540. *Synthetic Antimalarials. Part XLV. Reactions between Monosubstituted Cyanoguanidines and Grignard Reagents leading to* N-p-*Chlorophenylguanylamidines.*

By Stanley Birtwell.

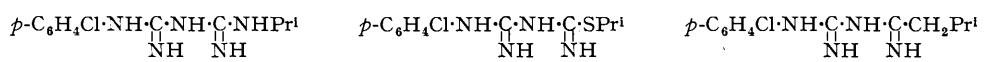
N-Cyano-*N'*-*p*-chlorophenylguanidine and ethylmagnesium iodide have been shown to undergo at least two reactions: (*a*) replacement of two or more of the acidic hydrogen atoms of the cyanoguanidine moiety by MgI to give a highly charged complex ion which by electron redistribution undergoes fission to more stable ions of smaller charge, appearing on ultimate hydrolysis as *p*-chlorophenylcyanamide and cyanamide, and (*b*) addition of the Grignard reagent to the C≡N group of the metalated cyanoguanidine derivatives, and possibly to dicyandiamide itself, with formation of a complex, eventually leading to N-p-*chlorophenylguanylpropionamidine*, *N*-*p*-chlorophenylguanidine, or N-*propionyl*-N'-p-*chlorophenylguanidine*, depending on the nature of the hydrolytic agent employed.

At 90—100° the complex formed by reaction (*b*) decomposes, giving, as one of the products, *p*-chlorophenylcyanamide (as the MgI derivative) which may add on any Grignard reagent present to give N-p-*chlorophenylpropionamidine* on hydrolysis.

The reaction has been employed with other Grignard reagents for the synthesis of a series of *N*-*p*-chlorophenylguanylamidines which have been tested for plasmodicidal activity on *P. gallinaceum* in chicks. All were ineffective.

The reactions appear to be general for monosubstituted cyanoguanidines, but in some cases the guanylamidine cannot be isolated owing to ready hydrolysis of the addition complex to the corresponding guanidine.

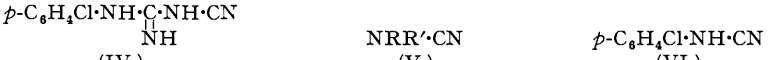
In Part XXX of this series (*J.*, 1948, 1645) it was shown that replacement of the terminal *iso*propylamino-group of "Paludrine" (I) by the *iso*propylthio-group, as in *N*-*p*-chlorophenylguanyl-*S*-*iso*propyl*iso*thiourea (II), entailed a complete loss of antimalarial activity. Nevertheless, on



(I.) (II.) (III.)

account of the formal resemblance of the guanylamidines to (I) [cf. *p*-chlorophenylguanyl*iso*-valeramidine (III)] it was considered desirable to determine the effect of a similar replacement of the terminal alkylamino-group by the next higher homologue of the alkyl residue.

One of the many possible methods of preparation of these new amidine derivatives lay in the reaction of cyanoguanidines, in particular *N*-cyano-*N'*-*p*-chlorophenylguanidine (IV) with Grignard reagents. It is known that linking a C≡N group through a nitrogen atom as in the



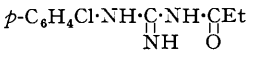
(IV.) (V.) (VI.)

cyanamides (V) does not fundamentally alter the normal addition reaction between the cyano-group and Grignard reagents, so that amidines are obtained on hydrolysis (Busch and Hobein, *Ber.*, 1907, **40**, 4296; Adams and Beebe, *J. Amer. Chem. Soc.*, 1916, **38**, 2768; Vuylsteke, *Bull. Acad. Sci. Belge*, 1926, **12**, 535), although the yields from monosubstituted cyanamides (V;

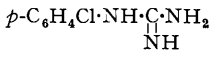
R′ = H) are reported to be low. The chances of obtaining guanylamidines by this method therefore appeared to be good. It was expected, however, that the adjacent guanyl group—(IV) may be regarded as *p*-chlorophenylguanylcyanamide—would modify the reactivity of the cyanamide, there being a somewhat loose analogy with the α- and β-amino-nitriles which undergo, besides normal addition, more complex reactions with Grignard reagents (see Migrdichian, "The Chemistry of Organic Cyanogen Compounds," Reinhold Publ. Corp., 1947, 253). The factor which eventually decided the selection of this method for investigation was the novel reaction observed in the previous communication, by which *p*-chlorophenylcyanamide (VI) was produced by the action of substituted aminomagnesium halides on *N*-cyano-*N*′-*p*-chlorophenylguanidine (IV), since, in the event of a similar formation of this substance by the action of Grignard compounds themselves the mechanism of the reaction might be more easily elucidated.

The reactions occurring between the cyanoguanidine (IV) and ethylmagnesium iodide have been studied. In ether at room temperature (IV) was recovered substantially unchanged on hydrolysis of the complex derived from equimolecular proportions of the reactants. A slight excess of Grignard reagent (3·2—3·4 mols.), however, gave a complex which on hydrolysis with ammonium chloride solution yielded *p*-chlorophenylcyanamide (VI), together with N-p-*chlorophenylguanylpropionamidine* (VII), *p*-chlorophenylguanidine (IX), and some unchanged (IV); under the optimum conditions [rapid addition of the ethylmagnesium iodide solution to a stirred suspension of (IV), and good agitation for a further 2 hours], the yields based on the cyanoguanidine were 20, 45, 21, and 10%, respectively. On the other hand, acid hydrolysis of a complex similarly derived led to the formation of N-*propionyl*-N′-p-*chlorophenylguanidine* (VIII) (60%), *p*-chlorophenylcyanamide (VI) (25%), *p*-chlorophenylguanidine (IX) (1—2%), and recovered (IV) (10%).

(VII.)

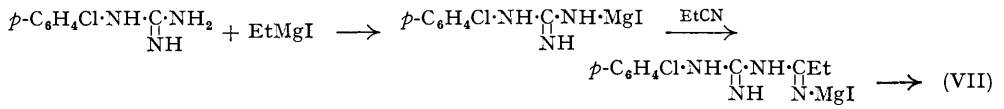


(VIII.)



(IX.)

The structure of (VIII) was confirmed by alkaline hydrolysis to *p*-chlorophenylguanidine (IX) and synthesis from this compound and propionyl chloride. Similarly, acid hydrolysis to *N*-propionyl-*N*′-*p*-chlorophenylguanidine (VIII), and synthesis in small yield from *p*-chlorophenylguanidinomagnesium iodide and propionitrile in anisole at 95—100° established the constitution of *N*-*p*-chlorophenylguanylpropionamidine (VII). The latter reaction is a



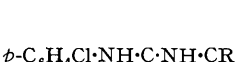
(VII)

modification of the method described by Hullin, Miller, and Short (J., 1947, 394) for the preparation of amidines from nitriles and substituted aminomagnesium halides.

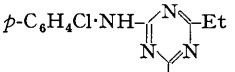
In their easy hydrolysis to acylguanidines, the guanylamidines so far examined differ markedly from the related diguanides and amidines. Their monoacid salts appear to be stable, the *acetate* and *picrate* of *N*-*p*-chlorophenylguanylpropionamidine (VII), for example, have been obtained pure, and the monohydrochloride in aqueous solution is largely unchanged after 24 hours, although in the presence of one molecule of hydrochloric acid in excess it is quantitatively converted into the propionylguanidine (VIII) at room temperature within 4 hours. Treatment with alkali gives the corresponding guanidines, but more vigorous conditions are required. In common with the N^1N^5-disubstituted diguanides the bases form red benzene-soluble copper complexes when shaken in benzene solution with ammoniacal copper sulphate solution (cf. Gage and Rose, *Ann. Trop. Med. Parasit.*, 1946, **40**, 333).

When the reaction between *N*-cyano-*N*′-*p*-chlorophenylguanidine (IV) and ethylmagnesium iodide was carried out at higher temperatures different products appeared. The gradual addition of 2—4 molecules of the Grignard reagent to a suspension of (IV) in anisole at 95—100° gave

(X.)



(XI.)



(XII.)

mainly *p*-chlorophenylcyanamide (VI) with minor quantities of *p*-chloroaniline, N-p-*chlorophenylpropionamidine* (X), and unchanged (IV). The propionamidine (X) was the major

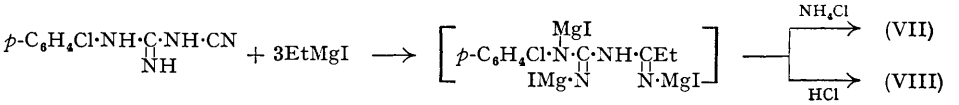
product when the quantity of the Grignard reagent was increased to 6 moles; its constitution was established by synthesis from propionitrile and *p*-chloroanilinomagnesium iodide (cf. Hullin, Miller, and Short, *loc. cit.*).

A slight modification of the above procedure, *viz.*, preparation of the reaction complex at room temperature with a slight excess of Grignard reagent, displacement of the ether by anisole, and heating at 95—100° for 1½ hours before decomposition with ammonium chloride solution gave *p*-chlorophenylcyanamide (VI) (60%), a trace of *p*-chloroaniline, and an oily mixture (20—30%). On suitable treatment the oil yielded *N*-*p*-chlorophenylguanylpropionamidine (VII) and a small amount of a less basic compound, proved to be 6-*amino*-2-p-*chloroanilino*-4-*ethyl*-1 : 3 : 5-*triazine* (XII) by independent synthesis from *p*-chlorophenyldiguanide and propionyl chloride (see Part XII, *J.*, 1947, 154).

A number of *N*-*p*-chlorophenylguanylamidines were prepared for examination of their antimalarial activity by similar (low-temperature) reactions between (IV) and various alkylmagnesium iodides and bromides. In no case did the reaction proceed so readily as with ethylmagnesium iodide, and a higher temperature (b. p. of ether) was required for approximate completion in 2—4 hours. Generally, the iodides were more satisfactory than the bromides, but phenylmagnesium bromide was exceptional in giving the best yield of guanylamidine in this series of experiments even when the reaction complex was decomposed by acid. In respect of the yields of *p*-chlorophenylcyanamide (VI) the converse was true, *iso*butylmagnesium bromide, for example, giving 48% of this product in one of a series of experiments.

The series of N-p-*chlorophenylguanylamidines* (XI; R = Me, Et, Pr^n, Pr^i, or Bu^i) was kindly tested for antimalarial activity in the Research Laboratories of I.C.I. (Dyestuffs Division) Ltd., Manchester, against *P. gallinaceum* in chicks. All were inactive.

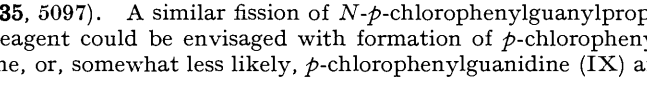
The mechanism of the formation of *N*-*p*-chlorophenylguanylpropionamidine (VII) and *N*-propionyl-*N'*-*p*-chlorophenyl guanidine (VIII) appears to be straightforward addition of the Grignard reagent to the C≡N group, amidine or amide resulting according to the alkaline or acid nature of the reagent employed for the hydrolysis of the complex, analagous to the well-known formation of imines or ketones from certain nitriles. From Zerewitinoff determination, it is known that *N*-cyano-*N'*-*p*-chlorophenylguanidine (IV) contains two active hydrogen atoms (Part XLIV), and from observations of the rate of evolution of ethane on treatment with ethylmagnesium iodide it seems probable that the metalation reaction approaches completion before appreciable addition has taken place. The overall reaction, then, may be :



(The actual hydrogen atoms indicated as being replaced by MgI have been selected arbitrarily as unaffecting the final product, and representation of the complexes by these formulæ is a matter of convenience since the true structure will no doubt be essentially ionic. This treatment will be applied to all subsequent formulæ for complexes, unless otherwise indicated.)

Although it was found necessary to use more than 3 moles of Grignard reagent, the method of analysis (Gilman *et al.*, *J. Amer. Chem. Soc.*, 1923, **45**, 150; 1929, **51**, 1576), and losses and decomposition during manipulation, probably account for the excess.

The mode of formation of *p*-chlorophenylcyanamide (VI) is less obvious. Besides *N*-cyano-*N'*-*p*-chlorophenylguanidine (IV), the more complex reaction products (VII), (VIII), and (IX) may all be regarded as *p*-chlorophenylcyanamide (IV) derivatives and potential sources of the same. For example, aryldiguanides are known to undergo thermal decomposition into their component guanidines and cyanamides (Kiitiro Sugino, *J. Chem. Soc. Japan*, 1939, **60**, 411; *Chem. Abs.*, 1941, **35**, 5097). A similar fission of *N*-*p*-chlorophenylguanylpropionamidine (VII) by the Grignard reagent could be envisaged with formation of *p*-chlorophenylcyanamide (VI) and propionamidine, or, somewhat less likely, *p*-chlorophenylguanidine (IX) and propionitrile.



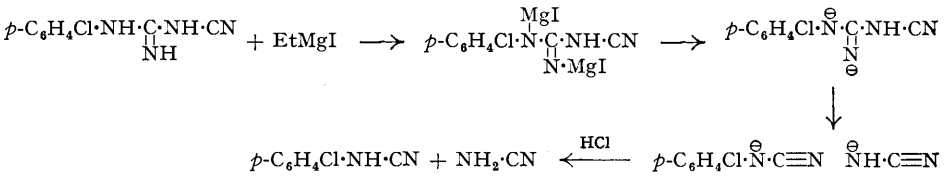
Equally feasible decompositions can be written for (VIII) and (IX).

Accordingly, the reactions between ethylmagnesium iodide and *N*-*p*-chlorophenylguanyl-

propionamidine (VII) and *p*-chlorophenylguanidine (IX) were separately studied at low (20—35°) and high temperature (90—100°). By this procedure—which is essentially metalation—it may be reasonably expected that the same magnesium complexes will be obtained as by the combined metalation and addition reactions between Grignard reagents and the cyanoguanidine (IV) (and subsequent fission, if any).

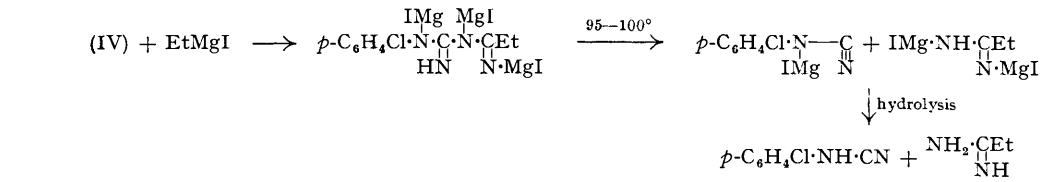
At low temperatures, *p*-chlorophenylcyanamide (VI) was obtained only from *N*-cyano-*N'*-*p*-chlorophenylguanidine (IV). In the main, the starting materials were recovered unchanged. The small amount of *p*-chlorophenylguanidine (X) which did accrue from *N*-*p*-chlorophenylguanylpropionamidine (VII) is considered to arise during the hydrolysis (discussed below) and not by the second of the postulated mechanisms given above.

It was concluded that *p*-chlorophenylcyanamide (VI) arose from a metalated *N*-cyano-*N'*-*p*-chlorophenylguanidine, but it could not be accurately established whether its formation preceded or accompanied hydrolysis of the complex. Some information on the latter point, however, was gained by addition of benzoyl chloride to the reaction mixture before its digestion with acid. In spite of gross decomposition, evidenced by the formation of *N*-benzoyl- and NN-*dibenzoyl*-p-*chloroaniline* and a welter of secondary reaction products most of which have not been identified, it was possible to isolate benzoylcyanamide and a trace of N-*benzoyl*-p-*chlorophenylcyanamide*. This indicates that *p*-chlorophenylcyanamide (VI) and cyanamide (as their MgI derivatives) are primary products of the reaction between (IV) and Grignard reagents, formed, it is suggested, by a " depolymerisation " mechanism. Since (IV) is largely recovered unchanged after reaction with one molecular proportion of Grignard reagent, the di- or tri-metalated products are probably involved, which after ionisation undergo rearrangement to the more stable cyanamide ions as depicted below. It is possible that the reaction is reversible.



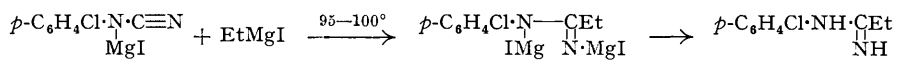
This reaction is reminiscent of the depolymerisation of dicyandiamide to cyanamide under the influence of potassium amide in liquid ammonia, observed by Hart (Thesis, Stanford Univ., 1926) (Franklin, " Nitrogen System of Organic Compounds," Reinhold Publ. Corp., p. 99). The previous isolation of the dipotassium salt of dicyandiamide indicates that in this case also the actual depolymerisation takes place by electronic rearrangement within an ion having two or more charges.

At higher temperatures (95—100°) in anisole, the magnesium complex formed between *p*-chlorophenylguanidine (IX) and ethylmagnesium iodide was practically unaffected, only a trace of *p*-chlorophenylcyanamide was formed, and >80% of the guanidine was recovered on subsequent hydrolysis. On the other hand, the tri(iodomagnesium) derivative of *p*-chlorophenylguanylpropionamidine (VII) under similar conditions gave >60% of *p*-chlorophenylcyanamide (VI)—almost the same yield as was obtained by similar treatment of (IV). It is evident, therefore, that at high temperatures a large proportion of the *p*-chlorophenylcyanamide (VI) is formed from (IV) by the following route :



The isolation of the second product of fission, propionamidine, has not been attempted, but evidence strongly supporting this mechanism was obtained by the isolation of small amounts of benzamidine (as the picrate) from low-temperature experiments (35°) involving phenylmagnesium bromide and either (IV) or its *iso*propyl analogue. By application of the benzoylation technique described above, it was shown that no cyanamide was produced by the thermal decomposition of the tri(iodomagnesium) derivative of *N*-*p*-chlorophenylguanylpropionamidine (VII), and more involved modes of decomposition thus appear to be ruled out.

The presence of *p*-chlorophenylcyanamide (VI) [as the tri(iodomagnesium) derivative] in the actual reaction mixture at high temperatures is proved by the formation of *N*-*p*-chlorophenylpropionamidine (X) in the presence of an excess of Grignard reagent:



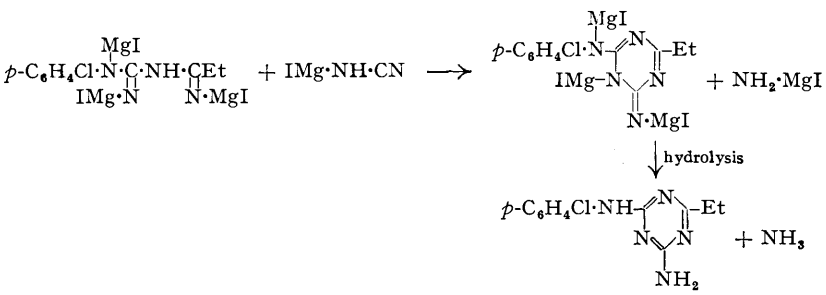
This reaction, which does not proceed at all at temperatures up to 35°, gives >70% yields at 95—100°.

p-Chlorophenylpropionamidine (X) appears to be the end-product of the series of reactions outlined above. It is relatively stable to excess of Grignard reagent under the experimental conditions used, although on recovery it is usually accompanied by small amounts of *p*-chloroaniline which evidently arise by hydrolysis.

In considering the mechanism of the formation of *p*-chlorophenylguanidine, fission of *N*-*p*-chlorophenylguanylpropionamidine (VII) (see above) was ruled out by failure to obtain any positive test for propionitrile (in the absence of excess of Grignard reagent). A further possibility, loss of the C≡N group of the cyanoguanidine (IV) to the magnesium of the Grignard reagent with simultaneous liberation of olefin was also rejected because the aqueous liquors after hydrolysis gave a negative test for cyanide.

A comparison of the yield of *p*-chlorophenylguanidine (IX) obtained by decomposition of the reaction complex from *N*-cyano-*N'*-*p*-chlorophenylguanidine (IV) and ethylmagnesium iodide with ammonium chloride (*ca.* 20%) and with hydrochloric acid (*ca.* 2%) supports these conclusions and suggests a differential hydrolytic attack of alkali and acid on the *N*-*p*-chlorophenylguanylpropionamidine–magnesium iodide complex. The former leads simultaneously to the guanidine (X) and to the parent guanylamidine (VII), and the latter to the propionylguanidine (VIII).

The formation of 6-amino-2-*p*-chloroanilino-4-ethyl-1 : 3 : 5-triazine (XII) during the reaction between *N*-cyano-*N'*-*p*-chlorophenylguanidine (IV) and ethylmagnesium iodide (*ca.* 3 mols.) is explicable by the following reaction:



It has been demonstrated above that the necessary intermediates are present in the reaction mixture, and, significantly, triazine formation does not occur in the reaction between *N*-*p*-chlorophenylguanylpropionamidine (VII) itself and ethylmagnesium iodide when cyanamidomagnesium iodide is demonstrably absent.

The reaction of other cyanoguanidines with Grignard reagents has also been examined. *N*-Cyano-*N'*-phenylguanidine, treated with an excess of methylmagnesium iodide in boiling ether in the usual way, gave phenylcyanamide (37% as its polymer) and phenylguanidine (52% as the picrate) on decomposition with ammonium chloride. Only a trace of material giving the requisite colour reaction for a guanylamidine was isolated. A similar result was obtained with ethylmagnesium iodide at room temperature but, when hydrolysis of the complex was carried out with hydrochloric acid, N-*propionyl*-N'-*phenylguanidine* resulted in 59% yield. Similarly *N*-cyano-*N'*-*p*-methoxyphenylguanidine and ethylmagnesium iodide gave, after decomposition with ammonium chloride, *p*-methoxyphenylcyanamide (18%), N-*propionyl*-N'-*p*-*methoxyphenylguanidine* (14%), and very crude *p*-methoxyphenylguanidine picrate (68%), whilst decomposition with acid resulted in the cyanamide and propionylguanidine in 22 and 70% yield, respectively.

The mechanism of the formation of these compounds is believed to be the same as deduced above for the *p*-chlorophenyl analogues. It appears that in these cases addition of the Grignard reagent takes place normally—evidenced by the good yield of *N*-propionyl-*N'*-phenyl- and -*N'*-*p*-methoxyphenyl-guanidine obtained by decomposition with acid—but the complexes are

much more sensitive than in the *p*-chlorophenyl series to the type of hydrolysis by alkali which results in the guanidine. Any guanylamidine which *is* formed by ammonium chloride decomposition may well remain in solution as its monoacid salt since it is to be expected that these compounds will be stronger bases than the *p*-chlorophenyl analogue and probably stronger than ammonia. The extent to which the guanylamidine is formed in (ammoniacal) solution may be surmised by subsequent acidification to give the alternative hydrolysis product—the propionylguanidine—which for the *p*-methoxyphenyl compound was 14%.

The reaction of dicyandiamide itself with Grignard reagents was found to be unaccountably slow. With 3·5 mols. of phenylmagnesium bromide or ethylmagnesium iodide in boiling ether, a large quantity of both reactants was unchanged after 24 hours. Evidence that some reaction had taken place was, however, obtained by benzoylation, benzoylcyanamide being isolated.

Reaction between *N*-cyano-*N'-iso*propylguanidine and phenylmagnesium bromide (3·5 mols.) was also sluggish, but was almost complete after 5—6 hours in boiling ether. The products of the reaction (after hydrolysis with acid) were N-iso*propylguanylbenzamidine* (as the picrate), benzamidine (as the picrate), a considerable quantity of unidentified infusible material (also obtained from experiment with dicyandiamide itself), phenol and diphenyl (always obtained from experiments utilising phenylmagnesium bromide), and an unidentified nitrogenous oil in the phenol and diphenyl fractions.

From this and the other example recorded previously it would appear that the guanylbenzamidines are much less sensitive to acid hydrolysis than are their alkyl analogues.

In conclusion, it is apparent that the fundamental reactions of the monosubstituted cyanoguanidines with Grignard reagents are the same, but different products may be isolated owing to the different degrees of sensitivity of the guanylamidine–magnesium iodide complexes to hydrolysis.

Experimental.

M.p.s are uncorrected. Analyses are by Drs. Weiler and Strauss of Oxford.

The Grignard reagents used in this work were prepared and standardised as previously indicated (preceding paper).

Beyond the use of carefully dried apparatus, no special precautions were taken during the measurement of the quantities of these reagents required in the various experiments, and a slight loss occurred by decomposition with atmospheric water vapour. The actual reactions were carried out with the usual precautions for the exclusion of moisture.

For the detection of excess of Grignard reagent or to follow the course of a reaction, the colour test with Michler's ketone (Gilman and Schulze, *J. Amer. Chem. Soc.*, 1925, **47**, 2002) was applied. Owing to the basic character of many of the reaction products it was necessary to modify the test slightly: after treatment with iodine solution, glacial acetic acid was added until all turbidity was removed.

Reaction of N-*Cyano*-N'-p-*chlorophenylguanidine* (IV) *with Ethylmagnesium Halides.*—(a) *Decomposition of reaction complex with ammonium chloride.* (i) To a well-stirred suspension of *N*-cyano-*N'-p*-chlorophenylguanidine (9·7 g.) (Part XXVIII, *J.*, 1948, 1634) in ether (50 c.c.) an ethereal solution of ethylmagnesium iodide (88 c.c.; 0·168 g.-mol.) was added as rapidly as the ensuing vigorous reaction would allow (2—3 minutes). After 15—20 minutes' stirring, the gas evolution was much reduced and the mixture was heated under reflux for approx. 1 hour. At this stage a slight positive colour test for excess of Grignard reagent was obtained with Michler's ketone (see above). The product, a heterogeneous mixture which separated into two liquid layers, was cooled and the magnesium complex hydrolysed by pouring the mixture into ammonium chloride solution (ammonium chloride, 20 g.; water, 50 c.c.; ice 100 g.). The ethereal layer was separated and the aqueous solution extracted with a further quantity of ether (*ca.* 100 c.c.). The combined ethereal extracts were then washed twice with water (50 c.c. portions), adding the first 50 c.c. to the aqueous mother-liquors. Acidic materials were extracted by shaking with 2N-sodium hydroxide (2 × 50 c.c.), and after further washing with water (total 100 c.c.) the ether was dried (Na_2SO_4) and evaporated to dryness, whereupon crude N-p-*chlorophenylguanylpropionamidine* (VII) (5·0 g.) remained. It was dissolved in 95% alcohol (20 c.c.) at 30—40°, decolorised with carbon, filtered, washed with alcohol (5 c.c.), and crystallised by the gradual addition of water (50 c.c.), giving the pure base as colourless prisms m. p. 134—135° (3·8 g.). A further crystallisation from benzene–*cyclo*hexane gave the base as colourless prisms, m. p. unchanged and not depressed on admixture with authentic material prepared as below (Found: C, 53·7; H, 6·0; N, 25·0. $C_{10}H_{13}N_4Cl$ requires C, 53·5; H, 5·8; N, 25·0%). The *acetate* crystallised as colourless aggregates of prisms, m. p. 141—142°, on gradual addition of an ethereal solution of glacial acetic acid to the pure base dissolved in ether, until neutral to litmus (Found: C, 50·4; H, 6·1. $C_{10}H_{13}N_4Cl,C_2H_4O_2$ requires C, 50·6; H, 6·0%). The *picrate* crystallised from alcohol in yellow needles, m. p. 164—165° (Found: N, 21·4. $C_{10}H_{13}N_4Cl,C_6H_3O_7N_3$ requires N, 21·6%).

The sodium hydroxide extract was then acidified with hydrochloric acid, with ice-cooling. The resulting suspension was extracted with ether, dried (Na_2SO_4), and evaporated to dryness under reduced pressure. The residue (2·6 g.) was triturated with warm dilute aqueous ammonia, and insoluble unchanged *N*-cyano-*N'-p*-chlorophenylguanidine (IV) filtered off, washed well with water, and dried (1·0 g.). After crystallisation from 50% ethanol it was obtained as glistening plates, m. p. and mixed m. p. 210—211° (Found: C, 49·4; H, 3·7; N, 29·0. Calc. for $C_8H_7N_4Cl$: C, 49·4; H, 3·6; N, 28·8%). The ammoniacal filtrates, acidified with hydrochloric acid with internal ice-cooling, deposited *p*-chloro-

phenylcyanamide (VI) which was collected, well washed with water, and dried *in vacuo* over calcium chloride. Yield, 1·3 g.; m. p. and mixed m. p. 105—106°.

The ammonia–ammonium chloride liquors from the initial decomposition of the magnesium complex gave, on acidification (ice-cooling) and extraction with ether, a further small quantity of *p*-chlorophenylcyanamide (0·2 g.).* Subsequent basification with concentrated sodium hydroxide solution until alkaline to Titan-yellow, and extraction of the resultant sludge with ether in a continuous extractor for three days, yielded on evaporation of the dried ethereal extract a tarry solid (1·85 g.) identified as *p*-chlorophenylguanidine (IX) by conversion into the *picrate*, yellow needles, m. p. 235°, identical with that obtained from an authentic specimen of (IX) (Part XXV, *J.*, 1948, 59) (Found: C, 39·8; H, 3·0; N, 21·0. $C_7H_8N_3Cl,C_6H_3O_7N_3$ requires C, 39·2; H, 2·8; N, 21·1%).

(ii) Similarly treated, *N*-cyano-*N'*-*p*-chlorophenylguanidine (IV) (9·7 g.) and ethylmagnesium bromide in ether (104 c.c.; 0·168 g.-mol.) required to be heated under reflux for 4 hours before the reaction was complete. The yield of *N*-*p*-chlorophenylguanylpropionamidine (VII), m. p. 132—134°, was 2·6 g. (4·25 g., crude), and that of *p*-chlorophenylcyanamide (VI), m. p. 102—104°, was 3·1 g.

(iii) In the same manner, *N*-cyano-*N'*-*p*-chlorophenylguanidine (IV) (9·7 g.) and ethylmagnesium bromide (93 c.c.; 0·15 g.-mol.) were allowed to react together at room temperature. Excess of Grignard reagent was present after 19 hours, and the reaction mixture then gave (IV) 2·0 g., *p*-chlorophenylcyanamide (VI) 2·1 g. (m. p. 105—107°), and *p*-chlorophenylguanylpropionamidine (VII) 2·1 g. (3·4 g. crude) (m. p. 132—134°).

(b) *Hydrolysis of the reaction complex with acid.* *N*-Cyano-*N'*-*p*-chlorophenylguanidine (IV) (9·7 g.) and ethylmagnesium iodide (84 c.c.; 0·158 g.-mol.) were allowed to react as in (*a*, i), but the reaction was completed by stirring at room temperature for 2—3 hours, whereafter only a slight excess of Grignard compound remained. The magnesium complex was hydrolysed by pouring the mixture into hydrochloric acid solution (10N-HCl, 25 c.c.; water, 50 c.c., ice, 100 g.), and the ethereal and aqueous layers were separated. The aqueous solution was extracted with a further quantity of ether, the combined extracts were washed with water (50 c.c.), and *very* dilute sodium thiosulphate or hydrogen sulphite solution, dried (Na_2SO_4), and evaporated to dryness at $\not>35°$. The residue consisted of *N*-cyano-*N'*-*p*-chlorophenylguanidine (IV) (0·95 g.; m. p. 202—203°), and *p*-chlorophenylcyanamide (VI) (1·9 g.; m. p. 105—106°) which were separated as described above (*a*, i).

The aqueous acid extract was set aside for 4 hours (to ensure complete hydrolysis), during which a considerable quantity of crystals was deposited. However, concentrated ammonia solution was added until the solution was strongly alkaline to brilliant-yellow, and the suspension stirred well for a few minutes to complete the neutralisation. The precipitate was collected, washed with water, and dried. Yield, 7·0 g.; m. p. 128—129°. On recrystallisation from 50% ethanol it was obtained as colourless needles, m. p. and mixed m. p. with N-*propionyl*-N'-p-*chlorophenylguanidine* (VIII) (see below) 134—135° (Found: C, 53·1; H, 5·3; N, 18·5. $C_{10}H_{12}ON_3Cl$ requires C, 53·2; H, 5·3; N, 18·6%). The *picrate* crystallised in yellow aggregates of prisms, m. p. 183—184°, from aqueous acetone (Found: N, 17·9. $C_{10}H_{12}ON_3Cl,C_6H_3N_3O_7$ requires N, 18·5%).

The filtrates were washed with ether, basified with concentrated sodium hydroxide solution, and extracted with ether in a continuous extractor for 48 hours, giving 0·1 g. of *p*-chlorophenylguanidine (IX) (identified as the picrate).

Hydrolysis of N-p-*Chlorophenylguanylpropionamidine* (VII).—(*a*) The base (VII) (1 g.) was suspended in water (15 c.c.) and 2N-hydrochloric acid (2—2·5 c.c.) added until a slightly acid reaction was obtained (litmus). The hydrochloride separated, but slowly redissolved on further addition of hydrochloric acid (2—2·5 c.c.), and after 2—3 hours at room temperature a clear solution was obtained. After 4 hours the solution gave no colour with ammoniacal copper sulphate solution and benzene (Gage and Rose, *loc. cit.*). Dilute aqueous ammonia was added gradually and the precipitate of *N*-propionyl-*N'*-*p*-chlorophenylguanidine collected, washed, and crystallised from 50% alcohol, whereafter it had m. p. and mixed m. p. 135—136°.

(*b*) The base (VII) (0·5 g.) was heated at 95—100° for 1·5 hours with 2N-sodium hydroxide (10 c.c.). After cooling, the product was extracted with ether, dried (Na_2SO_4), and evaporated to dryness. A test (Gage and Rose, *loc. cit.*) showed that unchanged (VII) was still present. However, by treatment with alcoholic picric acid solution, *p*-chlorophenylguanidine picrate was obtained, having m. p. and mixed m. p. 234°.

Hydrolysis of N-*Propionyl*-N'-p-*chlorophenylguanidine* (VIII).—The compound (VIII) (1·1 g.) was heated under reflux with 2N-sodium hydroxide for 15 minutes. An oil was obtained which solidified when cooled and scratched. Collected, well washed, and dried, it had m. p. 122—124° (0·5 g.). It crystallised from benzene in pale cream-coloured prisms (Found: C, 50·0; H, 4·7; N, 25·4. Calc. for $C_7H_8N_3Cl$: C, 49·6; H, 4·7; N, 24·8%), m. p. as before and not depressed on admixture with an authentic specimen of *p*-chlorophenylguanidine (IX).

Syntheses from p-*Chlorophenylguanidine* (IX).—(a) N-p-*Chlorophenylguanylpropionamidine* (VII). *p*-Chlorophenylguanidine (Part XXV, *loc. cit.*) (4·25 g.), freshly crystallised from benzene, was stirred in dry anisole while an ethereal solution of ethylmagnesium iodide (14 c.c.; 1·1 mols.) was added gradually. Ether was then distilled off until a liquid temperature of 95—100° was reached, and a solution of propionitrile (1·5 g.) in anisole (15 c.c.) was then introduced. The mixture was heated under reflux for 2½ hours, cooled, and hydrolysed by the addition of ammonium chloride solution (ammonium chloride, 10 g.; water, 25 c.c.; ice, 50 g.). It was necessary to stir for 1 hour at 25—30° before reaction was complete. Ether was then added to facilitate the separation of the two layers. The ether–anisole extract was washed with water, stirred, and neutralised with dilute aqueous hydrochloric acid until faintly acid to Congo-red. The acid extract was separated, immediately basified with ammonia (ice), and the oil which was deposited extracted into ether. After drying and evaporation, 0·75 g. of a basic oil was obtained. The initial aqueous (ammonium chloride) solution, when strongly basified with aqueous

* This extraction was usually omitted in subsequent experiments. Cases in which it was used will be indicated.

ammonia and extracted with ether, gave a further 0·3 g. of the same oil. The oils were combined, dissolved in alcohol (7 c.c.), and treated with decolorising carbon and the solution was diluted with water, whereupon crude *N*-*p*-chlorophenylguanylpropionamidine crystallised (0·5 g.). After 2 crystallisations from *cyclo*hexane and 2 from *cyclo*hexane–benzene it was obtained as colourless prisms, m. p. and mixed m. p. with a sample obtained above, 134—135°.

(b) N-*Propionyl*-N′-p-*chlorophenylguanidine* (VIII). Propionyl chloride (1·1 c.c.) in acetone (10 c.c.) was added dropwise to *p*-chlorophenylguanidine (IX) (4·25 g.) in acetone (25 c.c.), the temperature being kept at about 20° by external cooling. The reaction was completed by heating under reflux for ½ hour, and the bulk of the acetone then removed on the steam-bath. The residue was dissolved in 2N-hydrochloric acid (25 c.c.) and filtered from a trace of crystalline insoluble matter. After dilution of the mixture with much water, the product was reprecipitated by gradual addition of ice and aqueous ammonia until alkaline to brilliant-yellow. The precipitate was collected, dried, and dissolved in cold benzene (20 c.c.). Some insoluble matter was removed, and the filtrate evaporated to dryness to give the crude product which after successive crystallisations from *cyclo*hexane and 50% ethanol was obtained as colourless needles (0·7 g.), m. p. and mixed m. p. with material prepared above 134—135°.

Reaction between N-*Cyano*-N′-p-*chlorophenylguanidine* (IV) *and Ethylmagnesium Iodide at High Temperature.*—(a) *Gradual addition of* 4 *mols. of Grignard reagent.* Ethylmagnesium iodide in ether (112 c.c.; 0·2 g.-mol.) was added gradually during 65 minutes to a suspension of (IV) (9·7 g.) in anisole (100 c.c.) at 95—100°, the ether being simultaneously distilled off. After a further 30 minutes at this temperature, the solution was cooled and poured into dilute hydrochloric acid (10N-acid, 35 c.c.; ice, 150 g.). The two layers were separated and the anisole washed with water and extracted with dilute aqueous ammonia (2 × 50 c.c.). After clarification by shaking with benzene, the extract was acidified with hydrochloric acid and ice. The bulky precipitate was dissolved in ether, separated from water, and dried (Na_2SO_4). Crystalline *p*-chlorophenylcyanamide (VI) (3·1 g.), m. p. 106—107°, remained after removal of the solvent at low temperature. The initial acid layer was extracted further with benzene to remove traces of anisole, neutralised with aqueous ammonia, and extracted with chloroform. After drying and evaporation of the solvent, a basic oil remained (0·6 g.) which on acetylation with acetic anhydride and recrystallisation of the product from 50% ethanol gave *p*-chloroacetanilide (0·2 g.), needles, m. p. and mixed m. p. 179—180°. The aqueous mother-liquors were strongly basified with concentrated sodium hydroxide solution, and the precipitated magnesium hydroxide was filtered off. Both precipitate and filtrate were extracted with chloroform and, after drying, the solvent was distilled off leaving an oily residue which crystallised on cooling (2·0 g.). After two crystallisations from carbon tetrachloride this was obtained as almost colourless prisms, m. p. 79—81°, identified as *N*-*p*-chlorophenylpropionamidine (VII) by mixed m. p. with authentic material prepared as below.

(b) *Gradual addition of* 6 *mols. of Grignard reagent.* The reaction was carried out as in (*a*) above. The ethylmagnesium iodide solution (166 c.c.; 0·3 g.-mol.) was added during 80 minutes, and a considerable amount remained unaffected after a further ½ hour at 90—100°. After cooling, the reaction product was poured into dilute hydrochloric acid (10N-acid, 50 c.c.; ice, 200 g.). A solid which separated in the aqueous layer was filtered off, well washed with water, and dried (2·8 g.; m. p. 198—201°) (it was later found that this substance was appreciably soluble in water and that considerable amounts were lost). The product was dissolved in warm water and salted out by addition of potassium iodide. The precipitate was collected, dried, and dissolved in acetone. After decolorising with carbon, gradual addition of ether caused p-*chlorophenylpropionamidine hydriodide* to crystallise in very small prisms (1·5 g.), m. p. 203—204° (Found: C, 35·4; H, 3·8. $C_9H_{11}N_2Cl,HI$ requires C, 34·8; H, 3·9%), identified by dissolution in water and basification with sodium hydroxide solution to give the free base m. p. 80—81°, identical with an authentic specimen. The anisole extract, treated as described in (*a*), yielded *p*-chlorophenylcyanamide (VI) (1·2 g.), m. p. 103—106°, and the aqueous solution worked up in a similar manner gave *p*-chloroaniline (0·7 g.), crystallising from ligroin (b. p. 40—60°) in colourless prisms, m. p. 66—68°, and crude *N*-*p*-chlorophenylpropionamidine (VII) (2·7 g.).

(c) *Rapid addition of Grignard reagent* (3·35 *mols.*) *at low temperature with subsequent heating to* 95—100°. *N*-Cyano-*N*′-*p*-chlorophenylguanidine (IV) (9·7 g.) and ethylmagnesium iodide solution (88 c.c.; 0·168 g.-mol.) were allowed to react as previously described. After the mixture had been stirred at room temperature for 1½ hours, anisole (50 c.c.) was added and ether distilled off until the temperature reached 95°. The mixture was maintained at this temperature for 1 hour and then poured into dilute ammonium chloride solution (ammonium chloride, 25 g.; ice, 150 g.). Ether was added and the layers separated. The anisole–ether extract, after the usual treatment to give *p*-chlorophenylcyanamide (IV) (3·85 g.), m. p. 103—107°, was washed, dried, and evaporated to dryness *in vacuo*, leaving an oil (2·75 g.). *N*-*p*-Chlorophenylguanylpropionamidine (VII) was extracted by boiling this oil with *cyclo*hexane, and the residue was triturated with dilute hydrochloric acid. A slightly soluble hydrochloride (m. p. 214—216°) remained, which was dissolved in hot water, decolorised with carbon, and filtered. The filtrate, basified with ammonia, gave the base. A further quantity of base identical with this material crystallised from the aqueous ammoniacal layer (0·5 g.; m. p. 170—171°). After crystallisation successively from benzene and toluene it was obtained as colourless small prisms, m. p. 175—176°, and identified as 6-*amino*-2-p-*chloroanilino*-4-*ethyl*-1 : 3 : 5-*triazine* (XII) by mixed m. p. with material independently synthesised (see below) (Found: C, 52·9; H, 4·7. $C_{11}H_{12}N_5Cl$ requires C, 52·8; H, 4·8%). The aqueous ammoniacal filtrate from this substance was acidified with hydrochloric acid and extracted with ether, giving a further 0·7 g. of *p*-chlorophenylcyanamide (VI), m. p. 104—106°. The residual aqueous solution, again basified with ammonia, was treated with a boiling solution of picric acid (2 g.) in water (40 c.c.), whereupon *p*-chlorophenylguanidine picrate (0·2 g.) crystallised.

Preparation of N-p-*Chlorophenylpropionamidine* (X) *from* p-*Chloroaniline and Propionitrile* (cf. Hullin, Miller, and Short, *loc. cit.*).—*p*-Chloroaniline (12·7 g.) in ether (50 c.c.) was stirred rapidly while ethylmagnesium iodide (53 c.c.; 0·1 g.-mol.) was added dropwise. A white precipitate was formed, gradually dissolving with the addition of more Grignard reagent. The reaction was complete after stirring for ¼ hour. Propionitrile (5·5 g.) in ether (20 c.c.) was introduced gradually and the mixture heated under reflux for 1½ hours and then set aside overnight before decomposition by dilute hydrochloric

acid (10N-acid, 25 c.c.; ice, 100 g.) with cooling in an ice-bath. A precipitate which formed was filtered off, well washed with ether, and dried (9·8 g.; m. p. 189—192°). The heterogeneous filtrates were separated, and the ethereal layer was discarded. The aqueous solution was salted with sodium iodide (100 g.), and the precipitate filtered off and washed with sodium iodide solution. The two solids were combined and dissolved in warm water (250 c.c.), and the solution was clarified. The base was precipitated as an oil by addition of strong sodium hydroxide solution (external ice-cooling) and dissolved in chloroform. After drying, the solvent was evaporated leaving crude N-p-*chlorophenylpropionamidine* (VII) (12·5 g.) which, after crystallisation from *cyclo*hexane, was obtained as colourless prisms, m. p. and mixed m. p. 81—82° (Found: C, 59·2; H, 6·1; N, 15·2. $C_9H_{11}N_2Cl$ requires C, 59·2; H, 6·0; N, 15·3%). The *hydrochloride*, prepared by addition of an acetone solution of the base to anhydrous hydrogen chloride in benzene, crystallised in colourless prisms, m. p. 171—172° (Found: C, 49·5; H, 5·4; N, 12·4. $C_9H_{11}N_2Cl,HCl$ requires C, 49·3; H, 5·5; N, 12·8%).

6-*Amino*-2-p-*chloroanilino*-1 : 3 : 5-*triazine* (XII) (cf. Curd, Landquist, and Rose, *loc. cit.*).—To a mixture of *p*-chlorophenyldiguanide hydrochloride (2·5 g.) and sodium hydroxide (1·2 g.) in 50% aqueous dioxan (10 c.c.), propionylchloride (2·2 c.c.) was added dropwise with good agitation. After being kept overnight, the mixture was warmed on the steam-bath, made alkaline to Titan-yellow by addition of more sodium hydroxide solution, and heated to 90—100° for a further 10—15 minutes. It was then diluted with water (25 c.c.), and the precipitate filtered off, washed, and dried (1·6 g.; m. p. 158—168°). After successive crystallisations from toluene, chlorobenzene, and butanol, the triazine was obtained as colourless prisms (0·2 g.), m. p. and mixed m. p. 174—175°.

Reaction of (IV) *with Various Grignard Reagents.*—The technique employed was similar to that used in reactions involving ethylmagnesium iodide. Except where indicated, the amount of (IV) used was 9·7 g. (0·05 g.-mol.). In those experiments where reaction was largely incomplete, unchanged (IV) separated on hydrolysis of the magnesium complex and was filtered off. The filtrates were worked up as described previously.

N-p-*Chlorophenylguanylacetamidine* (XI; R = Me). Methylmagnesium iodide (82 c.c.; 0·153 g.-mol.) was treated with (IV) in the usual way, stirred for ½ hour, and heated under reflux for 1 hour, whereafter all the Grignard reagent had disappeared. By proceeding in the usual manner, (IV) (1·6 g.; m. p. 208—209°), *p*-chlorophenylcyanamide (VI) (2·5 g.; m. p. 103—105°), and N-p-*chlorophenylguanylacetamidine* (XI) (2·7 g.; m. p. 127—130°) were obtained. After 3 crystallisations from benzene (charcoal), (XI) was obtained as colourless prisms, m. p. 143—144° (Found: C, 51·2; H, 5·3; N, 26·1. $C_9H_{11}N_4Cl$ requires C, 51·3; H, 5·2; N, 26·6%).

N-p-*Chlorophenylguanyl*-n-*butyramidine* (XI; R = Pr^n). By a similar reaction with *n*-propylmagnesium iodide (120 c.c.; 0·168 g.-mol.), (IV) (1·1 g.) and *p*-chlorophenylcyanamide (VI) (2·4 g.) were obtained, with the crude *amidine* (4·5 g.), m. p. 113—116°. It was necessary to heat under reflux for 1½ hours before the reaction was complete. For purification, the crude material was crystallised twice from *cyclo*hexane, dissolved in ethanol (total, 15 c.c.), decolorised (carbon), and caused to crystallise by the gradual addition of water (30 c.c.). It was obtained as colourless prisms (2·1 g.), m. p. 121—122° (Found: C, 55·4; H, 6·6; N, 23·8. $C_{11}H_{15}N_4Cl$ requires C, 55·4; H, 6·3; N, 23·5%).

N-p-*Chlorophenylguanyl*iso*butyramidine* (XI; R = Pr^i). (IV) and *iso*propylmagnesium bromide (100 c.c.; 0·168 g.-mol.), stirred for ½ hour and then heated under reflux for 2½ hours before hydrolysis, gave *p*-chlorophenylcyanamide (VI) (2·7 g.), m. p. 103—105°, and a trace of unchanged (IV). The *amidine* was purified by two crystallisations from benzene–*cyclo*hexane (1 : 1), dissolved in ethanol (10 c.c.), filtered, and caused to crystallise by the gradual addition of water (10 c.c.), which gave colourless prisms, m. p. 127—128° (1·65 g.) (Found: C, 55·5; H, 6·3; N, 22·9. $C_{11}H_{15}N_4Cl$ requires C, 55·4; H, 6·3; N, 23·5%).

N-p-*Chlorophenylguanyl*iso*valeramidine* (XI; R = Bu^i). *iso*Butylmagnesium bromide (113 c.c.; 0·168 g.-mol.) and (IV), treated as usual, were heated under reflux for 3½ hours. Although an appreciable amount of unchanged Grignard reagent was still present, the mixture was hydrolysed. Unchanged (IV) (1·3 g.) was recovered, together with *p*-chlorophenylcyanamide (VI) (2·7 g.), m. p. 103—105°, and a basic oil from which the crude *base* was deposited on dilution with ligroin (b. p. 60—80°). After two crystallisations from *cyclo*hexane it was obtained as small, colourless needles (0·3 g.), m. p. 118° (after shrinking) (Found: C, 57·1; H, 6·8; N, 22·4. $C_{12}H_{17}N_4Cl$ requires C, 57·0; H, 6·7; N, 22·2%).

N-p-*Chlorophenylguanylbenzamidine* (XI; R = Ph). Phenylmagnesium bromide (52 c.c.; 0·110 g.-mol.) was added in the usual manner to (IV) (6·5 g.) and after being stirred for 15 minutes was heated under reflux for 2 hours. A slight excess of Grignard reagent then remained. The reaction mixture was cooled and poured into dilute hydrochloric acid (10N-acid, 16·5 c.c.; ice, 100 g.), and the hydrolysis completed by stirring for 1 hour. A bulky precipitate formed and was filtered off, washed with water and then with ether, and dried (7·2 g.; m. p. 198—199°). It was dissolved in hot water (200 c.c.) and poured into dilute sodium hydroxide solution and crushed ice. The precipitate of N-p-*chlorophenylguanylbenzamidine* was collected, well washed, and dried (5·8 g.; m. p. 170—171°). On crystallisation from absolute alcohol it was obtained as pale cream-coloured plates, m. p. 171—172° (Found: C, 62·0; H, 4·7; N, 20·1. $C_{14}H_{13}N_4Cl$ requires C, 61·7; H, 4·8; N, 20·6%). The main filtrate of both ethereal and aqueous layers was separated. The aqueous solution gave no precipitate on being made alkaline with aqueous ammonia, but addition of picric acid (3 g.) in boiling water (100 c.c.) to the alkaline solution gave a precipitate (0·8 g.) which crystallised from ethanol in long yellow needles, m. p. 239—240°, and was identified as benzamidine picrate by m. p. and mixed m. p. with an authentic specimen (Oxley and Short, *J.*, 1946, 149, give m. p. 238—239°; Dieckmann, *Ber.*, 1892, **25**, 547, gives m. p. 228°). The ethereal layer was washed with water, extracted with dilute sodium hydroxide solution, washed again with water, dried, and evaporated. An oil (0·8 g.) remained which, when kept, deposited crystals of diphenyl, m. p. and mixed m. p. 68—70°. The sodium hydroxide extract gave *p*-chlorophenylcyanamide (VI) (1·4 g.), m. p. 104—105°, on acidification. This material had a pronounced odour, probably owing to contamination with a trace of phenol.

Reaction between Benzoyl Chloride and the Magnesium Complex derived from N-*Cyano*-N′-p-*chlorophenylguanidine* (IV) *and Ethylmagnesium Iodide.*—The complex was formed in the manner previously

described. After completion of the reaction, the flask was immersed in an ice-bath, and a solution of benzoyl chloride (21 c.c.) in ether (100 c.c.) added during 1 hour with good stirring. The mixture was stirred at room temperature overnight and subsequently for 4 hours under reflux. After cooling it was poured into 2N-hydrochloric acid (200 c.c.) (maintained at 20—25°) and agitated for 2 hours to complete the hydrolysis. A small amount of insoluble solid was filtered off, the ethereal layer separated, and the aqueous layer discarded. After being washed with water (100 c.c.) and very dilute sodium sulphite solution (100 c.c.) the ethereal layer was extracted with dilute aqueous ammonia (2 × 25 c.c.) and then shaken with 2N-sodium hydroxide, whereupon crystals separated. These were collected, well washed, dried, and crystallised from benzene to constant m. p., the product being obtained as colourless needles, m. p. 216—217°. It has not been identified, but may be a dibenzoyl-*p*-chlorophenylguanidine (Found: C, 66·8; H, 4·2; N, 10·4; Cl, 9·9. Calc. for $C_{21}H_{16}O_2N_3Cl$: C, 66·8; H, 4·2; N, 11·1; Cl, 9·4%). The ammoniacal extract, cooled by addition of ice, was acidified with hydrochloric acid, and the precipitate filtered off, dried, and repeatedly extracted with boiling *cyclo*hexane (total, 100 c.c.). The residual benzoylcyanamide, after crystallisation from water, was obtained as colourless needles, m. p. and mixed m. p. 141—142° (Found: C, 65·6; H, 4·2; N, 18·7. Calc. for $C_8H_6ON_2$: C, 65·7; H, 4·1; N, 19·2%). The ethereal solution, when dried (Na_2SO_4), deposited a further quantity of crystals on the drying agent. The sodium sulphate was dissolved in hot water, and the insoluble material, after drying, crystallised from benzene. Crude benzo-*p*-chloroanilide was obtained, which, after being washed with chloroform and recrystallised from benzene, had m. p. and mixed m. p. with an authentic specimen 193—194°. The benzene filtrates from the initial crystallisation were evaporated to dryness, and the residue crystallised repeatedly from absolute alcohol, to give NN-*dibenzoyl*-p-*chloroaniline* as colourless needles, m. p. 159—160° undepressed on admixture with an authentic specimen prepared as directed below (Found: C, 71·6; H, 4·4; N, 4·05; Cl, 10·5. $C_{20}H_{14}O_2NCl$ requires C, 71·5; H, 4·2; N, 4·2; Cl, 10·6%). The dried ethereal solution was evaporated to dryness, giving a residue of tar and solid. This was stirred with a little ether and filtered from undissolved material (further amounts of benzoyl-*p*-chloroaniline, etc.) and allowed to crystallise. After successive crystallisations from methanol, ethanol, benzene–*cyclo*hexane, and carbon tetrachloride a small quantity of N-*benzoyl*-p-*chlorophenylcyanamide* (*cyanobenzo*-p-*chloroanilide*) was obtained as colourless prisms, m. p. 129—131°, giving a mixed m. p. 130—133° with an authentic sample prepared as below (Found: N, 10·4. $C_{14}H_9ON_2Cl$ requires N, 10·9%).

For comparison *NN*-dibenzoyl-*p*-chloroaniline was prepared by heating benzo-*p*-chloroanilide (21·7 g.) and benzoyl chloride (11 c.c.) at 220° for 4—5 hours. After slight cooling, benzene was added and the slightly soluble unchanged benzo-*p*-chloroanilide recovered (18·4 g.). The benzene solution was evaporated to dryness, and the excess of benzoyl chloride removed by heating to 200° *in vacuo*. The residue, after two crystallisations from ethanol, gave the required dibenzoyl derivative as colourless needles m. p. 159—160°. *N*-Benzoyl-*p*-chlorophenylcyanamide was prepared from *p*-chlorophenylcyanamide by the normal Schotten–Baumann procedure. It crystallised from benzene–*cyclo*hexane in colourless prisms, m. p. 134—135° (Found: N, 10·8%).

Decomposition of N-p-*Chlorophenylguanylpropionamidine* (VII) *with Ethylmagnesium Iodide.*—(*a*) Ethylmagnesium iodide in ether (40 c.c.; 0·076 g.-mol.) was added during 2—3 minutes to a stirred solution of the amidine (5·6 g.) in ether (25 c.c.). After being stirred at room temperature for 2 hours, although much of the Grignard reagent remained unchanged, the reaction mixture was hydrolysed by pouring it into ammonium chloride solution (ammonium chloride, 10 g.; water, 25 c.c.; ice, 50 g.). A precipitate which formed redissolved on addition of more water. The ethereal layer was separated and extracted with a further quantity of ether, and the extracts were combined. After being washed with water, the ethereal solution was shaken with 2N-sodium hydroxide (2 × 30 c.c.), washed, and dried, and the ether distilled off. The residue consisted of unchanged amidine (4·1 g.; m. p. 130—132°). The sodium hydroxide extract was acidified with hydrochloric acid, with ice-cooling. Extraction of the solution with ether and evaporation of the solvent after washing and drying gave only a trace of *p*-chlorophenylcyanamide (VI). Acidification of the original ammoniacal solution (addition of ice), followed by extraction with ether and evaporation as before, gave no further amount of *p*-chlorophenylcyanamide (VI). The acid solution was therefore basified with sodium hydroxide solution until alkaline to Titan-yellow, cooling internally with ice, and the resulting suspension extracted continuously with ether for 48 hours to yield crude *p*-chlorophenylguanidine (IX) (1·15 g.).

(*b*) The initial reaction was carried out similarly, but the mixture was subsequently heated under reflux for 2 hours until only a faint indication of excess of alkylmagnesium iodide was obtained by the Gilman–Schulze test. The procedure described above was followed for isolation of the products. There were obtained unchanged amidine (3·3 g.; m. p. 126—130°), *p*-chlorophenylcyanamide (VI) (approx. 0·1 g.; m. p. 102—103°), and crude *p*-chlorophenylguanidine (IX) (1·6 g.; contaminated with some guanylamidine) which crystallised from benzene in cream-coloured prisms, m. p. and mixed m. p. 120—121°.

(*c*) The magnesium complex was formed as described under (*b*), little alkylmagnesium iodide remaining after 2 hours' heating under reflux. Anisole (50 c.c.) was then introduced and ether distilled off on the steam-bath until an internal temperature of approx. 95° was obtained. The mixture was maintained at 90—100° for 1½ hours, cooled, and hydrolysed with ammonium chloride solution as before. Ether was added to facilitate separation and after the usual extractions the ether–anisole solution was evaporated to dryness under reduced pressure. Crude guanylamidine (1·3 g.) remained. The sodium hydroxide extract and the ammoniacal solution acidified as before gave *p*-chlorophenylcyanamide (VI) (total, 2·4 g.), m. p. 104—105°, and continuous extraction by ether of the basified mother-liquors gave an oil (0·6 g.) yielding *p*-chlorophenylguanidine picrate, m. p. 231—233°, on treatment with alcoholic picric acid.

Examination of the Products of the Reaction between N-p-*Chlorophenylguanylpropionamidine* (VII) *and Ethylmagnesium Iodide for Propionitrile and Cyanamide.*—The reaction between the amidine (11·2 g.) in ether (50 c.c.) and ethylmagnesium iodide (80 c.c.; 0·15 g.-mol.) was carried out in the usual manner and, on completion, dry anisole (150 c.c.) was introduced. Ether was distilled off on the steam-bath, and the pressure then gradually reduced until a total of approx. 150 c.c. of liquid had distilled off. The distillate was fractionated and a small fraction, b. p. 40—150°, was tested for nitrogen by fusion with sodium. Negative results were obtained and further search for propionitrile was abandoned.

The reaction mixture was then cooled and stirred during the gradual addition of benzoyl chloride (21 c.c.) in ether (100 c.c.) during ½ hour. After being kept overnight the mixture was heated under reflux for 3 hours, cooled, and poured into 2N-hydrochloric acid (200 c.c.), the temperature being kept at *ca.* 25°. When dissolution of the solid was complete, the ether–anisole extract was examined for benzoylcyanamide as described above (p. 2570). All the material was soluble in *cyclo*hexane, *i.e.*, no benzoylcyanamide was present.

Reaction of p-*Chlorophenylguanidine with Ethylmagnesium Iodide.*—(*a*) *p*-Chlorophenylguanidine (IX) (8·5 g.), suspended in ether (50 c.c.), was treated portionwise with ethymagnesium iodide (total, 93 c.c.; 0·175 g.-mol.) during 4 hours, until a positive reaction for excess of Grignard reagent was obtained and remained after ½ hour's stirring. The reaction mixture was then hydrolysed with acid and the ethereal layer separated and washed as described above (p. 2567). On evaporation of the ether, a residue of crude *p*-chlorophenylurea (0·75 g.) remained, which, after recrystallisation from water, was obtained as glistening plates, m. p. and mixed m. p. 213—214°. No *p*-chlorophenylcyanamide (VI) was detected. The aqueous extract was made alkaline with aqueous ammonia (ice-cooling) and extracted with ether. Removal of the solvent, after drying (Na_2SO_4), and acetylation of the product (0·5 g.) gave *p*-chloroacetanilide, m. p. 179—180° after crystallisation from 50% alcohol. The ammoniacal solution was then made strongly alkaline to Titan-yellow with sodium hydroxide solution and extracted with ether in a continuous extractor. After approx. 24 hours, 4·25 g. of *p*-chlorophenylguanidine (IX), m. p. 119—122° were recovered.

(*b*) In a similar experiment, the *p*-chlorophenylguanidine (IX) was treated with ethylmagnesium iodide (88 c.c.; 0·168 g.-mol.) duing a few minutes and stirred for 1½ hours. Ether was then displaced by anisole (50 c.c.) by the usual technique, and the mixture maintained at 95—100° for 1 hour. After cooling, it was hydrolysed by acid, and the ether–anisole and aqueous layers were separated and washed in the usual manner. By extraction of the ether–anisole layer with sodium hydroxide solution a small amount (0·2 g.) of *p*-chlorophenylcyanamide (VI), m. p. 105—106°, was obtained. The residual anisole–ether solution, on evaporation to dryness, gave crude *p*-chlorophenylurea (0·3 g.), m. p. 203—205°. The aqueous extract, on basification with aqueous ammonia and extraction with ether, yielded *p*-chloroaniline (0·65 g.) and, after being made strongly alkaline with sodium hydroxide solution and extracted in a continuous extractor with ether for 48 hours, gave *p*-chlorophenylguanidine, m. p. 122—124° (6·3 g.). A further 2 g. of *p*-chlorophenylguanidine (IX), m. p. 232—234°, was recovered (as its picrate) by treatment of the liquors (after the above extraction) with hydrochloric acid until they were clear, rebasifying with aqueous ammonia, and adding picric acid (2 g.) in water (40 c.c.) to the boiling solution.

Reaction between N-p-*Chlorophenylpropionamidine* (X) *and Ethylmagnesium Iodide.*—To a solution of *N*-*p*-chlorophenylpropionamidine (X) (9·1 g.) in anisole (100 c.c.), ethylmagnesium iodide (75 c.c.; 0·145 g.-mol.) was added rapidly and the whole stirred at room temperature for 1½ hours. The mixture was then heated to 90—100° for 2 hours, whereafter an excess of Grignard reagent was still present. However, after cooling, the product was hydrolysed with acid in the usual manner. The hydriodide of unchanged amidine (X) (11·2 g.), m. p. 203°, crystallised and was filtered off and converted into the base (5·0 g.), m. p. 84°. The anisole–ether extract yielded a trace only of phenolic products which were discarded. The acid solution was basified with aqueous ammonia and extracted with ether. An oil (1·65 g.) remained on evaporation of the solvent; one portion thereof, on acetylation in aqueous alcohol, gave *p*-chlorophenylacetanilide, m. p. 179—180°; the remainder, by dissolution in dilute hydrochloric acid and salting out with sodium iodide, gave a further quantity of the amidine hydriodide, m. p. 203—205°.

Reaction of p-*Chlorophenylcyanamide* (VI) *with Ethylmagnesium Iodide.*—(*a*) *p*-Chlorophenylcyanamide (VI) (3·8 g.) in ether (25 c.c.) was treated with ethylmagnesium iodide (26 c.c.; 0·05 g.-mol.), and the mixture stirred for 22 hours and then heated under reflux for 5 hours. A large excess of the Grignard reagent remained. The product was hydrolysed with hydrochloric acid (10N-acid, 10 c.c.; ice, 100 g.), and the ethereal extract worked up in the usual manner. 3·5 G. of *p*-chlorophenylcyanamide (VI) were recovered.

(*b*) With the same quantity of *p*-chlorophenylcyanamide (VI) and ethylmagnesium iodide (30 c.c., 0·057 g. mol.), the complex was formed in anisole, ether was distilled off, and the mixture heated at 90—100° for 2½ hours. A small amount of Grignard reagent remained unchanged. After cooling, the product was hydrolysed as in (*a*), a solid being deposited. This was filtered off, dissolved in warm water, and treated with aqueous sodium hydroxide. The base was extracted with ether, and on removal of the solvent under diminished pressure *N*-*p*-chlorophenylpropionamidine was obtained as a crystalline residue, m. p. 82—84° (1·05 g.). The ethereal and aqueous layers of the filtrate were separated. The aqueous solution was basified with aqueous sodium hydroxide until alkaline to Titan-yellow, and the sludge extracted with ether in a continuous extractor. On evaporation of the solvent a further quantity of the *N*-*p*-chlorophenylpropionamidine (2·25 g.), m. p. 70—80°, remained, crystallising from *cyclo*hexane in colourless prisms, m. p. 81—82°. The anisole–ether solution was extracted with aqueous sodium hydroxide, and the extract acidified, with ice-cooling. The precipitate which deposited was extracted with ether, and the solution washed, dried, and evaporated *in vacuo*, giving unchanged *p*-chlorophenylcyanamide (VI) (0·4 g.), m. p. 105—106°.

Reactions between Various Cyanoguanidines and Grignard Reagents.—(a) N-*Cyano*-N′-p-*methoxyphenylguanidine and ethylmagnesium iodide.* (i) An experiment similar to that described above (b, p. 2567), but with *N*-cyano-*N*′-*p*-methoxyphenylguanidine (Part X, *J.*, 1946, 734) (9·5 g.) in place of (IV), gave *p*-methoxyphenylcyanamide (1·65 g.; m. p. 86—88°) and N-*propionyl*-N′-p-*methoxyphenylguanidine*, (7·8 g.), m. p. 122—123°. The latter substance crystallised from 30% ethanol in colourless needles, m. p. 124—125° (Found: C, 59·3; H, 6·6; N, 19·6. $C_{11}H_{15}O_2N_3$ requires C, 59·7; H, 6·6; N, 19·0%).

(ii) In a similar experiment, but with hydrolysis with ammonium chloride (ammonium chloride, 20 g.; water 50 c.c.; ice, 100 g.), the technique described above (p. 2566) was then followed. The ethereal extract yielded a trace of material giving a red colour with ammoniacal copper sulphate–benzene (probably the guanylamidine) and *p*-methoxyphenylcyanamide (0·5 g.), m. p. 85—87°. The aqueous solution, on acidification and extraction with ether, gave a further quantity of *p*-methoxyphenyl-

cyanamide (0·85 g.), m. p. 76—80°. After *ca.* 48 hours the acid mother-liquors were basified with aqueous ammonia, giving a precipitate of *N*-propionyl-*N'*-*p*-methoxyphenylguanidine (1·6 g.), m. p. 123°.

A different technique was employed for the isolation of the *p*-methoxyphenylguanidine. Instead of basification with caustic alkali and continuous extraction with ether, the boiling ammoniacal solution was treated with picric acid (11·5 g.) in water (300 c.c.). The precipitate of crude *p*-methoxyphenylguanidine picrate (13·5 g.), m. p. 174—176°, was collected and recrystallised successively from butanol and water; it was deposited as yellow laminæ, m. p. and mixed m. p. with an authentic specimen 192—193°.

(b) *N-Cyano-N-phenyldicyandiamide and methylmagnesium iodide.* *N*-Cyano-*N*-phenylguanidine (Part X, *J.*, 1946, 733) (8·0 g.) and methylmagnesium iodide (90 c.c.; 0·165 g.-mol.) were allowed to react under the conditions described on p. 2566, and the technique there described was followed for the isolation of the products. The ethereal extract yielded the polymer of phenylcyanamide (triphenyl*iso*melamine) (1·05 g.), m. p. 184°, and a trace of basic oil giving the requisite colour reaction for *N*-phenylguanylacetamidine. The aqueous solution, by the treatment previously described, yielded a further amount of the *iso*melamine (1·15 g.). On basification and treatment with picric acid (7·0 g.) in boiling water (200 c.c.), pure phenylguanidine picrate (9·5 g.), m. p. and mixed m. p. 226—227°, crystallised.

(c) *N-Cyano-N'-phenylguanidine and ethylmagnesium iodide.* (i) A reaction similar to that described above but with ethylmagnesium iodide (33 c.c.; 0·158 g.-mol.) gave the unchanged cyanoguanidine (1·0 g.), polymeric phenylcyanamide (1·0 g.), an oil (0·6 g.) giving the required colour reaction for *N*-phenylguanylpropionamidine, and crude phenylguanidine picrate (10 g.), m. p. 210—215°.

(ii) Similarly treated, the cyanoguanidine (8·0 g.) and ethylmagnesium iodide (87 c.c.; 0·168 g.-mol.), on acid hydrolysis of the magnesium complex and isolation of the products after the manner described on p. 2567 (b), gave the following: unchanged cyanoguanidine, 0·6 g.; polymeric phenylcyanamide, 1·45 g.; *N-propionyl-N'-phenylguanidine hydriodide* (4·3 g.), m. p. 182—188°, which after dissolution in water, salting out with sodium iodide, and crystallisation of the dried precipitate from absolute alcohol was obtained in colourless needles, m. p. 190—191° (1·2 g.) (Found: C, 38·0; H, 4·4. $C_{10}H_{13}ON_3$,HI requires C, 37·6; H, 4·4%); and *N-propionyl-N'-phenylguanidine* (3·0 g.), crystallising from 50% ethanol in colourless needles, m. p. 127—128° (Found: C, 62·4; H, 6·8; N, 22·3. $C_{10}H_{13}ON_3$ requires C, 62·8; H, 6·8; N, 22·0%).

(d) *N-Cyano-N'-isopropylguanidine and phenylmagnesium bromide.* *N*-Cyano-N'-*iso*propylguanidine (Part XXVIII, *J.*, 1948, 1633) (4·2 g.) in ether (33 c.c.) was treated with phenylmagnesium bromide (52 c.c.; 0·11 g.-mol.), and the mixture heated under reflux for 5 hours until only a small amount of Grignard reagent remained unchanged. The reaction product was hydrolysed by being poured into acid (10N-acid, 16·5 c.c.; ice, 100 g.), and the two immiscible layers were separated and washed in the usual way. The ethereal solution was extracted with aqueous sodium hydroxide, washed, and evaporated to dryness, leaving a residue of crude diphenyl (1·0 g.) which on removal of contaminating oil on a porous tile had m. p. 60°, undepressed on admixture with authentic material. The alkaline extract on acidification and extraction with ether yielded, when the solvent was removed, a liquid (0·75 g.) identified as phenol by formation of the toluene-*p*-sulphonate, m. p. 94—96° (Found: C, 62·7; H, 4·9. Calc. for $C_{13}H_{12}O_3S$: C, 62·9; H, 4·8%). The aqueous acid solution was made alkaline with aqueous ammonia. On storage overnight an unidentified infusible solid (2·9 g.) was precipitated and filtered off. A hot solution of picric acid (6 g.) in water (100 c.c.) was added to the filtrate, whereupon a mixture of benzamidine picrate and N-iso*propylguanylbenzamidine picrate* crystallised (6·0 g.; m. p. 175°). The mixture was recrystallised from 50% ethanol and the resulting crystals and mother-liquors were worked up separately to yield pure products. The crystals were recrystallised successively from 50% ethanol, twice from ethanol (95%), and finally from methanol to give pure *N-iso*propylguanylbenzamidine picrate as yellow prisms, m. p. 195° (after shrinking at 188°; no amount of crystallisation improved the m. p.) (Found: C, 47·2; H, 4·6; N, 22·4. $C_{11}H_{16}N_4,C_6H_3O_7N_3$ requires C, 47·1; H, 4·4; N, 22·6%). The mother-liquors were evaporated until most of the ethanol was removed, and the solid which deposited on cooling was crystallised first from water and then from a small volume of ethanol, to yield benzamidine picrate as long yellow needles, m. p. and mixed m. p. 239° (Found: N, 19·8. Calc. for $C_7H_8N_2,C_6H_3O_7N_3$: N, 20·0%).

(e) *Dicyanodiamide and ethylmagnesium iodide. Decomposition of the product with benzoyl chloride.* Dicyandiamide (2·8 g.) in ether (33 c.c.) was heated under reflux for 24 hours with ethylmagnesium iodide (58 c.c.; 0·11 g.-mol.). A large excess of Grignard reagent was present even after this time. The reaction mixture was cooled and a solution of benzoyl chloride (15 c.c.) in ether (50 c.c.) introduced gradually so that steady reflux was maintained during the addition. After storage for 20 hours, the mixture was heated under reflux for 3 hours, and then cooled and hydrolysed by pouring it into 2N-hydrochloric acid (150 c.c.). The ethereal layer was separated and, after being washed with water, was extracted with dilute aqueous ammonia (total, 100 c.c.). The extract was cooled by addition of ice and acidified, and the precipitate dissolved in ether. This solution was dried (Na_2SO_4) and evaporated to dryness, giving a residue of benzoic acid and benzoylcyanamide from which benzoic acid was removed by extraction with boiling *cyclo*hexane. The residue of benzoylcyanamide (2·5 g.) was crystallised from water, whereafter it had m. p. and mixed m. p. 140—141° (yield, 1·6 g.).

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