235. *Antiplasmodial Action and Chemical Constitution. Part VIII. Guanidines and Diguanides.*

By Harold King and Isabel M. Tonkin.

The aim of this investigation was the development by chemical synthesis of the novel discovery that *p*-tolylguanidine nitrate had a very slight retarding action on a sporozoite-induced infection of *Plasmodium gallinaceum* in chicks. A large number of aromatic and aliphatic guanidines have been synthesised and also a number of aromatic diguanides. The most active compound found was *p*-anisylguanidine nitrate. Many variants of this molecular structure have been made, including all the ten possible *N*-methyl derivatives, without finding anything of superior activity.

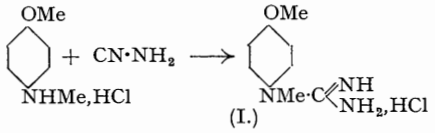
During the progress of a research on substances chemotherapeutically active against experimental typhus in mice (Andrewes, King, van den Ende, and Walker, *Lancet*, 1944, i, 777; Andrewes, King, and Walker, *Proc. Roy. Soc.*, 1946, *B*, **133**, 20) a large number of substances were synthesised for trial. At the end of the investigation it seemed worth while to test many of these compounds which were of comparatively small molecular build, and might therefore be capable of penetrating cells, on a sporozoite-induced infection of *P. gallinaceum* in the chick. Such an infection was known to undergo a tissue-phase development before the blood became infected, and a drug which could control the tissue phase might open up a new avenue in the therapy of human malaria.

At the time the work was undertaken it was known that plasmochin had a very slight action in this type of test (Mudrow, *Arch. Schiff. Trop. Hyg.*, 1940, **44**, 257; cf. however Schulemann, *Deut. med. Woch.*, 1940, **16**, 253) and that sulphadiazine and sulphapyrazine had a most marked action, malaria failing to develop (Coatney and Cooper, *U.S. Public Health Rep.*, 1944, **59**, 1455; Coggeshall, Porter and Laird, *Proc. Soc. Exp. Biol. Med.*, 1944, **57**, 286; Freire and Paraense, *Rev. Brasil Biol.*, 1944, **4**, 27).

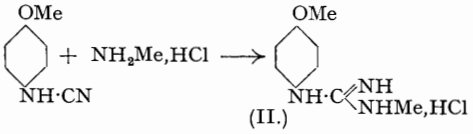
Among the substances tried on experimental typhus we found one, *p*-tolylguanidine nitrate, which had a slight action on sporozoite-induced infections of *P. gallinaceum* in the chick. A large number of aromatic guanidines and the corresponding diguanides were therefore prepared together with a few aliphatic guanidines; of these only *p*-anisylguanidine nitrate was found with definitely superior activity, but it was insufficient to produce cures. The effects of isomerism, of homologation, and of substituents such as chlorine or methoxyl on the *p*-anisylguanidine molecule were then explored. In addition the effect of alkyl substituents on the nitrogen atoms was thoroughly examined by the preparation of all the ten possible *N*-methyl derivatives and a number of higher alkyl derivatives.

In the aliphatic series all the possible *N*-methyl derivatives of guanidine are already known, but nothing comparable is known in the aromatic series so that methods had to be worked out for *N*-methylated aromatic guanidines.

By the action of cyanamide on *N*-methyl-*p*-anisidine hydrochloride, N-p-*anisyl*-N-*methylguanidine hydrochloride* (I) was readily obtained, but the isomeric N-p-*anisyl*-N′-*methylguanidine hydrochloride* (II) was prepared by treating *p*-anisylcyanamide in boiling butyl alcohol solution with methylamine hydrochloride.



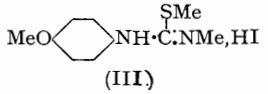
(I.)



(II.)

This method was also applicable to the preparation of N-p-*anisyl*-N′N′-*dimethylguanidine hydrochloride* and higher alkylated derivatives of similar type. The method would not, however, function with *p*-anisylmethylcyanamide, a mobile hydrogen atom being apparently essential for success, although Bhatnagar, Chopra, Narang, and Ray (*J. Ind. Chem. Soc.*, 1937, **14**, 344) claim to have made *N*-phenyl-*N′N′*-dimethylguanidine by heating aniline hydrochloride and dimethylcyanamide at 110—120°.

To secure the higher *N*-methylated derivatives an application of the method introduced by Wheeler and Jamieson (*J. Biol. Chem.*, 1908, **4**, 111) for the preparation of methyl- and dimethyl-guanidines proved to be quite satisfactory. Thus *p*-anisidine and methyl *iso*thiocyanate gave N-p-*anisyl*-N′-*methylthiourea* which added on methyl iodide to give N-p-*anisyl*-N′S-*dimethyl*isothiourea *hydriodide* (III); this by the action of alcoholic methylamine or dimethylamine at 80° gave N-p-*anisyl*-N′N″-*dimethylguanidine hydriodide* (IV) and N-p-*anisyl*-N′N′N″-*trimethylguanidine hydriodide* (V) respectively, a by-product in the former reaction being *s*-trimethylguanidine.



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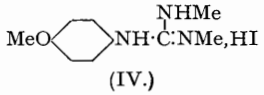

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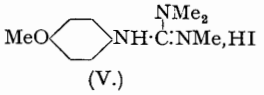
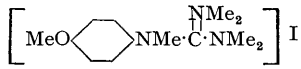


(V.)

In a similar manner N-p-*anisyl*-NS-*dimethyl*isothiourea *hydriodide* gave N-p-*anisyl*-NN′-*dimethylguanidine hydrochloride* and N-p-*anisyl*-NN′N′-*trimethylguanidine hydriodide* whilst N-p-*anisyl*-NN′S-*trimethyl*-

isothiourea *hydriodide* gave N-p-*anisyl*-NN'N''-*trimethylguanidine hydriodide* and N-p-*anisyl*-NN'N'N''-*tetramethylguanidine hydrochloride* (VI).

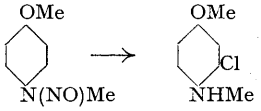
(VI.)



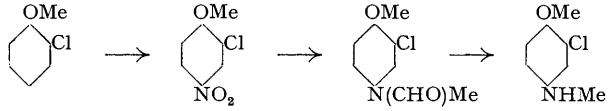
(VII.)

Finally (VI) as base readily added on methyl iodide to yield N-p-*anisyl*-NN'N'N''-*tetramethylguanidine methiodide* (VII).

In the Experimental section a method is described for the preparation of *N*-methyl- and *N*-ethyl-*p*-toluidines and -*p*-anisidines which avoids proceeding through the nitroso-derivatives to eliminate primary bases. At one stage of the investigation an *N*-methyl-*p*-anisidine was obtained containing some primary base, and an attempt was made to free it from primary base by treatment with nitrite, isolation of the nitroso-compound, and removal of the nitroso-group by treatment with cuprous chloride in hydrochloric acid by the method recommended for certain alkylanilines by Jones and Kenner (*J.*, 1932, 713). Considerable decomposition occurred during the cuprous chloride treatment, and during the isolation of the *N*-methyl-*p*-anisidine a monochloro-*N*-methyl-*p*-anisidine was obtained which could be either 2- or 3-chloro-4-methoxy-*N*-methylaniline (VIII or IX).



(VIII.)



(IX.)

To settle the constitution of the new base it would be sufficient to synthesize either of these two isomerides. Hurst and Thorpe (*J.*, 1915, **107**, 938) stated that when *p*-nitrophenetole was reduced under very vigorous conditions with tin and hydrochloric acid a 90% yield of 2-chloro-4-ethoxyaniline was obtained whereas if the reaction was moderated by running water a 50% yield ensued. They stated that the corresponding methoxy-derivative was obtained in a similar way. On repetition of this latter experiment under very vigorous conditions the maximum yield of 2-chloro-4-methoxyacetanilide obtained was below 5%, and the properties of the product agreed with those given by Hurst and Thorpe and by D.R.-P. 621,710. As the small yield precluded the use of this method, attention was turned to the synthesis of the isomeric base. This was readily accomplished by nitrating *o*-chloroanisole to give 2-chloro-4-nitroanisole which on reduction, formylation, and methylation gave eventually 3-*chloro*-4-*methoxy*-N-*methylaniline* (IX) as *hydrochloride* and *picrate*. These salts were quite different from the salts of the chloro-base obtained in the cuprous chloride reaction. This latter base must consequently be 2-chloro-4-methoxy-*N*-methylaniline (VIII), since chlorination of the *N*-methyl or the methoxyl group is unlikely.

Biological Results.—Sporozoite infections of *Plasmodium gallinaceum* in 10-day old chicks were induced by the intravenous injection of a suspension of ground-up infected mosquitoes, each chick receiving the equivalent of one infected mosquito. The drugs were administered orally, 2 hours before infection and twice daily thereafter for 4 days only. The percentage of parasitized red cells in the drug-treated birds was compared with that in the control birds at the peak of parasitæmia. Control chicks usually died two to three days after the peak of parasitæmia as a result of massive infection of the tissues with exoerythrocytic forms. True causal prophylactic action is manifested by a prolongation of life beyond that of the controls and by a retarded infection of the blood-stream.

About 70 guanidines and diguanides including all those mentioned in this paper and a few others derived from α- and β-naphthylamines have been tested in this way. The following compounds showed either a very slight action (+ −), a definite action (+), or a pronounced action (+ +).

		Total dose, mg./100 g. chick.
p-Tolylguanidine nitrate	+ −	60
N-*p*-Tolyl-*N*-methylguanidine nitrate	+ −	80
o-Xylyldiguanidine hydrochloride	+ −	12·5
p-Anisylguanidine nitrate	+	40—80
p-Phenetylguanidine nitrate	+ −	25
N-*p*-Anisyl-*N'*-ethylguanidine hydrochloride	+ −	100
Sulphadiazine	+ +	200

The action of *p*-anisylguanidine nitrate on exoerythrocytic forms was confirmed in tissue culture; a 0·5 mg. % solution markedly inhibited the growth of exoerythrocytic forms. (Tonkin, forthcoming publication.)

We are indebted to Dr. D. G. Davey of Imperial Chemical (Pharmaceuticals) Ltd. for confirmation of the causal prophylactic activity of *p*-anisylguanidine nitrate on sporozoite-induced *P. gallinaceum* infections in chicks. He writes " Chicks treated with this drug (each dose 4 mg. per 50 g. chick, dosed 2 hours before inoculation and 2 hours after inoculation and twice daily on each of the next 3 days) did not exhibit parasites in the blood until the 8th day and they did not die until the 11th—14th day. This compound, therefore, shows definite causal prophylactic activity ".

Dr. Ann Bishop, at the Molteno Institute, Cambridge, to whom our thanks are also due, tested *p*-anisyl-

guanidine nitrate against sporozoite and against trophozoite-induced infections of *P. relictum* in the canary. In both types of infection it was without action.

Experimental.

Guanidines.

m-*Chlorophenylguanidine Nitrate.*—*m*-Chloroaniline hydrochloride (4·0 g.) and cyanamide (2·1 g., 2 mols.) were boiled in absolute alcohol (20 c.c.) for 6 hours. The solvent was removed, the residue dissolved in water (10 c.c.), and ammonium nitrate added in excess. The *nitrate* (4·4 g.) readily crystallised out and when recrystallised from water (10 c.c.) separated in columns, m. p. 171—172° (Found: C, 36·0; H, 3·7; N, 24·4. $C_7H_8N_3Cl,HNO_3$ requires C, 36·1; H, 3·9; N, 24·1%).

p-*Bromophenylguanidine Nitrate.*—This *salt* (4·55 g.) was obtained similarly from *p*-bromoaniline hydrochloride (5·2 g.). It separated from water in large columns, m. p. 187—188° (Found: C, 30·5; H, 3·3; N, 20·5. $C_7H_8N_3Br,HNO_3$ requires C, 30·3; H, 3·3; N, 20·2%). The picrate had m. p. 224°; Braun, Erit, and Crooks (*J. Org. Chem.*, 1938, **3**, 146) give picrate, m. p. 220°.

o-*Tolylguanidine Nitrate.*—Prepared similarly from *o*-toluidine hydrochloride, this *salt* had m. p. 131—132° (Found: C, 45·4; H, 5·7. $C_8H_{11}N_3,HNO_3$ requires C, 45·3; H, 5·7%). Höchster Farbwerke, D.R.-P. 172,979, record m. p. 133° for the nitrate but give no preparation or analysis.

m-*Tolylguanidine Sulphate.*—Prepared by the method of Braun (*J. Amer. Chem. Soc.*, 1933, **55**, 1282) from *m*-toluidine and *S*-methyl*iso*thiourea sulphate, this salt melted when pure at 220—221°. Braun gives m. p. 215—217° (Found: C, 48·5; H, 6·0. Calc.: C, 48·5; H, 6·1%).

as.-o-*Xylylguanidine Nitrate.*—From *o*-xylidine hydrochloride (3·9 g.), this *salt* was obtained as needles, yield 4·8 g. Recrystallised from 6 parts of boiling water it separated in prisms, m. p. 184—185° (Found: C, 48·2; H, 6·2; N, 24·8. $C_9H_{13}N_3,HNO_3$ requires C, 47·8; H, 6·2; N, 24·8%).

as.-m-*Xylylguanidine nitrate* prepared similarly is soluble in 4 parts of boiling water and separates in small clusters of plates, m. p. 174—175° (Found: C, 47·9; H, 6·9. $C_9H_{13}N_3,HNO_3$ requires C, 47·8; H, 6·2%).

p-*Xylylguanidine nitrate* prepared in the same way crystallised from water in clusters of tiny prisms, m. p. 161—162° (Found: C, 47·9; H, 6·0. $C_9H_{13}N_3,HNO_3$ requires C, 47·8; H, 6·2%).

p-*Ethylphenylguanidine nitrate* prepared similarly had m. p. 124—125° and crystallised in needles (Found: C, 47·7; H, 6·2. $C_9H_{13}N_3,HNO_3$ requires C, 47·8; H, 6·2%).

p-*Acetophenylguanidine Hydrochloride and Nitrate.*—*p*-Aminoacetophenone hydrochloride (5·7 g.) was boiled with cyanamide (2·8 g., 2 mols.) in alcohol (20 c.c.) for 6 hours and the solution concentrated to a small volume. After keeping at 0° the required *hydrochloride* (2·8 g.) was collected, and on crystallisation from boiling absolute alcohol separated in large rhombs, m. p. 211° (Found: C, 50·7; H, 5·9; N, 19·3. $C_9H_{11}ON_3,HCl$ requires C, 50·6; H, 5·7; N, 19·7%). The mother liquors were combined and the solvent was replaced by water; on adding ammonium nitrate, the required *nitrate* separated as a crystalline meal, yield 1·0 g. It required 5·5 parts of boiling water for solution and separated in bold rough prisms with a yellow tinge, m. p. 242° (decomp.) (Found: C, 45·3; H, 5·1. $C_9H_{11}ON_3,HNO_3$ requires C, 45·0; H, 5·0%).

o-*Anisylguanidine nitrate* prepared from anisidine hydrochloride and cyanamide in the usual way was soluble in 4 parts of boiling water and separated in rugged tablets, m. p. 159—160° (Found: C, 42·0; H, 5·3; N, 24·5. $C_8H_{11}ON_3,HNO_3$ requires C, 42·1; H, 5·3; N, 24·6%).

p-*Anisylguanidine nitrate* prepared similarly separated from water in tablets, m. p. 218° (Found: C, 42·2; H, 5·0; N, 25·0. $C_8H_{11}ON_3,HNO_3$ requires C, 42·0; H, 5·3; N, 24·6%).

p-*Anisylguanidine Hydriodide.*—*p*-Anisyl-*S*-methyl*iso*thiourea hydriodide (3·24 g.) in alcohol (25 c.c.) was treated with aqueous ammonia (20 c.c., *d* 0·88) and boiled for 5 hours. The solution was evaporated to dryness and the residue taken up in ethyl alcohol. The *hydriodide* (1·58 g.) separated in clusters of tablets but on recrystallisation from alcohol formed short prisms, m. p. 179—180° (Found: C, 33·4; H, 4·2; N, 14·1. $C_8H_{11}ON_3,HI$ requires C, 32·8; H, 4·1; N, 14·3%).

p-*Phenetylguanidine nitrate*, prepared from *p*-phenetidine hydrochloride and cyanamide in quantitative yield, crystallised from 3 parts of boiling water in woolly needles, m. p. 171—172° (Found: C, 44·8; H, 5·5. $C_9H_{13}ON_3,HNO_3$ requires C, 44·6; H, 5·8%).

3 : 4-*Dimethoxyphenylguanidine hydrochloride* separated from the usual reaction mixture in needles, which were soluble in 8 parts of boiling alcohol and on recrystallisation had m. p. 225° (Found: C, 46·5; H, 6·1; N, 18·2. $C_9H_{13}O_2N_3,HCl$ requires C, 46·6; H, 6·1; N, 18·2%).

3-*Chloro*-4-*methoxyphenylguanidine hydrochloride* prepared in the usual way was soluble in 12 parts of boiling alcohol and separated in tablets, m. p. 216—217° (Found: C, 40·6; H, 4·5. $C_8H_{10}ON_3Cl$ requires C, 40·7; H, 4·7%).

3 : 4-*Methylenedioxyphenylguanidine hydrochloride* separated from the reaction mixture in excellent yield. It was recrystallised from 5 parts of boiling alcohol and separated in clusters of flattened needles, m. p. 182° (Found: C, 44·8; H, 4·7; N, 19·4. $C_8H_9O_2N_3,HCl$ requires C, 44·5; H, 4·7; N, 19·5%).

Benzylguanidine nitrate was prepared from benzylamine hydrobromide and cyanamide in the usual way, yield 62%. It crystallised from double its volume of boiling water as a mat of needles, m. p. 149—150°. Davis and Elderfield (*J. Amer. Chem. Soc.*, 1932, **54**, 1502) give m. p. 165°. A repetition of the preparation confirmed the lower m. p. (Found: C, 45·5; H, 5·6; N, 26·8. Calc.: C, 45·3; H, 5·7; N, 26·4%). The picrate had m. p. 190—191°, whereas Davis and Elderfield give m. p. 185·5°.

cyclo*Hexylguanidine Hydrochloride.*—Braun's process (*J. Amer. Chem. Soc.*, 1933, **55**, 1281) for the preparation of this salt was not found satisfactory. If the ethyl alcohol as solvent was replaced by butyl alcohol and the solution boiled for six hours a very good yield of the guanidine hydrochloride, m. p. 227°, was obtained.

n-*Butylguanidine Sulphate.*—This *salt* was prepared from butylamine and methyl*iso*thiourea sulphate in boiling 50% aqueous-alcoholic solution. It could be crystallised from 1·4 parts of boiling water and separated as needles, m. p. 215—216°. Davis and Elderfield (*loc. cit.*) give m. p. 206° when crystallised from methyl alcohol–butyl alcohol [Found: C, 36·7; H, 8·5; N, 25·3. $(C_5H_{13}N_3)_2,H_2SO_4$ requires C, 36·6; H, 8·6; N, 25·6%].

Alkylated Guanidines.

N-p-*Tolyl*-N-*methylguanidine Nitrate.*—*N*-Methyl-*p*-toluidine hydrochloride (2·8 g.) and cyanamide (1·4 g., 2 mols.) were boiled in alcohol (20 c.c.) for 5 hours, and a further equal quantity of cyanamide was added and the boiling continued for another 5 hours. The *nitrate* (2·3 g.) obtained in the usual way was recrystallised from 4 volumes of water and separated in clusters of prisms, m. p. 164—165° (Found: C, 47·9; H, 6·2; N, 25·1. $C_9H_{13}N_3,HNO_3$ requires C, 47·8; H, 6·2; N, 24·8%).

N-p-*Tolyl*-N′-*methylguanidine Hydrochloride.*—*p*-Tolylcyanamide (6·6 g.) and methylamine hydrochloride (3·7 g.) in

butyl alcohol (50 c.c.) were boiled for 12 hours. The solvent was removed, and the residue dissolved in water and extracted to remove unused *p*-tolylcyanamide (0·3 g.). The aqueous solution was then evaporated to dryness and the crystalline residue crystallised from absolute ethyl alcohol by careful addition of dry ether, yield 7·5 g. N-p-*tolyl*-N′-*methylguanidine hydrochloride* crystallises in hygroscopic leaflets, m. p. 145° (Found : C, 53·9; H, 6·9; N, 21·2. $C_9H_{13}N_3$,HCl requires C, 54·1; H, 7·1; N, 21·2%). The *picrate* requires 46 parts of boiling alcohol for solution and separates in compact balls of needles, m. p. 207—208° (Found : C, 45·9; H, 4·2. $C_9H_{13}N_3,C_6H_3O_7N_3$ requires C, 45·9; H, 4·1%).

N-p-*Tolyl*-N′N′-*dimethylguanidine Hydriodide*.—Tolylcyanamide (6·6 g.) and dimethylamine hydrochloride (4·1 g.) were boiled in *n*-butyl alcohol solution for 12 hours. The solvent was replaced by water, and the aqueous solution ether extracted and then treated with excess of solid sodium iodide. The crystalline precipitate was collected and crystallised from absolute alcohol and ether (yield 9·5 g.) from which the *salt* separated in prisms, m. p. 161—162° (Found : C, 39·5; H, 5·3; N, 13·7. $C_{10}H_{16}N_3$,HI requires C, 39·3; H, 5·3; N, 13·8%). The hydriodide (18·7 g.) was converted into the hydrochloride which crystallised from very concentrated aqueous solution at 0° in prisms as a *monohydrate*, m. p. 76—78°, yield 6·6 g. (Found : C, 52·4; H, 7·9; N, 17·7; H_2O, 5·9. $C_{10}H_{15}N_3$,HCl,H_2O requires C, 51·8; H, 7·8; N, 18·1; H_2O, 7·8%).

N-p-*Tolyl*-N′-*ethylguanidine Hydrochloride*.—This *salt* was prepared in the same way as the methyl compound in good yield. It is best recrystallised by solution in 0·6 parts of hot ethyl alcohol and addition of 1·4 parts of hot ethyl acetate, and separates in clusters of thin plates, m. p. 151° (Found : C, 55·7; H, 7·6; N, 19·9. $C_{10}H_{15}N_3$,HCl requires C, 56·2; H, 7·6; N, 19·7%).

N-p-*Tolyl*-N′-n-*butylguanidine Hydrochloride*.—Prepared in the same way this *salt* was recrystallised by moistening with absolute ethyl alcohol and adding excess of hot ethyl acetate to the clear solution. It crystallised in pearly leaflets, m. p. 114—115° (Found : C, 59·6; H, 8·4; N, 16·8. $C_{12}H_{19}N_3$,HCl requires C, 59·6; H, 8·3; N, 17·4%).

N-p-*Tolyl*-N′N′-*diethylguanidine Hydriodide*.—A solution of the hydrochloride prepared in the same way as the preceding could not be induced to crystallise. It was precipitated as the hydriodide with excess of potassium iodide and separated from 2 volumes of water as a *dihydrate*, m. p. 60° (Found : C, 39·5; H, 6·6; N, 11·1. $C_{12}H_{19}N_3$,HI,$2H_2O$ requires C, 39·0; H, 6·6; N, 11·4%).

N-p-*Tolyl*-N-*ethylguanidine Nitrate*.—*N*-Ethyl-*p*-toluidine hydrochloride (4·2 g.) and cyanamide (2·1 g.) were boiled in ethyl alcohol (20 c.c.) for 5 hours. The *nitrate* (4·0 g.) prepared in the usual way separated from water as pearly scales, m. p. 184° (Found : C, 49·7; H, 6·8. $C_{10}H_{15}N_3,HNO_3$ requires C, 50·0; H, 6·7%).

N-p-*Anisyl*-N-*methylguanidine Hydrochloride*.—*N*-Methyl-*p*-anisidine hydrochloride (4·3 g.) and cyanamide (2·1 g.) in alcohol (20 c.c.) were boiled for 6 hours. On concentration the solution deposited the required *hydrochloride* (3·75 g.) which was soluble in 4 parts of alcohol and separated in stout prisms, m. p. 233° (Found : C, 50·5; H, 6·8. $C_9H_{13}ON_3$,HCl requires C, 50·1; H, 6·5%).

N-p-*Anisyl*-N-*ethylguanidine Hydrochloride*.—This *salt* was prepared in a similar way from *N*-ethyl-*p*-anisidine hydrochloride. It separated from alcohol in elongated tablets, m. p. 231—232° (Found : C, 52·6; H, 7·2. $C_{10}H_{15}ON_3$,HCl requires C, 52·3; H, 7·0%).

N-p-*Anisyl*-N′-*methylguanidine Hydrochloride*.—*p*-Anisylcyanamide (5·0 g.) and methylamine hydrochloride (2·9 g.) were boiled in butyl alcohol (50 c.c.) for 12 hours. The solvent was replaced by water and ether soluble material (0·5 g.) removed. On concentration of the aqueous liquor to a small volume the *hydrochloride* crystallised. It was collected and recrystallised from absolute alcohol by addition of ether and separated in scales, yield 6·9 g., m. p. 165° (Found : C, 50·2; H, 6·6; N, 19·4. $C_9H_{12}ON_3$,HCl requires C, 50·1; H, 6·5; N, 19·5%).

N-p-*Anisyl*-N′-*ethylguanidine Hydrochloride*.—This salt was prepared in a similar way, yield 6·1 g. It was recrystallised by solution in 0·75 part of warm ethyl alcohol and addition of a larger volume of warm ethyl acetate; it separated in short rods, m. p. 167° (Found : C, 52·2; H, 6·5; N, 18·3. $C_{10}H_{15}ON_3$,HCl requires C, 52·3; H, 7·0; N, 18·3%).

N-p-*Anisyl*-N′N′-*diethylguanidine Hydriodide*.—A solution of the hydrochloride was prepared as in the preceeding example but the salt could not be crystallised. It was converted by addition of excess of solid potassium iodide into the crystalline *hydriodide monohydrate*; this could be recrystallised from two volumes of water and separated in stout prisms, m. p. 66° (Found : C, 39·4; H, 6·5; N, 11·2. $C_{12}H_{19}ON_3$,HI,H_2O requires C, 39·2; H, 6·0; N, 11·4%).

N-p-*Anisyl*-N′-*butylguanidine Hydrochloride*.—This *salt* was prepared in a similar way to the *N*′-methyl derivative described above. The product was best crystallised by solution in its own volume of warm alcohol and addition of excess of ethyl acetate, and then separated in clear rhombs, m. p. 124—125° (Found : C, 55·9; H, 7·7. $C_{12}H_{19}ON_3$,HCl requires C, 55·9; H, 7·8%). The *picrate* separates from alcohol in which it is very readily soluble in clusters of plates, m. p. 127—128° (Found : C, 47·9; H, 4·8. $C_{12}H_{19}ON_3,C_6H_3O_7N_3$ requires C, 48·0; H, 4·9%).

When the original reaction was carried out in ethyl alcohol instead of butyl alcohol, the ethereal extract of the aqueous solution of the reaction products gave a crystalline substance on evaporation which on crystallisation from absolute alcohol separated in bold diamond-shaped plates, m. p. 218°. This substance is probably 1 : 3 : 5-*trianisyl*iso*melamine* produced by polymerisation of *p*-anisylcyanamide (Found : C, 64·8; H, 5·4. $C_{24}H_{24}O_3N_6$ requires C, 64·8; H, 5·5%).

N-p-*Anisyl*-N′N′-*dimethylguanidine Hydriodide*.—A solution of the hydrochloride was prepared in the usual way but could not be induced to crystallise directly. It was converted into the *hydriodide* by addition of sodium iodide. This very soluble salt separated from its own volume of water in clusters of prisms, m. p. 169—170° (Found : C, 37·7; H, 5·2; N, 12·9. $C_{10}H_{15}ON_3$,HI requires C, 37·4; H, 5·0; N, 13·1%). The *hydrochloride* separated from absolute alcohol on addition of dry ether as a crystalline crust, m. p. 184—185° (Found : C, 51·7; H, 7·2; N, 18·2. $C_{10}H_{15}ON_3$,HCl requires C, 52·3; H, 7·0; N, 18·3%).

N-p-*Anisyl*-N′-iso*propylguanidine Hydriodide*.—*p*-Anisylcyanamide (10·1 g.) and carefully dried *iso*propylamine hydrochloride (9·5 g.) were boiled in butyl alcohol (100 c.c.) for 16 hours. The solvent was removed, water added, and ether soluble material (0·6 g.) removed. The solution was concentrated to about 25 c.c. and excess of potassium iodide added with stirring. The *hydriodide* separated as an oil which eventually solidified, yield 17·53 g. It crystallised from its own volume of ethyl acetate in pointed plates, m. p. 125—126° (Found : C, 39·6; H, 5·6; N, 12·3. $C_{11}H_{17}ON_3$,HI requires C, 39·4; H, 5·4; N, 12·5%).

N-p-*Anisyl*-N′N″-*dimethylguanidine Hydrochloride*.—(*a*) At 100°. Two sealed tubes each containing *N*-*p*-anisyl-*N*′*S*-dimethyl *iso*thiourea hydriodide (6·76 g.) and alcoholic methylamine (20 c.c. of 33%) were heated at 100° for 16 hours. The combined solution containing long white needles was evaporated to dryness, water added, and the crystalline solid (2·4 g.) collected. On crystallisation from water (10 c.c.) this substance separated in long white prisms, m. p. 350°, which proved to be *s*-trimethylguanidine hydriodide (Found : C, 21·4; H, 5·5. Calc. for $C_4H_{11}N_3$,HI : C, 21·0; H, 5·3%). Schenck (*Z. physiol. Chem.*, 1912, **77**, 366) described this salt as needles, unmelted at 290°. Its identity was confirmed by conversion into the picrate, needles, m. p. 215—216° (Found : N, 25·5. Calc. for $C_4H_{11}N_3,C_6H_3O_7N_3$: N, 25·5%). Schenck and Kirchhof (*ibid.*, 1926, **153**, 162) give m. p. 216°. The *hydrochloride monohydrate* separates from alcohol in which it is readily soluble in fine needles, which show partial melting below 100° when air-dried, but when dried at 100° have m. p. 260—262° (Found : C, 30·9; H, 9·2. $C_4H_{11}N_3$,HCl,H_2O requires C, 30·9; H, 9·1%).

The aqueous mother liquor on extraction with ether gave *p*-anisidine (2·1 g.) and on fractional crystallisation of the

solids obtained from the aqueous mother liquor from alcohol there were obtained a further quantity (2·12 g.) of *s*-trimethylguanidine hydriodide and N-p-*anisyl*-N'N''-*dimethylguanidine hydriodide* (2·87 g.) as the more soluble component, crystallising in large tablets, m. p. 168—169° (Found: C, 37·6; H, 5·5; N, 13·2. $C_{10}H_{15}ON_3$,HI requires C, 37·4; H, 5·0; N, 13·1%).

(*b*) At 80°. Three sealed tubes each containing the quantities of starting material as described above were heated at 80° for 8 hours. On fractionation the same substances were isolated as above but in different proportions, thus: *p*-anisidine (0·75 g.), *s*-trimethylguanidine hydriodide (2·0 g.), and *N*-p-anisyl-*N'N''*-dimethylguanidine (15·2 g.). The last was converted into the *hydrochloride* which was best recrystallised by solution in its own volume of boiling alcohol and adding 3·5 volumes of dry ethyl acetate. It separated in tablets, m. p. 185—186° (Found: C, 52·4; H, 7·0. $C_{10}H_{15}ON_3$,HCl requires C, 52·3; H, 7·0%).

N-p-*Anisyl*-N'N'N''-*trimethylguanidine Hydriodide.*—Two sealed tubes each containing *N-p*-anisyl-*N'S*-dimethyl*iso*thiourea hydriodide (3·38 g.) and alcoholic dimethylamine (10 c.c. of 32%) were heated at 80° for 8 hours. The contents of the two tubes were evaporated to dryness, dissolved in water and extracted with ether which removed *p*-anisidine (0·18 g.). The aqueous mother liquor was again evaporated to dryness with addition of absolute alcohol to facilitate the process, and the solid crystalline residue (7·2 g.) was crystallised from dry ethyl acetate (400 c.c.) by careful addition to the boiling solution of just enough absolute alcohol to effect solution. N-p-*Anisyl*-N'N'N''-*trimethylguanidine hydriodide* separated in long prisms, m. p. 140° (Found: C, 39·5; H, 5·7; N, 12·8. $C_{11}H_{17}ON_3$,HI requires C, 39·4; H, 5·4; N, 12·5%).

N-p-A*nisyl*-NN'-*dimethylguanidine Hydrochloride.*—Two sealed tubes each containing *N-p*-anisyl-*NS*-dimethyl*iso*thiourea hydriodide (6·76 g.) and alcoholic methylamine (20 c.c. of 33%) were heated at 80° for 8 hours. The alcohol was removed and replaced by water, and *N*-methyl-*p*-anisidine (0·3 g.) extracted by ether. The water was again removed; the residue on treatment with alcohol crystallised, but attempts to obtain a pure salt by direct crystallisation from alcohol and ether were not successful. On addition of excess of saturated aqueous sodium picrate solution, the *picrate* (10·0 g.) was obtained. It was crystallised from 3 volumes of boiling alcohol in tablets, m. p. 154° (Found: C, 45·8; H, 4·4. $C_{10}H_{15}ON_3$,$C_6H_3O_7N_3$ requires C, 45·5; H, 4·3%). It was converted into the *hydrochloride*, a hygroscopic salt which separated from absolute alcohol and dry ether in crystalline form, m. p. 158—159° (Found: C, 51·8; H, 7·2; N, 18·2. $C_{10}H_{15}ON_3$,HCl requires C, 52·3; H, 7·0; N, 18·3%).

N-p-*Anisyl*-NN'N'-*trimethylguanidine Hydriodide.*—*N-p*-anisyl-*NS*-dimethyl*iso*thiourea hydriodide (13·52 g.) and alcoholic dimethylamine (40 c.c. of 33%) were heated at 80° under pressure for 8 hours. The above *hydriodide* (11·4 g.) was readily obtained from aqueous solution and crystallised in plates, m. p. 178—179° (Found: C, 39·7; H, 5·8; N, 12·5. $C_{11}H_{17}ON_3$,HI requires C, 39·4; H, 5·4; N, 12·5%).

N-p-*Anisyl*-NN'N''-*trimethylguanidine Hydriodide.*—*N-p*-Anisyl-*NN'S*-trimethyl*iso*thiourea hydriodide (14·08 g.) and alcoholic methylamine (40 c.c. of 33%) were heated at 80° under pressure for 8 hours. The solution was evaporated to dryness, the residue dissolved in water, and *N*-methyl-*p*-anisidine (1·2 g.) removed by ether extraction. On concentration of the aqueous liquor *s*-trimethylguanidine hydriodide (1·54 g., m. p. 342°) separated. The aqueous liquor was now evaporated to dryness and the residue crystallised from alcohol by addition of dry ether. The required hydriodide (10·06 g.) could now be crystallised as a *monohydrate* from water, m. p. 58—60°. On drying over sulphuric acid it lost water and had m. p. 136—138°. The hydrated forms crystallised in tablets (Found: C, 37·8; H, 5·8; N, 11·9. $C_{11}H_{17}ON_3$,HI,H_2O requires C, 37·4; H, 5·7; N, 11·9%).

N-p-*Anisyl*-NN'N'N''-*tetramethylguanidine Hydrochloride.*—*N-p*-Anisyl-*NN'S*-trimethyl*iso*thiourea hydriodide (14 g.) and alcoholic dimethylamine (40 c.c. of 32%) were heated at 80° for 8 hours. The solvent was removed, the residue dissolved in water and *N*-methyl-*p*-anisidine (1·2 g.) removed by ether extraction. The aqueous solution was treated with excess of saturated sodium picrate solution and the p-*anisyltetramethylguanidine picrate* (10·6 g.) collected. On crystallisation from 3 parts of methyl alcohol it separated in well-formed tablets, m. p. 122° (Found: C, 48·3; H, 5·2; N, 18·4. $C_{12}H_{19}ON_3$,$C_6H_3O_7N_3$ requires C, 48·0; H, 4·9; N, 18·7%). It was converted into the *hydrochloride* which crystallised from a little absolute alcohol in extremely hygroscopic plates, m. p. 142° (Found: Cl, 13·8; $C_{12}H_{19}ON_3$,HCl requires Cl, 13·8%).

N-p-*Anisyl*-NN'N'N''-*tetramethylguanidine Methopicrate.*—The preceding hydrochloride was treated with concentrated sodium hydroxide solution and the oily base which separated was taken up in amyl alcohol. The amyl alcoholic solution was shaken with potassium hydroxide pellets, then decanted and treated with excess of methyl iodide under reflux on the water-bath. A crystalline methiodide mixed with potassium iodide readily separated and a further quantity was obtained from the mother liquor on addition of ether. The combined iodides in water were converted into chlorides and the potassium chloride was removed by evaporating to dryness and extracting the organic methochloride with absolute alcohol. Attempts to crystallise this methochloride were unsuccessful, so it was converted into the *methopicrate* which separated from 4 volumes of absolute alcohol in tablets, m. p. 103—104° (Found: C, 48·8; 49·2; H, 5·3; 5·1; N, 17·6, 17·7. $C_{13}H_{22}ON_3$,$C_6H_2O_7N_3$ requires C, 49·1; H, 5·2; N, 18·1%).

The methochloride regenerated from the methopicrate failed to crystallise. It was dissolved in less than its own weight of water and treated with excess of a hot saturated solution of sodium iodide. An oil separated which soon solidified. The *methiodide* was collected and conveniently crystallised from *iso*propyl alcohol, from which it separated in delicate plates, m. p. 173—174° (Found: C, 42·9; H, 6·2. $C_{13}H_{22}ON_3I$ requires C, 43·0; H, 6·1%).

Intermediates.

N-*Ethyl*-p-*toluidine Hydrochloride.*—The following process avoids intermediate purification through a nitroso-derivative. Form-*p*-toluidide (13·5 g.) and ethyl iodide (15·6 g.) were dissolved in alcohol (20 c.c.) and a solution of potassium hydroxide (5·6 g.) in alcohol (40 c.c.) added. The mixture was boiled for 1 hour, then cooled, and one-half the above quantities of ethyl iodide and alcoholic potash added. The solution was then boiled for a further two hours. The alcohol was removed, water added, and the form-*N*-ethyl-*p*-toluidide extracted with ether. The residue left on removing the ether was hydrolysed with hydrochloric acid (20 c.c. of 16%) by boiling for two hours. On evaporation of the solution to dryness with addition of absolute alcohol at intervals the residue crystallised, yield 11·1 g. N-*Ethyl*-p-*toluidine hydrochloride* crystallises from alcohol in hexagonal plates, m. p. 162° (Found: C, 62·5; H, 8·3. $C_9H_{13}N$,HCl requires C, 62·9; H, 8·2%).

N-*Methyl*-p-*anisidine Hydrochloride.*—This salt was prepared in 85% yield by the same process as in the preceeding using form-*p*-anisidide and methyl iodide. The *hydrochloride* was crystallised either from methyl ethyl ketone or absolute alcohol and separated in needles, m. p. 119—120° (Found: C, 55·2; H, 7·2. $C_8H_{11}ON$,HCl requires C, 55·3; H, 7·0%).

N-*Ethyl*-p-*anisidine hydrochloride* was prepared in a similar way; when crystallised from alcohol it separated in tablets, m. p. 153° (Found: C, 57·7; H, 7·6. $C_9H_{13}ON$,HCl requires C, 57·6; H, 7·5%).

p-*Tolylcyanamide.*—This was obtained by an application of (i) Berger's method (*Monatsh.*, 1884, **5**, 219) or (ii) Pierron's method (*Ann. Chim.*, 1908, **15**, 163).

(i) *p*-Tolylthiourea (33·2 g.) and lead acetate (100 g.) were added to a solution of potassium hydroxide (50 g.) in water (500 c.c.) and the mixture was heated on the boiling water-bath for about 15 minutes. The solution was filtered through

a thin layer of kieselguhr to remove lead sulphide and then made just acid to litmus by adding glacial acetic acid. The precipitate which still contained a colourless lead compound was collected, treated with 2N-ammonia (100 c.c.), filtered, and the filtrate acidified with glacial acetic acid. *p*-Tolylcyanamide, m. p. 68°, separated in 62% yield.

(ii) *p*-Tolylthiourea (33·2 g.) was dissolved in boiling water (500 c.c.) containing potassium hydroxide (50 g.) and a solution of copper sulphate (50 g.) in water (500 c.c.) was added. After boiling for 15 minutes the solution was filtered and acidified with glacial acetic acid. The crude *p*-tolylcyanamide, yield 91%, melted at 63°

p-*Tolylmethylcyanamide.*—*N*-*p*-Tolyl-*N*-methylthiourea (9·0 g.) was suspended in a solution of potassium hydroxide (12·5 g.) in water (125 c.c.). Lead acetate (25 g.) was added and the mixture was heated on the water-bath for 15 minutes. The solution was filtered and the collected lead sulphide was extracted with boiling alcohol. On removal of the solvent *p*-tolylmethylcyanamide (3·5 g.), m. p. 45°, was obtained (Found: C, 74·4; H, 6·4; N, 19·5. Calc. for $C_9H_{10}N_2$: C, 74·0; H, 6·8; N, 19·2%).

p-*Anisylcyanamide.*—This was prepared in 74% yield by Berger's method using lead acetate as described above for *p*-tolylcyanamide. It crystallised from benzene in plates, m. p. 88° (Found: C, 65·1; H, 5·6. $C_3H_8ON_2$ requires C, 64·8; H, 5·4%). When prepared by Pierron's method the yield was 81%.

N-p-*Anisyl*-N-*methylurea.*—N-p-*Anisyl*-N-*methylthiourea* (9·8 g.) suspended in a solution of potassium hydroxide (12·5 g.) in water (125 c.c.) was treated with lead acetate (25 g.) and the solution heated for 15 minutes on the boiling water-bath. After removal of lead sulphide the aqueous solution was neutralised with glacial acetic acid and concentrated to a small volume. Clusters of striated plates, m. p. 157°, separated which proved on analysis to be *N*-*p*-anisyl-*N*-methylurea (Found: C, 60·2; H, 6·5; N, 15·4. Calc. for $C_9H_{12}O_2N_2$: C, 60·0; H, 6·7; N, 15·5%). Hjort, de Beer, Buck, and Ide (*J. Pharm. Exp. Ther.*, 1935, 55, 152) give m. p. 157°.

N-p-*Anisyl*-S-*methylisothiourea.*—*p*-Anisylthiourea was prepared in the usual way from *p*-anisidine hydrochloride and ammonium thiocyanate in 80% yield. It melted on recrystallisation from water at 220° and crystallised in jagged plates. The m. ps. given in the literature are much lower. Dyson and George (*J.*, 1924, **125**, 1708) give m. p. 210—211°, Dienske (*Rec. Trav. chim.*, 1931, **50**, 407) gives m. p. 213°, whilst Capps and Dehn (*J Amer. Chem. Soc.*, 1932, **54**, 4304) give m. p. 210°.

For conversion into N-p-*anisyl*-S-*methylisothiourea hydriodide*, the parent thiourea (9·1 g.) was digested gently for 30 minutes in alcohol (9 c.c.) with methyl iodide (4 c.c.). The required hydriodide (15·2 g.) was recrystallised from alcohol (20 c.c.) and separated in diamond-shaped plates, m. p. 164—165° (Found: N, 8·7. $C_9H_{12}ON_2S$,HI requires N, 8·6%). The free *base* liberated by ammonia separated from alcohol in large rhombs, m. p. 115° (Found: C, 55·3; H, 6·2. $C_9H_{12}ON_2S$ requires C, 55·1; H, 6·2%). The *hydrochloride* crystallises from water in needles, m. p. 165° (Found: C, 46·7; H, 5·6; N, 12·0. $C_9H_{12}ON_2S$,HCl requires C, 46·4; H, 5·6; N, 12·0%).

N-p-*Anisyl*-NS-*dimethylisothiourea hydriodide* was prepared from *N*-*p*-anisyl-*N*-methylthiourea similarly. Recrystallised from 5 volumes of boiling alcohol it separated in striated tablets, m. p. 197° (Found: C, 35·9; H, 4·5; N, 8·2. $C_{10}H_{14}ON_2S$,HI requires C, 35·5; H, 4·5; N, 8·3%).

N-p-*Anisyl*-N′-*methylthiourea.*—*p*-Anisidine (25·9 g.) in alcohol (13 c.c.) was treated with methyl *iso*thiocyanate (15·4 g.); on keeping the *thiourea* crystallised out, yield 33·3 g. It was recrystallised from 20 volumes of boiling alcohol from which it separated in prismatic needles, m. p. 169° (Found: C, 55·5; H, 6·4; N, 14·6. $C_9H_{12}ON_2S$ requires C, 55·1; H, 6·2; N, 14·3%). It was converted into N-p-*anisyl*-N′S-*dimethylisothiourea hydriodide* in the usual way. This salt was soluble in 6 parts of boiling alcohol and separated in elongated filmy leaflets, m. p. 179° (Found: C, 35·9; H, 4·2; N, 9·2. $C_{10}H_{14}ON_2S$,HI requires C, 35·5; H, 4·5; N, 9·6%).

N-p-*Anisyl*-NN′-*dimethylthiourea.*—*N*-Methyl-*p*-anisidine (32·65 g.) and methyl *iso*thiocyanate (17·4 g.) in alcohol (16 c.c.) gave on keeping the *thiourea* (38·0 g.). It was recrystallised from boiling alcohol in which it is readily soluble and separated in long prisms, m. p. 106° (Found: C, 57·5; H, 6·5; N, 12·9. $C_{10}H_{14}ON_2S$ requires C, 57·1; H, 6·7; N, 13·3%). It was converted into N-p-*anisyl*-NN′S-*trimethylisothiourea hydriodide* in the usual way. This is a very soluble salt and to effect crystallisation most of the solvent had to be removed. It could be crystallised from a small volume of alcohol from which it separated in six-sided tablets, m. p. 95—97° (Found: C, 37·4; H, 4·9; N, 8·0. $C_{11}H_{16}ON_2S$,HI requires C, 37·5; H, 4·9; N, 8·0%).

Action of Cuprous Chloride on N-*Nitroso*-N-*methyl*-p-*anisidine.*—*N*-Methyl-*p*-anisidine hydrochloride (34·9 g.) containing a small proportion of non-methylated base was diazotised in hydrochloric acid solution and added to a solution of cuprous chloride (40 g.) in concentrated hydrochloric acid (286 c.c., *d* 1·16). The solution was heated on the water-bath until there was no further evolution of gas. The copper was removed as sulphide, the solution made alkaline, and the base, which coloured up very rapidly, extracted by ether and fractionally distilled, giving 13·4 g., b. p. 135—136°/19 mm. It was converted into the hydrochloride and fractionated from methyl ethyl ketone; *N*-methyl-*p*-anisidine hydrochloride (6·7 g,. m. p. 118°) was the least soluble fraction, and from the mother liquor 2-*chloro*-4-*methoxy*-N-*methylaniline hydrochloride* (1·3 g.) was obtained. It crystallised from methyl ethyl ketone in octahedra, m. p. 156° (Found: C, 46·3; H, 5·2. $C_8H_{10}ONCl$,HCl requires C, 46·2; H, 5·3%). The *picrate* separated from alcohol in clusters of slender prisms, m. p. 125° (Found: C, 42·4; H, 3·5; N, 13·9. $C_8H_{10}ONCl,C_6H_3O_7N_3$ requires C, 41·9; H, 3·3; N, 14·0%).

2-*Chloro*-4-*nitroanisole.*—Smooth nitration of 2-chloroanisole proved difficult. Reverdin and Eckland (*Ber.*, 1899, **32**, 2622) obtained this chloronitroanisole in unstated yield by adding one part of nitric acid (*d* 1·4) to chloroanisole. An experiment on these lines gave less than a 10% yield of required nitro-compound. After many trials the following two-stage process was adopted. Chloroanisole (7·1 g.) and acetic anhydride (7 c.c.) were heated with stirring to 80° and nitric acid (5·1 c.c., *d* 1·4) was added dropwise. When all had been added, the flask was heated in the boiling water-bath for 2·5 hours and then diluted with water. The semi-solid mass was separated and pressed to free it from oil; yield of crude 2-chloro-4-nitroanisole, m. p. 94°, 46%. The oil from a series of batches was recovered and dried and re-nitrated under similar conditions; most of it then became converted into the required chloronitroanisole. One crystallisation from methyl alcohol gave the pure material.

3-*Chloro*-4-*methoxyformanilide.*—The foregoing nitro-compound was reduced with tin and hydrochloric acid in presence of alcohol and the base obtained in excellent yield, m. p. 62° in agreement with Reverdin and Eckhard (*loc. cit.*). It gave a *hydrochloride*, pearly scales from alcohol, m. p. 278—279° (Found: C, 43·5; H, 4·7. C_7H_8ONCl,HCl requires C, 43·3; H, 4·7%).

3-Chloro-4-methoxyaniline (5·5 g.) and formic acid (5 c.c., 98%) were boiled for 3 hours and the 3-chloro-4-methoxyformanilide (5·2 g.) was isolated by appropriate ether extraction. It separated from 3 parts of benzene in clusters of needles, m. p. 84° (Found: C, 52·0; H, 4·6; N, 8·0. $C_8H_8O_2NCl$ requires C, 51·8; H, 4·3; N, 7·6%).

3-*Chloro*-4-*methoxy*-N-*methylformanilide.*—3-Chloro-4-methoxyformanilide (4·63 g.) and methyl iodide (3·55 g.) in alcohol (25 c.c.) were heated with a solution of potassium hydroxide (1·4 g.) in alcohol (10 c.c.) and the resulting solution was boiled for 1 hour. The solution was cooled and one-half the above quantities of methyl iodide and alcoholic potash added; the solution was then boiled for a further 1 hour. The solvent was removed, water added, and the product isolated by ether extraction. 3-*Chloro*-4-*methoxy*-N-*methylformanilide* (3·6 g.) crystallised from alcohol in diamond-shaped plates, m. p. 72—73° (Found: C, 54·4; H, 5·4; N, 6·8. $C_9H_{10}O_2NCl$ requires C, 54·1; H, 5·1; N, 7·0%). On hydrolysis with boiling 16% hydrochloric acid it gave 3-*chloro*-4-*methoxy*-N-*methylaniline hydrochloride* as columns or tablets from absolute alcohol, m. p. 189° (Found: C, 46·0; H, 5·3; N, 6·8. $C_8H_{10}ONCl$,HCl

requires C, 46·1; H, 5·3; N, 6·7%). The *picrate*, fine needles from water, had m. p. 97°, but when dried at 95° it had m. p. 141—143° (Found: loss at 100°, 3·4. $C_8H_{10}ONCl,C_6H_3O_7N_3,H_2O$ requires H_2O, 4·3%. On dried salt: C, 41·9; H, 3·3. $C_8H_{10}ONCl,C_6H_3O_7N_3$ requires C, 41·9; H, 3·3%). Both these salts were quite different from the two parallel salts from the chloro-*N*-methyl-*p*-anisidine described above.

Reduction of p-*Nitroanisole with Tin and Hydrochloric Acid.*—*p*-Nitroanisole (20 g.), tin foil (40 g.), and concentrated hydrochloric acid (100 c.c.) were allowed to react as violently as possible (Hurst and Thorpe, *J.*, 1915, **107**, 938). The reaction is over in one or two minutes but is very slow if granulated tin is used. The total base produced was recovered as hydrochloride, yield 19·3 g. It was dissolved in water (100 c.c.) and fractionally basified by addition of 13 portions, each of 6 c.c., of 2N-sodium hydroxide. Each fraction was extracted once with chloroform (10 c.c.). On removing the chloroform from each fraction the residues, with the exception of the first, readily crystallised and all except the first two had the m. p. of *p*-anisidine. Only the first two gave the copper-wire test for presence of halogen. The second fraction on acetylation proved to be mainly *p*-anisidine, but the first fraction (1·0 g.) on acetylation solidified and gave 2-chloro-4-methoxyacetanilide, 0·53 g. from benzene, m. p. 110—111° (Found: C, 54·4; H, 5·4; N, 6·8. Calc. for $C_9H_{10}O_2NCl$: C, 54·1; H, 5·1; N, 7·0%), and the benzene mother liquor on addition of petrol gave acet-*p*-anisidide, 80 mg.

Diguanides.

For the preparation of the diguanides from anilines, the hydrochloride of the aniline and the dicyanodiamide were boiled together in aqueous solution for 6 hours, the diguanide often separating from the solution when cold. The following new diguanides were prepared in good yield in this way. m-*Chlorophenyldiguanide hydrochloride*, m. p. 197—198°, fine needles from water (Found: C, 38·8; H, 4·4; N, 28·0. $C_8H_{10}N_5Cl,HCl$ requires C, 38·7; H, 4·5; N, 28·2%). p-*Chlorophenyldiguanide hydrochloride*, m. p. 255°, plates from water (Found: C, 39·1; H, 4·2; N, 27·8. $C_8H_{10}N_5Cl,HCl$ requires C, 38·7; H, 4·5; N, 28·2%). Strukov, Sychra, and Smirnov (*J. Chem. Ind. U.S.S.R.*, 1941, **18**, 22) have described this salt as having m. p. 226°. p-*Bromophenyldiguanide hydrochloride*, m. p. 259°, plates from water (Found: C, 33·4; H, 3·9. $C_8H_{10}N_5Br$, HCl requires C, 32·8; H, 3·8%). o-*Tolyldiguanide hydrochloride*, m. p. 242—243°, stout prisms from water (Found: C, 47·8; H, 6·2; N, 30·6. $C_9H_{13}N_5,HCl$ requires C, 47·5; H, 6·2; N, 30·8%). Beutel (*Annalen*, 1900, **310**, 337) describes a hemihydrate which loses water in the air and has m. p. 229°. m-*Tolyldiguanide hydrochloride*, m. p. 225—226°, rods from water (Found: C, 47·8; H, 6·2. $C_9H_{13}N_5,HCl$ requires C, 47·5; H, 6·2%). Beutel (*loc. cit.*) describes a hemihydrate which readily loses water in the air and has m. p. 211°; he attributes a similar degree of hydration to *p*-tolyldiguanide hydrochloride, for which he gives m. p. 235° (anhydrous). Braun (*J. Amer. Chem. Soc.*, 1933, **55**, 1282) finds the *p*-tolyl salt to be anhydrous with m. p. 245—247°, and this agrees with our own finding. 3 : 4-*Xylyldiguanide hydrochloride*, m. p. 225—226°, needles from water (Found: C, 50·2; H, 6·4; N, 28·7. $C_{10}H_{15}N_5,HCl$ requires C, 49·7; H, 6·7; N, 29·0%). 2 : 4-*Xylyldiguanide hydrochloride*, m. p. 256°, flat needles from water (Found: C, 50·1; H, 6·8; N, 28·7. $C_{10}H_{16}N_5,HCl$ requires C, 49·7; N, 28·7; N, 28·7%). 2 : 5-*Xylyldiguanide hydrochloride*, m. p. 219—220°, tablets from water (Found: C, 50·0; H, 6·7; N, 28·7. $C_{10}H_{15}N_5HCl$ requires C, 49·7; H, 6·7; N, 29·0%). p-*Ethylphenyldiguanide hydrochloride*, m. p. 225—226°, clusters of needles from water (Found: C, 49·8; H, 6·4. $C_{10}H_{15}N_5,HCl$ requires C, 49·7; H, 6·7%). p-*Acetophenonediguanide hydrochloride*, m. p. 222°, needles from water (Found: C, 47·4; H, 5·3. $C_{10}H_{13}ON_5,HCl$ requires C, 47·0; H, 5·5%). o-*Anisyldiguanide hydrochloride monohydrate*, m. p. 216—217°, short stout prisms from water (Found: C, 41·9; H, 5·7; N, 26·6; H_2O, 5·7. $C_9H_{13}ON_5,HCl$ requires C, 41·3; H, 6·2; N, 26·8; H_2O, 6·9%). 3 : 4-*Methylenedioxyphenyldiguanide hydrochloride*, m. p. 237—238°, square plates from water (Found: C, 42·3; H, 4·6; $C_9H_{11}O_2N_5,HCl$ requires C, 41·9; H, 4·7%). N-p-*Tolyl*-N-*methyldiguanide hydrochloride*, m. p. 231°, clusters of pointed tablets from water (Found: C, 50·1; H, 6·8; N, 29·3. $C_{10}H_{15}N_5,HCl$ requires C, 49·7; H, 6·7; N, 29·0%). N-p-*Tolyl*-N-*ethyldiguanide hydrochloride*, m. p. 186—187° from alcohol on addition of ethyl acetate, clusters of tiny needles which change on keeping in contact with the saturated solution into plates (Found: C, 51·6; H, 7·3; N, 27·0. $C_{11}H_{17}N_5,HCl$ requires C, 51·6; H, 7·1; N, 27·4%). N-p-*Anisyl*-N-*methyldiguanide hydrochloride dihydrate*, m. p. 203°, needles from water (Found: C, 41·1; H, 6·9; H_2O, 12·4. $C_{10}H_{16}ON_5,HCl,2H_2O$ requires C, 40·9; H, 6·8; H_2O, 12·3%). N-p-*Anisyl*-N-*ethyldiguanide hydrochloride*, m. p. 189°, stout crystals from alcohol (Found: C, 49·0; H, 7·0. $C_{11}H_{17}ON_5,HCl$ requires C, 48·6; H, 6·7%).

p-Anisyldiguanide hydrochloride was obtained by Lumière and Perrin (*Bull. Soc. chim.*, 1905, **33**, 206) by melting together *p*-anisidine hydrochloride and dicyanodiamide with m. p. 221—222°. When prepared in boiling aqueous solution we find m. p. 235—236° (Found: C, 44·7; H, 5·7. Calc. for $C_9H_{13}ON_5,HCl$: C, 44·3; H, 5·8%).

p-Phenetyldiguanide hydrochloride prepared by Lumière and Perrin (*loc. cit.*) by melting together the components is recorded as having m. p. 209—210°. Cohn (*J. pr. Chem.*, 1911, **84**, 400) prepared it in boiling aqueous solution and records m. p. 170—172°. We have repeated Cohn's preparation and find the salt to crystallise in stout plates, m. p. 220° (Found: C, 46·9; H, 6·0; N, 27·7. Calc. for $C_{10}H_{15}ON_5,HCl$: C, 46·6; H, 6·3; N, 27·2%).

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National Institute for Medical Research,
Hampstead, London, N.W. 3.

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