyethanol in pale yellow prisms, m. p. 243—244° (Found: C, 46·8; H, 3·2; N, 33·95. $C_8H_7O_2N_5$ requires C, 46·8; H, 3·4; N, 34·1%).

p-*Chlorophenyldicyandiamide* (XIX).—The suspension obtained by cooling a solution of *p*-chloroaniline (128 g.) in hot 5N-hydrochloric acid (500 c.c.) was diazotised by adding sodium nitrite (70 g.) in water (200 c.c.), and added to dicyandiamide (92 g.) dissolved in water (2·8 l.) at 20°. Anhydrous sodium carbonate was added during 1½ hours to maintain an alkaline reaction and the suspension was then filtered off. The washed and pressed triazene was added during ½ hour to a stirred mixture of β-ethoxyethanol (500 c.c.) and 10N-hydrochloric acid (112 c.c.) at 33—36°. After ½ hour, water (4·5 l.) was added and the crystalline precipitate collected, washed, and dried. The crude *p*-chlorophenyldicyandiamide (150 g.) had m. p. 192—194°; after purification as described above for the phenyl derivative the product (108 g.) had m. p. 200—202°; recrystallised from ethanol it formed colourless needles, m. p. 202·5—203°. Walther and Grieshammer (*loc. cit.*) give m. p. 197—198°.

N^1-p-*Chlorophenyl*-N^1-*methyldicyandiamide*.—Methyl sulphate (25 c.c.) in methanol (25 c.c.) was added during 20 minutes to *p*-chlorophenyldicyandiamide (19·5 g.) dissolved in methanol (50 c.c.) and 10N-sodium hydroxide (37 c.c.) stirred at 15—20°. After 1 hour water (250 c.c.) was added, and the precipitate collected and dried. The crude product, extracted with hot benzene (100 c.c.) and re-precipitated by adding light petroleum (50 c.c.), gave 5·2 g., m. p. 160—164°, which, recrystallised from water, yielded the *compound* in colourless needles, m. p. 166—168° (Found: C, 51·4; H, 4·4; N, 26·2. $C_9H_9N_4Cl$ requires C, 51·7; H, 4·3; N, 26·8%). The orientation of the methyl group was determined by heating the chlorophenylmethyldicyandiamide (3 g.) in β-ethoxyethanol (5 c.c.) with ammonia (*d* 0·88, 2·5 c.c.) and ammonium chloride (1·5 g.) for 14 hours in a sealed tube at 150°. The contents of the tube were acidified with hydrochloric acid, the solvent was distilled off under reduced pressure, and the oil formed on adding sodium hydroxide was extracted with ether. The residue after evaporation of the ether was heated with acetic anhydride in acetic acid; water was added and the solution then evaporated to dryness. The oily residue solidified on cooling and was washed on to a filter with water and dried. Yield, 1·65 g., m. p. 71—85°. After recrystallisation twice from light petroleum it gave colourless needles, m. p. 90·5—91·5° not depressed by admixture with an authentic specimen of *p*-chloro-*N*-methylacetanilide made by acetylation of *p*-chloro-*N*-methylaniline itself obtained by hydrolysis in boiling sulphuric acid (60%) of p-*chloro*-N-*methyltosylanilide*. The last named substance [needles from light petroleum, m. p. 92·5—93·5° (Found: Cl, 11·7; S, 11·1. $C_{14}H_{14}O_2NClS$ requires Cl, 12·0; S, 10·8%)] was formed by slow addition of methyl sulphate (5 mol.) to p-*chlorotosylanilide* [from *p*-chloroaniline and the theoretical amount of tosyl chloride in pyridine at 100° for 1 hour; colourless prisms from benzene, m. p. 118—119° (Found: C, 55·55; H, 4·35; S, 12·8. $C_{13}H_{12}O_2NClS$ requires C, 55·4; H, 4·25; S, 12·6%)], kept dissolved in water at 85—90° by additions of 10N-sodium hydroxide.

Diguanides.

N^1-p-*Chlorophenyl*-N^5-*β-diethylaminoethyldiguanide*, (X; R = $[CH_2]_2$·NEt_2) (3374).—*p*-Chlorophenyldicyandiamide (XX, 15 g.), β-ethoxyethanol (15 c.c.), β-diethylaminoethylamine (13 c.c.), and copper sulphate pentahydrate (9 g.) in water (18 c.c.), were refluxed with stirring for 2 hours. The semi-solid left by decantation after diluting with water (250 c.c.) was dissolved in N-hydrochloric acid (300 c.c.) and a concentrated aqueous solution of sodium sulphide nonahydrate (15 g.) stirred in. Decolourising charcoal was added and the copper sulphide filtered off. The solid obtained by adding excess of sodium hydroxide to the filtrate was collected and dried (14 g.), m. p. 126—128°. From light petroleum (b. p. 100—120°) the *compound* formed colourless needles, m. p. 137—139° (Found: N, 26·75. $C_{14}H_{23}N_6Cl$ requires N, 27·0%).

N^1-p-*Chlorophenyl*-N^5-*γ-diethylaminopropyldiguanide* (X; R = $[CH_2]_3$·NEt_2).—Similarly prepared from *p*-chlorophenyldicyandiamide and γ-diethylaminopropylamine, decantation from the initial reaction product being omitted, this was obtained as an oil which when extracted by ether, dried (KOH), and crystallised from light petroleum gave the *compound* as hygroscopic colourless prisms, m. p. 81—83° (Found: Cl, 11·1. $C_{15}H_{25}N_6Cl$ requires Cl, 10·9%).

N^1-p-*Chlorophenyl*-N^5-*δ-diethylamino-α-methylbutyldiguanide* (X; R = CHMe·$[CH_2]_3$·NEt_2) (5114).—*p*-Chlorophenyldicyandiamide (19·5 g.), ethanol (150 c.c.), δ-diethylamino-α-methylbutylamine (19 g.), and copper sulphate pentahydrate (12·5 g.) in water (60 c.c.), were refluxed with stirring for 20 hours. The semi-solid precipitate, formed on adding water (500 c.c.) to the purple solution, redissolved on adding 10N-hydrochloric acid (50 c.c.). Sodium sulphide nonahydrate (40 g.) in concentrated aqueous solution was added, the copper sulphide filtered off, and the filtrate made strongly alkaline with sodium hydroxide. The semi-solid precipitate was washed several times by decantation with water and the diguanide finally freed from excess of amine reactant by stirring with copper sulphate (25 g.) dissolved in excess dilute ammonia, to convert it into the insoluble copper complex. This was washed well with water, redissolved in dilute hydrochloric acid, decomposed as before with sodium sulphide, and the sticky precipitate formed after adding sodium hydroxide dried in a vacuum over sodium hydroxide for 4 days. The resultant glassy solid could not be induced to crystallise, but the diguanide was obtained as the *carbonate* (13·8 g.), m. p. 78—80° (decomp.) (Found: C, 52·4; H, 8·15; N, 20·85. $C_{17}H_{29}N_6Cl,H_2CO_3$ requires C, 52·1; H, 7·5; N, 20·3%), by passage of carbon dioxide into a solution of the base in acetone (200 c.c.) and water (1 c.c.).

N^1-p-*Chlorophenyl*-N^5-*β-diethylaminoethyl*-N^5-*ethyldiguanide* (4172).—*p*-Chlorophenyldicyandiamide (9·5 g.), ethanol (50 c.c.), β-diethylaminoethylethylamine (20 c.c.), and copper sulphate (6·25 g.) in water (30 c.c.), were refluxed with stirring for ½ hour. The copper complex, precipitated by adding water (250 c.c.), was collected, redissolved in 1·5N-hydrochloric acid (300 c.c.), and decomposed with sodium sulphide (20 g.) as described above. The crude oily diguanide obtained by adding sodium hydroxide to the acid filtrate was converted into the hydrochloride by passing dry hydrogen chloride into a solution in ether previously dried (KOH). The hydrochloride was dissolved in water and made alkaline with sodium hydroxide, and the solid base collected and dried in a vacuum over sodium hydroxide. The *hemihydrate* was obtained as colourless needles, m. p. 78·5—79·5°, from light petroleum (b. p. 100—120°) (Found: C, 55·95; H, 7·25; N, 24·0. $C_{16}H_{27}N_6Cl,\frac{1}{2}H_2O$ requires C, 56·0; H, 8·05; N, 24·15%).

N^1-p-*Chlorophenyl*-N^5-*methyldiguanide* (X; R = Me) (5093).—Prepared as described for 5114, from *p*-chlorophenyldicyandiamide (9·7 g.) and methylamine (20% aqueous solution, 30 c.c.), the mixture being refluxed for 1½ hours and reconversion to the copper complex omitted. The crude base (6·6 g.) was redissolved in water (75 c.c.) and sufficient hydrochloric acid at 40°, treated with charcoal, and the filtrate made faintly alkaline with dilute ammonia. On cooling, the *hydrochloride* crystallised out; it recrystallised from water (40 c.c.) in colourless needles (3·6 g.), m. p. 227—228° (Found: C, 41·0; H, 4·75; N, 26·35. $C_9H_{12}N_5Cl,HCl$ requires C, 41·2; H, 4·95; N, 26·7%). The base obtained by adding sodium hydroxide to a solution of the hydrochloride gave colourless needles from toluene, m. p. 85—86°, but no satisfactory analytical figures were obtained because of the rapidity with which it absorbed carbon dioxide from the atmosphere.

N^1-p-*Chlorophenyl*-N^5 : N^5-*dimethyldiguanide* (4134).—Similarly prepared from *p*-chlorophenyldicyandiamide (9·5 g.) and dimethylamine (20% aqueous solution, 40 c.c.) by an almost instantaneous reaction. The *base* formed colourless plates (5·0 g.) from toluene, m. p. 169° (Found: C, 50·0; H, 5·45; N, 28·9. $C_{10}H_{14}N_5Cl$ requires C, 50·0; H, 5·8; N, 29·1%).

N^1-p-*Chlorophenyl*-N^5-*ethyldiguanide* (X; R = Et) (4967).—Similarly prepared from *p*-chlorophenyldicyandiamide (9·7 g.) and ethylamine (30% aqueous solution, 12 c.c.), the mixture being refluxed for 16 hours. The copper complex was not isolated, but, before it was decomposed, the ethanol was distilled off. The crude base, purified by reprecipitation by sodium hydroxide from a solution in cold dilute acetic acid, was finally isolated as the *acetate* (7·5 g.) by addition of glacial acetic acid (2·6 c.c.) to a solution in acetone (100 c.c.); colourless crystals, m. p. 160—161° (Found: C, 47·85; H, 5·95; N, 23·4. $C_{10}H_{14}N_5Cl,CH_3{\cdot}CO_2H$ requires C, 48·1; H, 6·0; N, 23·35%). The *base*, obtained from the acetate by treatment with sodium hydroxide, gave colourless prisms from benzene, m. p. 113—114° (Found: C, 49·6; H, 6·0; N, 29·85. $C_{10}H_{14}N_5Cl$ requires C, 50·0; H, 5·8; N, 29·1%).

N^1-p-*Chlorophenyl*-N^5 : N^5-*diethyldiguanide* (XI) (3936).—Similarly prepared using diethylamine (10 c.c.). The *base* formed colourless needles from light petroleum (b. p. 100—120°), m. p. 133—134° (Found: C, 53·6; H, 7·05; N, 25·9. $C_{12}H_{18}N_5Cl$ requires C, 53·6; H, 6·7; N, 26·1%).

N^1-p-*Chlorophenyl*-N^1-*methyl*-N^5 : N^5-*diethyldiguanide* (XIII) (4094).—Prepared as described for (X; R = Me) from *p*-chlorophenylmethyldicyandiamide (9·8 g.) and diethylamine (100%, 10 c.c.), and isolated as the *hydrochloride* by making the solution obtained after filtration from the copper sulphide just alkaline with ammonia. Recrystallisation from water gave colourless prisms, m. p. 182—184° (Found: C, 46·5; H, 6·7; N, 20·45; Cl′, 10·7. $C_{13}H_{20}N_5Cl,HCl,H_2O$ requires C, 46·4; H, 6·8; N, 20·8; Cl′, 10·6%).

N^1-p-*Chlorophenyl*-N^5-n-*propyldiguanide* (X; R = Pr^{α}) (4887).—Prepared as described for (X; R = Et) from *p*-chlorophenyldicyandiamide (9·5 g.) and *n*-propylamine (15 c.c.). The *acetate* was obtained as colourless prisms, m. p. 164—165° (Found: C, 49·85; H, 5·85; N, 22·6. $C_{11}H_{16}N_5Cl,CH_3{\cdot}CO_2H$ requires C, 49·75; H, 6·35; N, 22·3%), and the *base* as colourless prisms from aqueous ethanol, m. p. 58·5—60° (Found: C, 48·55; H, 6·05; N, 26·2. $C_{11}H_{16}N_5Cl,\frac{1}{2}H_2O$ requires C, 48·4; H, 6·6; N, 25·8%).

N^1-p-*Chlorophenyl*-N^5-iso*propyldiguanide* (X; R = Prβ) (4888).—Similarly prepared from *p*-chlorophenyldicyandiamide (9·5 g.) and *iso*propylamine (15 c.c.). The *acetate* was obtained as colourless needles from ethanol, m. p. 184—185° (Found: C, 48·4; H, 6·1; N, 21·85. $C_{11}H_{16}N_5Cl,CH_3{\cdot}CO_2H,\frac{1}{2}H_2O$ requires C, 48·35; H, 6·5; N, 21·7%), and the *base* as colourless rectangular plates from toluene, m. p. 129° (Found: C, 51·95; H, 6·2; N, 27·1. $C_{11}H_{16}N_5Cl$ requires C, 52·0; H, 6·3; N, 27·6%). The *hydrochloride*, obtained by the method described for (XIII), formed colourless needles from water, m. p. 243—244° (Found: Cl′, 12·8. $C_{11}H_{16}N_5Cl,HCl$ requires Cl′, 12·6%).

N^1-p-*Chlorophenyl*-N^5-*methyl*-N^5-n-*propyldiguanide* (4329).—Prepared as described for 4172, using methyl *n*-propylamine (7 c.c.), the mixture being refluxed for 5 hours. The crude *base* (6·5 g.) obtained after decomposition of the copper complex yielded colourless plates from toluene, m. p. 125—126° (Found: C, 54·15; H, 6·6; N, 25·8. $C_{12}H_{18}N_5Cl$ requires C, 53·7; H, 6·7; N, 26·1%).

N^1-p-*Chlorophenyl*-N^5-*methyl*-N^5-iso*propyldiguanide* (4430).—Similarly prepared from methyl *iso*propylamine (20 c.c.). The crude *base* (9·4 g.) yielded colourless needles from toluene, m. p. 174—175° (Found: C, 53·7; H, 6·95; N, 25·65. $C_{12}H_{18}N_5Cl$ requires C, 53·7; H, 6·7; N, 26·1%); the *acetate* had m. p. 212° (Found: C, 51·5; H, 6·6; N, 21·3. $C_{12}H_{18}N_5Cl,CH_3{\cdot}CO_2H$ requires C, 51·3; H, 6·7; N, 21·35%).

N^1-p-*Chlorophenyl*-N^1-*methyl*-N^5-iso*propyldiguanide* (5393).—Prepared as described for (XIII) from *p*-chlorophenylmethyldicyandiamide (7·5 g.) and *iso*propylamine (5 c.c.) and isolated as the *base*, which formed colourless prisms from light petroleum (b. p. 100—120°), m. p. 98—100° (Found: N, 25·7. $C_{12}H_{18}N_5Cl$ requires N, 26·1%). The *hydrochloride* (from acetone) formed colourless prisms from ethanol, m. p. 229—230° (Found: C, 47·75; H, 5·7; N, 23·1. $C_{12}H_{18}N_5Cl,HCl$ requires C, 47·6; H, 6·25; N, 23·0%).

N^1-p-*Chlorophenyl*-N^5-*allyldiguanide* (X; R = $CH_2{\cdot}CH{:}CH_2$) (4968).—Prepared as described for (X; R = Et) and isolated as the *base*, which formed colourless prisms from toluene, m. p. 99—101° (Found: C, 52·2; H, 5·7; N, 27·5. $C_{11}H_{14}N_5Cl$ requires C, 52·5; H, 5·55; N, 27·8%).

N^1-p-*Chlorophenyl*-N^5-n-*butyldiguanide* (X; R = Bu^{α}) (4565).—Prepared as described for 4172 using *n*-butylamine (10 c.c.), the mixture being refluxed for 16 hours. The crude base could not well be crystallised, but formed an *acetate* in acetone, colourless prisms (6·2 g.), m. p. 158° (Found: C, 52·0; H, 6·75; N, 21·15; $C_{12}H_{18}N_5Cl,CH_3{\cdot}CO_2H$ requires C, 51·3; H, 6·7; N, 21·4%). The *hydrochloride*, obtained by making slightly alkaline with ammonia a solution of the base in excess of dilute hydrochloric acid, formed colourless prisms from water, m. p. 208° (Found: Cl′, 11·4. $C_{12}H_{18}N_5Cl,HCl$ requires Cl′, 11·7%).

N^1-p-*Chlorophenyl*-N^5-iso*butyldiguanide* (X; R = Bu^{β}) (4567).—Prepared similarly from *iso*butylamine (10 c.c.). The base formed an acetate in acetone, colourless leaflets (4·5 g.), m. p. 166—167°, and a *hydrochloride*, colourless plates from ethanol, m. p. 233—235·5° (Found: C, 47·25; H, 6·1; N, 23·2; Cl′, 12·1. $C_{12}H_{18}N_5Cl,HCl$ requires C, 47·3; H, 6·2; N, 23·0; Cl′, 11·7%).

N^1-p-*Chlorophenyl*-N^5-tert.-*butyldiguanide* (X; R = Bu^{γ}) (4568).—Prepared similarly from *tert.*-butylamine (10 c.c.). The base formed a *hydrochloride* (1·7 g.) in acetone, colourless prisms from ethanol, m. p. 232—234° depressed in admixture with the hydrochloride from (X, R = Bu^{β}) (Found: N, 22·95; Cl′, 11·8. $C_{12}H_{18}N_5Cl,HCl$ requires N, 23·0; Cl′, 11·7%).

N^1-p-*Chlorophenyl*-N^5 : N^5-*di*-n-*butyldiguanide* (4095).—Prepared as described for 4172, using dibutylamine, the mixture being refluxed for 3 hours. The copper complex was decomposed by stirring with N-sulphuric acid (500 c.c.) which

left the sparingly soluble diguanide *sulphate*, colourless prisms from aqueous ethanol, m. p. 180—182° (Found: C, 50·8; H, 6·9; N, 18·1. $C_{16}H_{26}N_5Cl,\frac{1}{2}H_2SO_4$ requires C, 51·5; H, 7·2; N, 18·7%). The more soluble acetate, m. p. 156°, was employed in the antimalarial test.

N¹-p-*Chlorophenyl*-N⁵-n-*amyldiguanide* (X; R = C_5H_{11}[a]) (4635).—Prepared as described for (X; R = Me) from *n*-amylamine (10 c.c.), the mixture being refluxed for 20 hours. The *hydrochloride*, isolated as described for that of (X, R = Me), formed colourless needles (4·6 g.) from water, m. p. 229° (Found: C, 49·15; H, 6·5; N, 21·45. $C_{13}H_{20}N_5Cl,HCl$ requires C, 49·0; H, 6·6; N, 22·0%).

N¹-p-*Chlorophenyl*-N⁵-cyclo*hexyldiguanide* (X; R = C_6H_{11}).—Prepared as described for (X; R = $[CH_2]_2{\cdot}NEt_2$) from *p*-chlorophenyldicyandiamide (19·5 g.) and *cyclo*hexylamine (15 g.). The *base* (yield, 12·1 g.) formed colourless plates from benzene, m. p. 172—173° (Found: C, 57·2; H, 6·8; N, 23·45. $C_{14}H_{20}N_5Cl$ requires C, 57·2; H, 6·8; N, 23·85%).

N¹-p-*Chlorophenyl*-N⁵ : N⁵-cyclo*tetramethylenediguanide* (4204).—Prepared as described for 4172 using pyrrolidine (10 c.c.). The *base* formed colourless plates from toluene, m. p. 206 (Found: C, 54·2; H, 5·8; N, 26·1. $C_{12}H_{16}N_5Cl$ requires C, 54·15; H, 6·0; N, 26·3%).

N¹-p-*Chlorophenyl*-N⁵ : N⁵-cyclo*pentamethylenediguanide* (3926).—(*a*) Prepared as described for (X; R = $[CH_2]_2{\cdot}NEt_2$) from *p*-chlorophenyldicyandiamide (9·5 g.) and piperidine (6·4 g.), the mixture being refluxed for 4 hours. The *base* (yield, 2·8 g.) formed colourless needles from xylene, m. p. 190—192° (Found: C, 56·8; H, 6·5; N, 24·65. $C_{13}H_{18}N_5Cl$ requires C, 55·7; H, 6·45; N, 25·0%). (*b*) *p*-Chlorophenyldicyandiamide (3·9 g.), piperidine (3 c.c.), ethanol (40 c.c.), and copper bronze powder (3·8 g.), refluxed for 16 hours, gave a solution of the copper complex which, when worked up in the usual manner, yielded crude base (2·2 g.), and needles (1·1 g.) from xylene identical with material from (*a*). (*c*) *p*-Chlorophenyldicyandiamide (3·9 g.) refluxed for 16 hours in piperidine (5 c.c.) also gave the base (0·2 g.) from xylene, m. p. 185° undepressed in admixture with material from (*a*).

N¹-p-*Chlorophenyl*-N⁵ : N⁵-*anhydrobis*-(*β-hydroxyethyl*)*diguanide* (5157).—Prepared as described for (X; R = $[CH_2]_2{\cdot}NEt_2$) from *p*-chlorophenyldicyandiamide (9·7 g.) and morpholine (10 c.c.). The *base* formed colourless needles (yield, 5·6 g.) from toluene, m. p. 188—189° (Found: C, 51·4; H, 5·7; N, 24·15. $C_{12}H_{16}ON_5Cl$ requires C, 51·15; H, 5·65; N, 24·85%). The *acetate*, prepared in acetone, formed colourless needles, m. p. 207—208° (Found: C, 49·35; H, 5·8; N, 20·2. $C_{12}H_{16}ON_5Cl,CH_3{\cdot}CO_2H$ requires C, 49·2; H, 5·85; N, 20·5%).

N¹-p-*Chlorophenyl*-N⁵-*methoxydiguanide* (X; R = OMe) (5234).—Prepared as described for (X; R = Et) from *p*-chlorophenyldicyandiamide (8·3 g.) and methoxylamine hydrochloride (3·8 g.) with an added equivalent of sodium hydroxide, the mixture being refluxed for 10 hours. The *base* (yield, 1·25 g.) formed colourless needles from toluene, m. p. 161—161·5° (Found: C, 45·3; H, 5·15; N, 28·0; Cl, 14·4. $C_9H_{12}ON_5Cl$ requires C, 44·7; H, 5·0; N, 29·0; Cl, 14·7%).

N¹-p-*Chlorophenyl*-N⁵-*methyl*-N⁵-*β-methoxyethyldiguanide* (4171).—Prepared as described for 4172 using *β*-methoxyethylmethylamine (10 c.c.). The *base* (yield, 2·5 g.) formed colourless needles from aqueous methanol, m. p. 91—93° (Found: C, 50·65; H, 6·1; N, 24·0. $C_{12}H_{18}ON_5Cl$ requires C, 50·7; H, 6·3; N, 24·65%).

N¹-*Phenyl*-N⁵-*methyl*-N⁵-iso*propyldiguanide* (4461).—Prepared as described for 4172 using phenyldicyandiamide (9·0 g.) and methyl*iso*propylamine (13 c.c.), the mixture being refluxed for 1½ hours. The *base*, isolated after decomposition of the copper complex, gave colourless prisms (5·1 g.) from light petroleum (b. p. 100—120°), m. p. 101·5—103° (Found: C, 60·9; H, 7·4; N, 29·65. $C_{12}H_{19}N_5$ requires C, 61·8; H, 8·15; N, 30·0%). The acetate, prepared in acetone, had m. p. 188—191°.

N¹-*Phenyl*-N⁵ : N⁵-*diethyldiguanide* (4210).—Similarly prepared from phenyldicyandiamide (8 g.) and diethylamine (10 c.c.). The *base* formed colourless prisms from light petroleum (b. p. 100—120°), m. p. 100—101° (Found: C, 61·5; H, 7·55; N, 29·25. $C_{12}H_{19}N_5$ requires C, 61·8; H, 8·15; N, 30·0%).

N¹-*Phenyl*-N⁵ : N⁵-*di*-n-*butyldiguanide* (4492).—Similarly prepared using di-*n*-butylamine (15 c.c.). The crude base was an oil, which was converted into the sparingly soluble solid iodide by adding excess of potassium iodide to a solution of the hydrochloride, and thence into a solution of the base in ether by shaking with dilute sodium hydroxide. The ethereal solution was dried (KOH) and treated with glacial acetic acid (1 c.c.); the acetate then crystallised out as colourless needles, m. p. 139—140° (Found: C, 61·1; H, 8·9; N, 19·7. $C_{16}H_{27}N_5,CH_3{\cdot}CO_2H$ requires C, 61·9; H, 8·9; N, 20·0%).

N¹-p-*Tolyl*-N⁵ : N⁵-*dimethyldiguanide* (4175).—Prepared as described for the *p*-chlorophenyl analogue (4134) using *p*-tolyldicyandiamide (8·7 g.). The base formed colourless plates (4·5 g.), m. p. 149—149·5°, which rapidly absorbed carbon dioxide from the atmosphere and, therefore, by neutralising a solution in excess dilute hydrochloric acid with ammonia, was isolated as the hydrochloride which crystallised from water in colourless needles, m. p. 224—225° (Found: C, 51·95; H, 7·05; N, 26·65. $C_{11}H_{17}N_5,HCl$ requires C, 51·6; H, 7·05; N, 27·4%).

N¹-3′ : 4′-*Xylyl*-N⁵ : N⁵-*diethyldiguanide* (4969).—Prepared, as described for (X; R = Et), using 3 : 4-xylyldicyandiamide (9·4 g.) and diethylamine (5 g.). The *acetate* (3·8 g.), prepared in benzene in place of acetone, had m. p. 182—184° (Found: C, 59·65; H, 7·85; N, 22·0. $C_{14}H_{23}N_5,CH_3{\cdot}CO_2H$ requires C, 59·8; H, 8·4; N, 21·8%), and was converted into the *base*, which formed colourless plates from light petroleum (b. p. 60—80°), m. p. 70—71° (Found: C, 63·8; H, 8·4; N, 26·6. $C_{14}H_{23}N_5$ requires C, 64·4; H, 8·8; N, 26·8%).

N¹-p-*Anisyl*-N⁵ : N⁵-*dimethyldiguanide* (4174).—Prepared as described for the *p*-tolyl analogue 4175 using *p*-anisyldicyandiamide (9·7 g.). The *base* (6·2 g.) formed colourless prisms from toluene, m. p. 142—143° (Found: C, 56·25; H, 7·05; N, 29·35. $C_{11}H_{17}ON_5$ requires C, 56·15; H, 7·2; N, 29·8%).

N¹-p-*Anisyl*-N⁵ : N⁵-*diethyldiguanide* (4125).—Similarly prepared using diethylamine (10 c.c.), the mixture being refluxed overnight. The *base* formed colourless prisms, m. p. 93—94° (Found: C, 58·95; H, 7·45; N, 26·4. $C_{13}H_{21}ON_5$ requires C, 59·3; H, 8·0; N, 26·6%).

N¹-p-*Anisyl*-N⁵ : N⁵-cyclo*pentamethylenediguanide* (3781).—(*a*) Prepared as described for (X; R = $[CH_2]_2{\cdot}NEt_2$) using *p*-anisyl dicyandiamide (9·5 g.) and piperidine (6·4 g.). The *base* formed colourless prisms (4·5 g.) from toluene, m. p. 144—146° (Found: C, 61·2; H, 8·1; N, 25·6. $C_{14}H_{21}ON_5$ requires C, 61·1; H, 7·6; N, 25·4%).

(*b*) *p*-Anisyldicyandiamide (9·5 g.), piperidine (12·7 g.), dioxan (12 c.c.), and 5N-hydrochloric acid (10 c.c.) refluxed for 15 hours gave after crystallisation from toluene a base (2·9 g.) identical with that prepared as in (*a*).

N¹-p-*Nitrophenyl*-N⁵ : N⁵-*diethyldiguanide* (4376).—Prepared as described for 4172 from *p*-nitrophenyldicyandiamide (10 g.) and diethylamine (10 c.c.), the mixture being refluxed for 3 hours, the copper complex digested with the hydrochloric acid at 70° and the *base* isolated and crystallised from aqueous *β*-ethoxyethanol, from which it separated in yellow leaflets, m. p. 121—122° (Found: N, 20·7. $C_{12}H_{18}O_2N_6$ requires N, 21·0%).

N¹-p-*Acetamidophenyl*-N⁵-*methyl*-N⁵-iso*propyldiguanide* (4566).—Prepared similarly from *p*-acetamidophenyldicyandiamide (19 g.) and methyl*iso*propylamine (20 c.c.), the mixture being refluxed for 1½ hours; the precipitated copper complex was digested with cold 1·5N-hydrochloric acid (700 c.c.) and decomposed by sodium sulphide; the filtrate, made alkaline with sodium hydroxide, saturated with common salt, and kept overnight, deposited the crude base (5 g.) which was converted into the *acetate* in acetone, giving colourless prisms, m. p. 206—208° (Found: C, 54·85; H, 7·15. $C_{14}H_{22}ON_6$ requires C, 54·85; H, 7·4%).

$N^1 : N^5$-*Diphenyldiguanide* (4202).—Phenyldicyandiamide (5 g.), aniline hydrochloride (6·5 g.), dioxan (25 c.c.), and water (10 c.c.) were refluxed for 2 hours and cooled, and the precipitate was crystallised from water to give colourless needles of the *hydrochloride* (2·2 g.), m. p. 232° (Found: Cl′, 12·2. $C_{14}H_{15}N_5$,HCl requires Cl′, 12·2%). The base, formed by adding sodium hydroxide to a solution in hot water, gave needles from methanol, m. p. 145—146°.

N^1-p-*Chlorophenyl*-N^5-*phenyldiguanide*.—Similarly prepared from *p*-chlorophenyldicyandiamide (19·5 g.) and aniline hydrochloride (26 g.). The *hydrochloride* formed colourless plates from aqueous methanol, m. p. 248° (Found: Cl′, 11·0. $C_{14}H_{14}N_5Cl$,HCl requires Cl′, 10·95%). The base formed colourless plates from aqueous methanol, m. p. 149°.

N^1-p-*Chlorophenyl*-N^5-p-*anisyldiguanide* (4123).—Similarly prepared using *p*-anisidine (24·6 g.), and with addition of 10N-hydrochloric acid (18 c.c.). The initial precipitate, redissolved in boiling 2N-hydrochloric acid (500 c.c.), filtered from solid impurity, and made alkaline with sodium hydroxide, gave the *base*, which formed colourless needles (12·5 g.) from ethanol, m. p. 155° (Found: C, 56·05; H, 4·9; N, 21·8. $C_{15}H_{16}ON_5Cl$ requires C, 56·6; H, 5·0; N, 22·0%).

N^1-p-*Chlorophenyl*-N^5-*β-naphthyldiguanide* (4970).—Similarly prepared using β-naphthylamine (28·6 g.) previously dissolved in hot 2N-hydrochloric acid (90 c.c.), the mixture being refluxed for 6 hours. The crude *hydrochloride* which formed colourless prisms from aqueous β-ethoxyethanol, m. p. 249—250° (Found: C, 57·35; H, 4·2; N, 19·5. $C_{18}H_{16}N_5Cl$,HCl requires C, 57·75; H, 4·5; N, 18·7%), was converted into the crystalline *base*, m. p. 142—143°, by adding 10N-sodium hydroxide (15 c.c.) to a suspension in hot methanol (250 c.c.) (Found: C, 64·1; H, 4·95; N, 19·9. $C_{18}H_{16}N_5Cl$ requires C, 63·9; H, 4·7; N, 20·7%).

$N^1 : N^5$-*Di*-p-*anisyldiguanide* (4124).—Similarly prepared from *p*-anisyldicyandiamide (9·5 g.) and *p*-anisidine (12·3 g.) dissolved in 5N-hydrochloric acid (20 c.c.). The *hydrochloride* (11 g.) formed colourless prisms from water, m. p. 222° (Found: C, 55·2; H, 5·85; N, 19·85. $C_{16}H_{19}O_2N_5$,HCl requires C, 54·85; H, 5·45; N, 20·0%).

$N^1 : N^5$-*Di*-p-*tolyldiguanide*.—Similarly prepared from *p*-tolyldicyandiamide (8·7 g.) and *p*-toluidine (10·7 g.) dissolved in 5N-hydrochloric acid (20 c.c.). The *hydrochloride* formed colourless needles from water, m. p. 231—234° (Found: N, 21·7; Cl′, 11·4. $C_{16}H_{19}N_5$,HCl requires N, 22·05; Cl′, 11·2%). The *base* formed colourless plates from ethanol, m. p. 187° (Found: C, 67·75; H, 6·45; N, 24·6. $C_{16}H_{19}N_5$ requires C, 68·3; H, 6·75; N, 24·9%).

N^1-p-*Chlorophenyl*-$N^3 : N^3$-*dialkylguanidines*.

Methyl sulphate (30 c.c.) was added cautiously to a hot suspension of *N*-*p*-chlorophenylthiourea (55·8 g.) in ethanol (300 c.c.) and the whole was refluxed 4 hours. One-sixth of the total volume of the resultant cooled solution was caused to react with dialkylamines as under.

N^1-p-*Chlorophenyl*-$N^3 : N^3$-*dimethylguanidine*.—An aliquot part of the alcoholic solution was refluxed for 3 hours with aqueous dimethylamine (25%, 27 c.c.), the ethanol distilled off, and the residual syrup dissolved in water (10 c.c.) and sufficient 10N-hydrochloric acid. The *hydriodide*, precipitated by adding potassium iodide, was recrystallised from water giving 7·7 g., m. p. 155—156° (Found: I′, 33·8. $C_9H_{12}N_3Cl$,HI,$3H_2O$ requires I′, 33·5%).

N^1-p-*Chlorophenyl*-$N^3 : N^3$-*diethylguanidine* (XIV).—Similarly prepared using diethylamine (11 g.). The *hydriodide* separated from water as colourless needles, m. p. 67—68° (Found: I′, 34·0; after drying in vacuum at 50°. $C_{11}H_{16}N_3Cl$,HI requires I′, 34·1%).

IMPERIAL CHEMICAL INDUSTRIES, LTD.,
RESEARCH LABORATORIES, BLACKLEY, MANCHESTER, 9.

[*Received, February 14th*, 1946.]