HYPOGLYCAEMIC AGENTS. PART I

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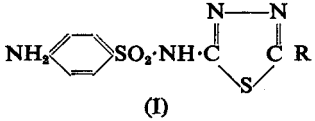
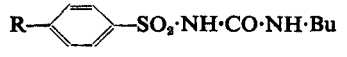
Some structural analogues of the active compounds (I), (II) and (III) are described. Their biological study failed to reveal significant hypoglycaemic activity.

WE began a search for new hypoglycaemic agents in 1956 when the main structural types exciting attention were: (*a*) derivatives of 5-alkyl-2-*p*-aminobenzenesulphonamido-1,3,4-thiadiazole (cf. I), which had been



(I)

discovered by Loubatières in 1944 and (*b*) analogues of 1-butyl-3-benzenesulphonylurea (II) [Compare Franke and Fuchs (1955) and Miller and Dulin (1956) who reported on the *p*-aminophenyl (carbutamide; II;



(II)

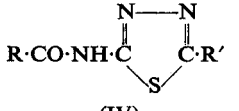
R = NH_2) and *p*-tolyl (tolbutamide; II; R = Me) analogues respectively.] A year later Ungar, Freedman and Shapiro (1957) and Pomeranze, Fujiy and Mouratoff (1957), described phenformin (N^1-phenethylbiguanide; *N*-β-phenethylformamidinyliminourea) (III), the first example of a

(III)

non-sulphamoyl compound to survive clinical studies for hypoglycaemic activity.

Initially we prepared a few compounds related to structures (I) and (II).

Analogues of (I) were synthesised in which the *p*-aminophenyl group was replaced by a *p*-carboxyphenyl, by a 2-pyridyl and by a 4-acetamido-2-pyridyl group. These compounds were readily obtained by reaction of the appropriate sulphonyl chlorides with 2-amino-5-t-butyl-1,3,4-thiadiazole in pyridine solution. Related types (IV) in which the sulphonyl group



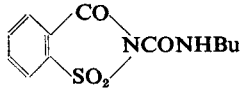
(IV)

was replaced by a carbonyl group were also synthesised. The R = *p*-tolyl, 3-pyridyl and 2-furyl analogues (IV; R′ = CMe_3) were prepared from the

appropriate acid chlorides and the aminothiadiazole. The *p*-aminophenyl derivative (IV; R = *p*-$NH_2.C_6H_4$, R′ = CMe_3) was obtained directly using thionylaminobenzoyl chloride (cf. Graf and Langer, 1937) or by reduction of the corresponding nitro-compound (IV; R = *p*-$NO_2 \cdot C_6H_4$; R′ = CMe_3). In addition, the 5-carbamoyl (IV; R′ = $CONH_2$) and 5-carbamoylmethyl (IV; R′ = CH_2CONH_2) derivatives of 2-amino- and 2-acetamido-1,3,4-thiadiazole (IV; R = Me, R′ = H) were prepared.

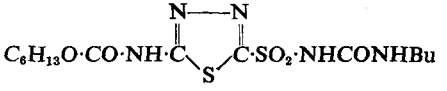
Attention was then directed to analogues of 1-butyl-3-sulphonylurea (II). These included the higher homologues (II; R = $AcNHCH_2$· and $AcNH(CH_2)_2$) of carbutamide, as well as the 1-butyl-3-(2-thienyl), 1-butyl-3-(2-pyridyl) and 1-butyl-3-(3-pyridyl) ureas. 1-Butyl-3-(3-nicotinoyl)-urea (V) and the corresponding isonicotinoyl urea were also synthesised. By condensing saccharin with butyl isocyanate, the carboxybutylamide (VI) was obtained which contained both the 1-butyl-3-carbonylurea and

(V)



(VI)

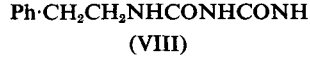
1-butyl-3-benzenesulphonylurea moieties. 1-Butyl-3-(2-hexyloxycarbonamido-1,3,4-thiadiazole-5-sulphonyl)urea (VII), a mixed type resembling



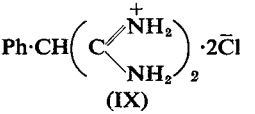
(VII)

both (I) and (II) was similarly obtained from 2-hexyloxycarbonamido-1,3,4-thiadiazole-5-sulphonamide (Petrow, Stephenson, Thomas and Wild, 1956).

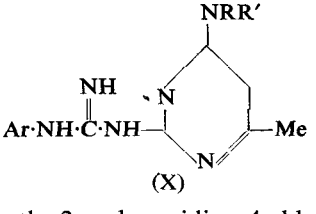
Later, when reports on phenformin (III) became available, the related 1-phenethylbiuret (VIII) and β-phenylmalondiamidine (IX) were synthesised. In addition, the guanidinotetrahydropyrimidines (X) were



(VIII)



(IX)



(X)

obtained by condensing the 2-arylguanidino-4-chloro-6-methylpyrimidines with phenethylamine or with 1,2,3,6-tetrahydropyridine. Some derivatives of thiosemicarbazide, which cannot be classified with the previous groups of compounds are reported in the Experimental.

Biological study of the above compounds by Dr. A. David and his colleagues failed to reveal hypoglycaemic activity superior to that of the parent structures.

EXPERIMENTAL

2-(2-*Pyridinesulphonamido*)-5-*t*-*butyl*-1,3,4-*thiadiazole*

(*a*) *Pyridine-2-sulphonyl chloride.* A solution of 2-mercaptopyridine (58 g.) (Thirtle, 1946) in concentrated hydrochloric acid (649 ml.) and ice water (142 ml.) was cooled below 10° and chlorine passed through the solution until absorption of the gas was complete (*ca* 90 min.). Ice-water (1740 ml.) was then stirred into the mixture, which was cooled to 0°. The crystalline *product* which separated was collected, washed with cold water and drained as far as possible. It was used without delay for the next stage of the reaction.

(*b*) The foregoing crude sulphonyl chloride was added in portions to a solution of 2-amino-5-t-butyl-1,3,4-thiadiazole (42 g.) in pyridine (160 ml.) at below 40°. Reaction was completed by heating at 60° for 35 min. when the mixture was cooled, added to ice and acidified. The *product* (66 g.) had m.p. 167° (decomp.) after crystallisation from aqueous ethanol. Found: C, 44·5; H, 4·6; N, 18·7; S, 21·7. $C_{11}H_{14}N_4O_2S_2$ requires C, 44·3; H, 4·7; N, 18·8; 21·5 per cent.

2-(5-*Acetamido*-2-*pyridinesulphonamido*)-5-*t*-*butyl*-1,3,4-*thiadiazole*, was prepared by reaction of 5-acetamidopyridine-2-sulphonyl chloride (Caldwell and Kornfeld, 1942) with 2-amino-5-*t*-butyl-1,3,4-thiadiazole in pyridine. It had m.p. 210° (decomp.) after crystallisation from aqueous ethanol. Found: N, 19·8; S, 18·2. $C_{13}H_{17}N_5O_3S_2$ requires N, 19·7; S, 18·0 per cent.

2-(4-*Carboxybenzenesulphonamido*)-5-*t*-*butyl*-1,3,4-*thiadiazole*, had m.p. 370° (decomp.) after crystallisation from pyridine or a large volume of acetic acid. Found: N, 12·0. $C_{13}H_{15}N_3O_4S_2$ requires N, 12·3 per cent.

2-(*p*-*Aminobenzamido*)-5-*t*-*butyl*-1,3,4-*thiadiazole*

(*a*) 2-(*p*-*Nitrobenzamido*)-5-*t*-*butyl*-1,3,4-*thiadiazole*, prepared by reaction of 2-amino-5-t-butyl-1,3,4-thiadiazole (6·3 g.) with *p*-nitrobenzoyl chloride (7·4 g.) in pyridine (30 ml.) had m.p. 296-297° after crystallisation from glacial acetic acid. Found: C, 50·9; H, 4·8; S, 10·5. $C_{13}H_{14}N_4O_3S$ requires C, 51·0; H, 4·5; S, 10·6 per cent.

A suspension of the foregoing nitro-compound (1·53 g.) in boiling ethanol (100 ml.) was treated with hydrazine hydrate (1·0 g.) and Raney nickel (*ca* 2 g.) and the mixture heated under reflux for 5 hr. It was then filtered, concentrated and diluted with water. The product was dissolved in hydrochloric acid, reprecipitated by neutralisation and recrystallised from acetic acid. It had m.p. 323–325° (some decomp.). Found: C, 56·1; H, 5·9; N, 20·2; S, 11·6. $C_{13}H_{16}N_4OS$ requires C, 56·5; H, 5·8; N, 20·3; S, 11·6 per cent.

(*b*) *p*-Thionylaminobenzoyl chloride (1·56 g.) and 2-amino-5-t-butyl-1,3,4-thiadiazole (1·21 g.) were dissolved in pyridine (5 ml.) and the mixture heated on the steam bath for 30 min. The solution was poured into cold

water to yield the *product* m.p. 323–325° (some decomp.) after purification as described above.

2-*Nicotinamido*-5-*t*-*butyl*-1,3,4-*thiadiazole*

Nicotinic acid (17·2 g.) was dissolved in dry pyridine (70 ml.), heated on the steam bath, and thionyl chloride (14 ml.) added with stirring. After 30 min., a solution of 2-amino-5-*t*-butyl-1,3,4-thiadiazole (22 g.) dissolved in the minimum volume of pyridine was added and the mixture heated for a further hr. It was then cooled and diluted with ice-water. The *product* was collected and washed with cold water. It (26 g.) had m.p. 206–207° after crystallisation from ethanol. Found: C, 55·4; H, 5·2. $C_{12}H_{14}N_4OS$ requires C, 54·9; H, 5·4 per cent.

2-(*p-Methylbenzamido*)-5-*t*-*butyl*-1,3,4-*thiadiazole*, had m.p. 217–218° after crystallisation from ethanol. Found: C, 60·8; H, 5·9; N, 15·3; S, 11·7. $C_{14}H_{17}N_3OS$ requires C, 61·1; H, 6·2; N, 15·3; S, 11·6 per cent.

2-(2-*Furoylamido*)-5-*t*-*butyl*-1,3,4-*thiadiazole*, had m.p. 174–175° after crystallisation from ethanol. Found: C, 52·5; H, 4·8; N, 16·8. $C_{11}H_{13}N_3O_2S$ requires C, 52·6; H, 5·2; N, 16·7 per cent.

2-*Amino*-5-*carbamoyl*-1,3,4-*thiadiazole*. Thiosemicarbazide (18·2 g.) and phosphorus oxychloride (35·4 g.) were mixed carefully with cooling. Ethoxalyl chloride (27·4 g.) was then added carefully with cooling and reaction completed by heating at 60° for 1 hr. The cooled mixture was poured into ice water and neutralised with sodium bicarbonate.

2-*Amino*-5-*ethoxycarbonyl*-1,3,4-*thiadiazole* (11 g.), m.p. 165–167° (decomp.), was obtained by crystallisation from water. The compound is unstable in solution. It (2 g.) was added to aqueous ammonia (10 ml., d = 0·880) and water (5 ml.) and the mixture left at room temperature for 2 days. The *product* which separated was crystallised from acetic acid and had m.p. 307° (decomp.). Found: C, 25·2; H, 2·7. $C_3H_4N_4OS$ requires C, 25·0; H, 2·8 per cent.

2-*Acetamido*-5-*ethoxycarbonyl*-1,3,4-*thiadiazole* was obtained when the amine (2 g.) was heated with acetic anhydride (10 ml.) and anhydrous sodium acetate (0·5 g.) for 5 min. It (1·6 g.) had m.p. 230° after crystallisation from acetic acid. Found: C, 39·2; H, 4·3; N, 19·8. $C_7H_9N_3O_3S$ requires C, 39·1; H, 4·2; N, 19·5 per cent.

2-*Acetamido*-5-*carbamoyl*-1,3,4-*thiadiazole*. (*a*) The foregoing ester (13 g.) was dissolved in aqueous ammonia (45 ml., d = 0·880) and water (15 ml.). The *product* (8·9 g.) which separated was collected after 1 day and washed with cold water. It had m.p. >350°. Found: C, 31·9; H, 3·2; N, 29·8; S, 17·1. $C_5H_6N_4O_2S$ requires C, 32·3; H, 3·2; N, 30·1; S, 17·2 per cent.

(*b*) 2-Amino-5-carbamoyl-1,3,4-thiadiazole (17·5 g.) was refluxed with acetic anhydride (75 ml.) and anhydrous sodium acetate (5 g.) for 20 min. Water was added to decompose excess anhydride and the *product* was collected and washed with water. It had m.p. >350°. 2-*Acetamido*-5-*ethoxycarbonylmethyl*-1,3,4-*thiadiazole* was obtained by heating the corresponding 2-amino-compound (4 g.) (Ohta, 1952) with acetic anhydride (10 ml.) for 5 min. It (4·3 g.) had m.p. 193–194° after crystallisation from

acetic acid. Found: C, 41·5; H, 5·0; N, 18·2; S, 14·1. $C_8H_{11}N_3O_3S$ requires C, 41·9; H, 4·8; N, 18·3; S, 14·0 per cent.

1-*Butyl*-3-(2-*pyridinesulphonyl*) *urea*

(*a*) 2-*Pyridinesulphonamide*. Moist pyridine-2-sulphonyl chloride (72 g.) was added with stirring at below 10° to aqueous ammonia (400 ml., d = 0·880). When the addition was complete, excess of ammonia was boiled off and the residue was evaporated to dryness at reduced pressure. The residual solid was triturated with water and collected. It had m.p. 140–142° after crystallisation from water. Found: C, 37·8; H, 3·9 N, 17·8. $C_5H_6N_2O_2S$ requires C, 38·0; H, 3·8; N, 17·7 per cent.

(*b*) A solution of the foregoing sulphonamide (14·4 g.) in water (65 ml.) containing sodium hydroxide (4 g.) was treated with acetone (30 ml.) and cooled to 10°. Butyl isocyanate was added dropwise with stirring which was continued for a further hr. The solution was diluted with an equal volume of water, filtered and the filtrate acidified with hydrochloric acid. The solids were collected, washed with water and dissolved in dilute ammonia solution (100 ml.). The filtered solution was acidified with hydrochloric acid yielding the *product* (19 g.), m.p. 164° after crystallisation from ethanol. Found: N, 16·4; S, 12·6. $C_{10}H_{15}N_3O_3S$ requires N, 16·3; S, 12·5 per cent.

1-*Butyl*-3-(3-*pyridinesulphonyl*)*urea*, had m.p. 104–105° after crystallisation from aqueous ethanol. Found: C, 47·0; H, 5·5; N, 15·9. $C_{10}H_{15}N_3O_3S$ requires C, 46·7; H, 5·9; N, 16·3 per cent.

1-*Butyl*-3-(2-*thiophensulphonyl*)*urea*

(*a*) *Thiophen*-2-*sulphonamide* (described by Langer in 1884). Thiophene-2-sulphonyl chloride (10 g.) was added with stirring to aqueous ammonia (50 ml., d = 0·880) at 0°. After addition was complete the mixture was kept at 0° for 6 hr., then allowed to warm slowly to room temperature when reaction was completed by warming to 40° for 30 min. The solid which separated (7·6 g.), had m.p. 143–145° after crystallisation from water. Found: C, 29·1; H, 3·1; N, 8·9; S, 39·3. Calc. for $C_4H_5NO_2S_2$: C, 29·4; H, 3·1; N, 8·6; S, 39·3 per cent.

(*b*) The foregoing sulphonamide (8·15 g.) was dissolved in a solution of sodium hydroxide (2 g.) in water (35 ml.) and acetone (15 ml.). The solution was cooled to 10° and treated slowly with butyl isocyanate (5·5 g.) added dropwise over 75 min. Stirring was continued for a further 90 min. when a small amount of insoluble material was filtered off and the filtrate acidified with dilute hydrochloric acid. The solid (12 g.) was collected and had m.p. 150–152° after crystallisation from aqueous ethanol. Found: C, 41·3; H, 5·3; S, 23·7. $C_9H_{14}N_2O_3S_2$ requires C, 41·2; H, 5·4; S, 24·4 per cent.

1-(*p-Acetamidomethylbenzenesulphonyl*)-3-*ethylurea*, had m.p. 198–199° (decomp.) after crystallisation from aqueous 2-ethoxyethanol. Found: C, 48·3; H, 5·5; N, 14·0; S, 10·9. $C_{12}H_{17}N_3O_4S$ requires C, 48·1; H, 5·7; N, 14·0; S, 10·7 per cent.

1-(*p-Acetamidomethylbenzenesulphonyl*)-3-*propylurea*, m.p. 176–177°, (from ethanol). Found: C, 49·8; H, 5·9; N, 13·0; S, 9·9. $C_{13}H_{19}N_3O_4S$ requires C, 49·8; H, 6·1; N, 13·4; S, 10·2 per cent.

1-(*p-Acetamidomethylbenzenesulphonyl*)-3-*butylurea*, m.p. 158–160°, (from ethanol). Found: C, 51·4; H, 6·2; N, 12·6; S, 9·6. $C_{14}H_{21}N_3O_4S$ requires C, 51·4; H, 6·5; N, 12·8; S, 9·8 per cent.

1-[*p*-2-(*Acetamidoethyl*)*benzenesulphonyl*]-3-*butylurea*, had m.p. 150–152° after crystallisation from ethanol. Found: C, 52·9; H, 6·9; N, 12·2; S, 8·9. $C_{15}H_{23}N_3O_4S$ requires C, 52·8; H, 6·8; N, 12·3; S, 9·4 per cent.

1-*Benzenesulphonyl*-3-*butylguanidine*. Benzenesulphonyl chloride (30 g.) was added with stirring to a solution of butylguanidine hydrochloride in 10 per cent sodium hydroxide solution (300 ml.) at 0° and stirring continued until the odour of sulphonchloride had disappeared. The *product* was collected and washed with water. It had m.p. 120–122° (from ethanol). Found: C, 52·0; H, 6·9; N, 16·2. $C_{11}H_{17}N_3O_2S$ requires C, 51·8; H, 6·7; N, 16·5 per cent.

1-*Acetylsulphanilyl*-3-*butylguanidine*. Butylguanidine sulphate (1·64 g.) was dissolved in warm pyridine (2·0 ml.) and treated, in portions, with acetylsulphanilyl chloride (2·34 g.). The mixture was heated at 60° for 1 hr., cooled and triturated with ice water. The solid (1·6 g.) was collected and washed with water. It had m.p. 157–159° (from ethanol). Found: C, 49·9; H, 6·4; N, 18·0. $C_{13}H_{20}N_4O_3S$ requires C, 50·0; H, 6·5; N, 17·9 per cent.

N-*Butylcarbamoyl-o-benzoicsulphimide*, had m.p. 130–131° (from aqueous acetone). Found: C, 51·3; H, 5·0; N, 9·8; S, 11·3. $C_{12}H_{14}N_2O_4S$ requires C, 51·1; H, 5·0; N, 9·9; S, 11·4 per cent.

1-*Butyl*-3-(2-*hexyloxycarbamido*-1,3,4 *thiadiazole*-5-*sulphonyl*)*urea*. A solution of 2-hexyloxycarbamido-1,3,4-thiadiazole-5-sulphonamide (10·3 g.), butyl isocyanate (5 g.) and triethylamine (5 ml.) in benzene (40 ml.) was heated under reflux for 10 hr. on the steam bath when volatile material was distilled off at reduced pressure. The gummy residue was dissolved in aqueous ethanol and acidified with acetic acid and the *product* (9·3 g.) collected. It had m.p. 172–173° after crystallisation from aqueous ethanol. Found: C, 41·5; H, 5·9; N, 16·9. $C_{14}H_{25}N_5O_5S_2$ requires C, 41·3; H, 6·2; N, 17·2 per cent.

1-*Butyl*-3-*isonicotinoylurea*. A mixture of isonicotinoyl chloride hydrochloride (44·5 g.) and butylurea (29 g.) in pyridine (40 ml.) was heated on the steam bath for 2 hr., cooled and triturated with water. The solids were collected, dissolved in boiling ethanol and filtered to remove about 5 g. of high melting insoluble material. Dilution of the filtrate with water yielded the *product* (28 g.) m.p. 110–111°. Found: C, 59·5; H, 7·0; N, 19·0. $C_{11}H_{15}N_3O_2$ requires C, 59·7; H, 6·8; N, 19·0 per cent.

1-*Butyl*-3-*nicotinoylurea*, m.p. 103–105° (aqueous ethanol). Found: C, 59·5; H, 6·7; N, 18·6 per cent.

1-*p-Toluoylsemicarbazide*, had m.p. 226–227° (decomp.) (from water). Found: C, 56·4; H, 5·5; N, 21·4. $C_9H_{11}N_3O_2$ requires C, 56·0; H, 5·7; N, 21·8 per cent.

1-*Acetylsulphanilyl*-4-o-*tolylthiosemicarbazide.* A solution of acetylsulphanilylhydrazide (17·4 g.) in ethanol (400 ml.) was treated with *o*-tolyl isothiocyanate (11·4 g.) and the mixture heated under reflux for 12 hr. on the steam bath. The solids (25 g.) were collected, washed with ethanol and had m.p. 228–229° (decomp.) (from acetic acid). Found: C, 50·8; H, 4·6; N, 14·7; S, 17·0. $C_{16}H_{18}N_4O_3S_2$ requires C, 50·8; H, 4·8; N, 14·8; S, 16·9 per cent.

4-o-*Tolyl*-1-*tosylthiosemicarbazide*, had m.p. 204° (decomp.) (from ethanol). Found: C, 54·1; H, 4·8; N, 12·0; S, 19·1. $C_{15}H_{17}N_3O_2S_2$ requires C, 53·7; H, 5·1; N, 12·5; S, 19·1 per cent.

4-*Allyl*-1-*tosylthiosemicarbazide*, had m.p. 174–175° (decomp.) (from ethanol). Found: C, 46·6; H, 5·7; N, 14·6; S, 22·1. $C_{11}H_{15}N_3O_3S_2$ requires C, 46·3; H, 5·3; N, 14·7; S, 22·5 per cent.

1-*Phenethylbiuret.* A solution of phenethylamine (17 g.) and nitrobiuret (20 g.) in 50 per cent ethanol (200 ml.) was warmed at 50–60° for 1 hr. then concentrated to remove most of the ethanol. The product which separated on cooling had m.p. 140–141° after crystallisation from water. Found: C, 58·0; H, 6·2; N, 20·1. $C_{10}H_{13}N_3O_2$ requires C, 58·0; H, 6·3; N, 20·3 per cent.

1-*Diguanidino*-1,2,3,6-*tetrahydropyridine.* A mixture of dicyandiamide (8·4 g.), 1,2,3,6-tetrahydropyridine (9·15 g.) and copper sulphate pentahydrate (12·5 g.) in 2-ethoxyethanol (20 ml.) and water (23 ml.) was heated under reflux with stirring for 2 hr. The mixture was diluted with water and the purple-brown copper complex was collected, washed with water and dissolved in N hydrochloric acid (390 ml.). Copper ions were removed with hydrogen sulphide and the filtered solution evaporated to dryness at reduced pressure. The residual gum crystallised from aqueous ethanol to yield the *product* (9·85 g.), m.p. 220–223°. Found: C, 33·5; H, 6·5; N, 28·1; Cl, 28·7. $C_7H_{15}Cl_2N_5 \cdot \frac{1}{2}H_2O$ requires C, 33·7; H, 6·5; Cl. 28·5; N, 28·1 per cent.

β-Phenylmalondiamidine dihydrochloride. A solution of β-phenylmalononitrile (62·5 g.) in ether (500 ml.) and ethanol (51·4 ml.) was saturated with hydrogen chloride at 0° and left at this temperature overnight. The imino-ether which separated was collected and washed with ether. It (100 g.) was dissolved in 12 per cent methanolic ammonia (1 litre) and kept at room temperature for 4 days. The solution was concentrated and mixed with ether. The *product* (62·5 g.) was collected and crystallised from ethanol-ether, from which it separated as a *monohydrate*, m.p. 208° (decomp.). Found: C, 40·9; H, 6·4; Cl, 26·9. $C_9H_{16}Cl_2ON_4$ requires C, 40·5; H, 6·0; Cl, 26·5 per cent.

6-*Methyl*-4-*phenethylamino*-2-*phenylguanidinopyrimidine.* A mixture of 4-chloro-6-methyl-2-phenylguanidinopyrimidine (16·5 g.) (prepared as described by Curd and Rose, 1946), sodium hydroxide (9·1 g.) and phenethylamine (9·2 g.) in chlorobenzene (60 ml.) and water 960 ml.) was heated under reflux with stirring for 30 min. when the chlorobenzene was distilled off in steam. The *product* was collected, washed with water and then with ethanol. It (13·5 g.) had m.p. 194–195° after crystallisation from ethanol.

Found: C, 69·1; H, 6·0; N, 24·7. $C_{20}H_{22}N_6$ requires C, 69·4; H, 6·4; N, 24·3 per cent.

2-p-*Chlorophenylguanidino-6-methyl-4-phenethylaminopyridine*, obtained in 95 per cent yield, had m.p. 208–211° (from 2-ethoxyethanol). Found: C, 63·2; H, 5·3; Cl, 9·3; N, 22·2. $C_{20}H_{21}ClN_6$ requires C, 63·1; H, 5·6; Cl,9·3; N, 22·1 per cent.

2-p-*Chlorophenylguanidino-6-methyl-4-(1,2,3,6-tetrahydropyridino) pyrimidine*, m.p. 178–180° (from acetone) was obtained in 67 per cent yield. Found: C, 59·10; H, 5·5; Cl, 10·5; N, 23 9. $C_{17}H_{19}ClN_6$ requires C, 59·6; H, 5·6; Cl, 10·3; N, 24·5 per cent.

2-p-*Bromophenylguanidino-6-methyl-4-(1,2,3,6-tetrahydropyridino) pyrimidine*, obtained in 60 per cent yield, had m.p. 172–175° (from acetone). Found: C, 52 9; H, 4·9; N, 21·5; Br, 20·8. $C_{17}H_{19}BrN_6$ requires C, 52·7; H, 4·9; Br, 20·6; N, 21·7 per cent.

2-p-*Bromophenylguanidino-6-methyl-4-phenethylaminopyrimidine*, had m.p. 210–212° (from ethoxyethanol). Found: C, 56·4; H, 4·9; Br, 18·5; N, 19·7. $C_{20}H_{21}BrN_6$ requires C, 56·5; H, 5·0; Br, 18·8; N, 19·8 per cent.

2-0-*Methoxyphenylguanidino-6-methyl-4-phenethylaminopyrimidine*, obtained in 60 per cent yield, had m.p. 218° (from 2-ethoxyethanol). Found: C, 67·2; H, 6·3; N, 22·2. $C_{21}H_{24}N_6O$ requires C, 67·0; H, 6·4; N, 22·3 per cent.

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