# Synthesis, Properties, and Electron Impact Fragmentation of Fluorinated 1-Arylbiguanides

By **N. P. Buu-Hoï,*** **P. Jacquignon,** and **M. Mangane,** Institut de Chimie des Substances Naturelles du C.N.R.S., 91-Gif-sur-Yvette
**S. Béranger** and **H. Pinhas,** Research Department, Laboratories Laroche Navarron 91-Leuville-sur-Orge, France

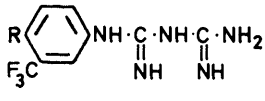
A number of 1-aryl-, 1,5-diaryl-, and 1-aryl-5-alkyl-biguanides bearing fluoro- and trifluoromethyl substituents on the aromatic ring have been synthesised; their chemical properties are described. Electron impact fragmentation in various 1-arylbiguanides has been investigated. Several of the compounds reported show anti-inflammatory, anorexigenic, and antimicrobial activities.

ALTHOUGH many biguanides have been synthesised and tested for antimalarial activity [1] or as hypoglycaemia-inducing agents of potential use in treatment of diabetes,[2] 1-arylbiguanides bearing fluoro- or trifluoromethyl substituents, or both, on the aromatic ring have only lately attracted attention. We recently reported [3] that some 1-(trifluoromethylphenyl)biguanides, such as compounds (I) and (II), are potent hypoglycaemia- and anorexia-inducing agents; compound (II), for instance, is ten times more active in rats as a hypoglycaemia promoter than the standard 1,1-dimethylbiguanide. This led us to a more detailed study of the synthesis and properties of fluorinated aromatic biguanides, and, especially, of their behaviour under electron impact. No mass spectra of biguanides have hitherto been reported, although the mass spectrometry of some simple guanidines has recently been thoroughly investigated.[4] Some non-fluorinated 1-arylbiguanides were therefore also studied in the present work.

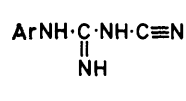
The 1-arylbiguanides were readily prepared by condensing the appropriate fluorinated arylamines with cyanoguanidine in aqueous medium; [5] in this way were obtained the previously unknown 4-trifluoromethyl-

[1] F. H. S. Curd and F. L. Rose, *J. Chem. Soc.*, 1946, 729; F. H. S. Curd, G. Davey, and F. L. Rose, *Ann. Trop. Med.*, 1945, **39**, 208.
[2] S. L. Shapiro, V. A. Parino, E. Rogow, and L. Freedman, *J. Amer. Chem. Soc.*, 1959, **81**, 3725.
[3] N. P. Buu-Hoï, S. Béranger, P. Jacquignon, A. Krikorian-Manoukian, and M. Courmarcel, *Compt. rend.*, 1967, **265***D*, 930.
[4] J. H. Beynon, J. A. Hopkinson, and A. E. Williams, *Org. Mass Spectrometry*, 1968, **1**, 169.
[5] *Cf.* A. L. Lumière and F. Perrin, *Bull. Soc. chim. France*, 1905, **3**, 33.

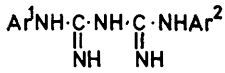
phenyl, 2-chloro-5-fluoromethylphenyl, 2-bromo-5-trifluoromethylphenyl, 3,5-bistrifluoromethylphenyl,



(I) R = H
(II) R = F

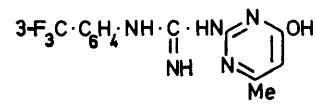


(III)

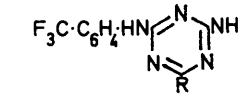


(IV)

and 2,3,4,5-tetrafluorophenyl derivatives. The 1,5-disubstituted biguanides (IV) were prepared by von Walther's procedure [6] as modified by Curd and Rose: [7] acetate, ethyl oxalate, and ethyl trifluoroacetate afforded the aminotriazines (VI), (VII), and (VIII), respectively.



(V)



(VI) R = Me
(VII) R = $CO_2Et$
(VIII) R = $CF_3$

1-Arylbiguanides bearing several fluoro-substituents are only very weakly basic; for example, 1-(3,5-bistrifluoromethylphenyl)biguanide failed to give a stable salt in dilute hydrochloric acid. For the preparation of 1-arylbiguanides bearing one 5-alkyl substituent, a more convenient procedure than the classic method [6,7] was

TABLE 1

5-Substituted 1-(3-trifluoromethylphenyl)biguanides

| Substituents | M.p. (°C) | Formula | Found (%) C | Found (%) H | Found (%) N | Reqd. (%) C | Reqd. (%) H | Reqd. (%) N |
|---|---|---|---|---|---|---|---|---|
| 5,5-Diethyl [a] | 86—87 | $C_{13}H_{18}F_3N_5$ | 52·1 | 6·2 | 23·5 | 51·8 | 6·0 | 23·2 |
| hydrochloride [b] | 238 | $C_{13}H_{19}ClF_3N_5$ | 46·1 | 5·8 | 21·0 | 46·2 | 5·7 | 20·8 |
| 5,5-Oxybisethylene [a] | 78—79 | $C_{13}H_{16}F_3N_5O$ | 49·3 | 5·3 | 21·8 | 49·5 | 5·1 | 22·2 |
| hydrochloride | 270—272 | $C_{13}H_{17}ClF_3N_5O$ | 44·5 | 4·9 | 19·9 | 44·4 | 4·9 | 19·9 |
| 5-*m*-Tolyl [c] | 127 | $C_{16}H_{16}F_3N_5$ | 57·0 | 5·1 | | 57·0 | 4·8 | |
| hydrochloride | 267 | $C_{16}H_{17}ClF_3N_5$ | 51·6 | 4·6 | 18·8 | 51·7 | 4·6 | 18·9 |
| 5-*p*-Anisyl | 111 | $C_{16}H_{16}F_3N_5O$ | 54·2 | 4·6 | 19·9 | 54·7 | 4·6 | 19·9 |
| hydrochloride | 221 | $C_{16}H_{17}ClF_3N_5O$ | 49·2 | 4·7 | 18·6 | 49·5 | 4·6 | 18·9 |
| 5-*p*-Chlorophenyl hydrochloride | 251 | $C_{15}H_{14}Cl_2F_3N_5$ | | | 18·0 | | | 17·9 |
| 5-(5-Chloro-2-methylphenyl) hydrochloride | 260—261 | $C_{16}H_{16}Cl_2F_3N_5$ | 47·4 | 4·1 | 17·2 | 47·3 | 4·0 | 17·2 |
| 5-(5-Quinolyl) | 248 | $C_{18}H_{15}F_3N_6$ | 57·9 | 4·0 | 22·7 | 58·1 | 4·1 | 22·6 |
| dihydrochloride | 255 | $C_{18}H_{17}Cl_2F_3N_6$ | 48·6 | 3·9 | | 48·6 | 3·9 | |
| 5-(8-Quinolyl) | 183 | $C_{18}H_{15}F_3N_6$ | 58·0 | 4·2 | 22·3 | 58·1 | 4·1 | 22·6 |
| | | | | Cl (%) | | | Cl (%) | |
| 5-Methyl [d] (hydrochloride) | 208—210 | $C_{10}H_{13}ClF_3N_5$ | | 12·0 | | | 12·1 | |
| 5-Ethyl (hydrochloride) | 240 | $C_{11}H_{15}ClF_3N_5$ | | 11·4 | | | 11·5 | |
| 5-Allyl (hydrochloride) | 198 | $C_{12}H_{15}ClF_3N_5$ | | 11·5 | | | 11·1 | |
| 5-Butyl (hydrochloride) | 196—198 | $C_{13}H_{19}ClF_3N_5$ | | 10·4 | | | 10·5 | |
| 5-Isopentyl (hydrochloride) | 186 | $C_{14}H_{21}ClF_3N_5$ | | 10·0 | | | 10·1 | |

[a] Recrystallised from water; all the other bases were recrystallised from aqueous ethanol. [b] All the hydrochlorides were recrystallised from water or methanol–ether. [c] Picrate, yellow prisms, m.p. 158—160° (toluene). [d] This and the following compounds were prepared by the sodium hydride–alkyl halide method; yields 45—60%.

the appropriate aliphatic or cyclic primary amine was condensed with a 1-aryl-3-cyanoguanidine (III) (itself prepared by coupling the relevant diazonium salt with cyanoguanidine to give a triazene which then loses nitrogen); in this condensation, heterocyclic amines such as morpholine and aminoquinolines could be successfully used. The fluorinated 1-arylbiguanides of types (I) and (II) readily underwent the various cyclisation reactions which had been reported previously for more simple biguanides; [8] for instance, the biguanide (I) readily condensed with ethyl acetoacetate to give the hydroxypyrimidine (V), and similar reactions with ethyl

found in direct substitution of the corresponding arylbiguanide by treatment of the sodio-derivative (made with sodium hydride in tetrahydrofuran) with the appropriate alkyl bromide or iodide; the alkylation occurred exclusively at N-5, as testified by the ready formation of the known 1-*p*-chlorophenyl-5-isopropylbiguanide (Paludrin) [7] from 1-*p*-chlorophenylbiguanide and isopropyl iodide. Several new 1,5-disubstituted biguanides were thus prepared (Table 1).

Apart from the intrinsic interest of the behaviour of the biguanides under electron impact, [9] the study of their mass spectra was further prompted by the difficulties frequently encountered in obtaining satisfactory carbon and nitrogen analyses for the fluorine-containing compounds. All the biguanides investigated gave molecular

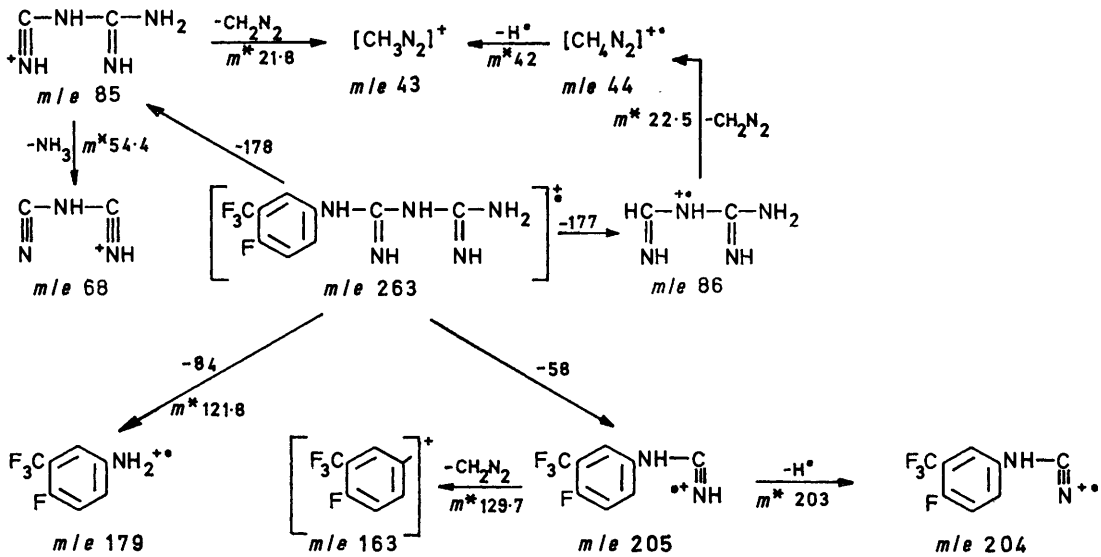
[6] R. von Walther and W. Grieshammer, *J. prakt. Chem.*, 1915, **251**, 92.
[7] I.C.I., B.P. 603,069/1948 and 618,613/1949.
[8] S. L. Shapiro, V. A. Parino, and L. Freedman, *J. Org. Chem.*, 1960, **25**, 371; H. C. Carrington, A. F. Crowther, and G. J. Stacey, *J. Chem. Soc.*, 1954, 1017.
[9] Ref. 4; see also A. G. Loudon, A. Maccoll, and K. S. Webb, International Mass Spectrometry Conference, Berlin, Sept. 1967.

TABLE 2

Mass spectral features * of some arylbiguanides ArNH·C(:NH)·NH·C(:NH)·NR¹R²

| Ion | Compd. (II) | Ar = 3-$F_3C$·$C_6H_4$ $R^1 = R^2 = Et$ | Ar = 3-$F_3C$·$C_6H_4$ $R^1 = Pr^i$, $R^2 = H$ | Ar = $R^1$ = 3-$F_3C$·$C_6H_4$ $R^2 = H$ | Ar = 3-$F_3C$·$C_6H_4$ $R^1$ = 8-quinolyl, $R^2 = H$ |
|---|---|---|---|---|---|
| $M^+$ | 263(100) | 301(35) | | 389(70) | 372(50) |
| $ArNH_2^+$ | 179(73) | 161(60) | 161(95) | 161(90) | 161(40) |
| $R^1NH_2^+$ | | | 59(25) | 161(90) | 144(100) |
| $Ar^+$ | 163(45) | 145(35) | 145(75) | 145(38) | 145(40) |
| $R^{1+}$ | | | | 145(38) | 128(25) |
| ArNH·C≡NH$^+$ | 205(50) | 187(10) | 187(50) | 187(84) | 187(40) |
| $R^1R^2N$·C≡NH$^+$ | | | | 187(84) | 170(40) |
| ArNH·C(:NH)·NH·C≡NH$^+$ | | | 229(40) | 229(100) | 229(40) |
| $R^1R^2$NH·C(:NH)·NH·C≡NH$^+$ | | | | 229(100) | 212(35) |
| +HN≡C·NH·C(:NH)·$NH_2$ | 85(82) | | | | |
| $[C_2H_3N_3]^+$ | 69(15) | | 69(34) | | |
| $[CH_3N_2]^+$ | 43(52) | 43(40) | 43(50) | 43(29) | 43(12) |
| $[CH_2N]^+$ | 28(19) | 28(35) | 28(39) | 28(24) | 28(18) |

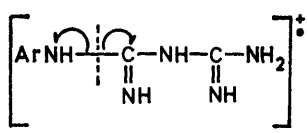
* A.E.I. MS9 instrument; *m/e* values, with relative intensities (%) in parentheses.




SCHEME Fragmentation of compound (II). The molecular ion peak appeared at *ca.* 8 eV, and the fragmentation was distinctly evident at *ca.* ⩾20 eV, a similar pattern applied for the other biguanides investigated.

ion peaks, which confirmed the structures assigned, with the exception of 1-isopropyl-5-(3-trifluoromethylphenyl)-biguanide, whose identification was in any case unequivocal.

Fragmentation of the biguanide portion of the compounds investigated led to some of the ions already reported by Beynon *et al.*;[4] however, differences in the nature and number of substituents at N-1 and N-5 gave rise to extensive variations in the patterns of fragmentation (Table 2). The mass spectrum of compound (II) (Scheme) is characteristic for those 1-arylbiguanides



(A)

which bear no substituent *ortho* to the biguanide system and none at N-5. The base peak corresponds to the molecular ion and the main fragments are (*a*) the peak corresponding to the rearrangement ion $ArNH_2^+$, and (*b*) the ion of *m/e* 85 formed by the simple rupture (A); this ion led to the ion *m/e* 43 which, as Beynon *et al.* suggested,[4] might possess the hybrid structures (IX). There was a

$$H_2\overset{+}{N}{-}C{\equiv}NH \rightleftharpoons NH_2{-}C{\equiv}\overset{+}{N}H \rightleftharpoons H_2\overset{+}{N}{=}C{=}NH$$

(IX)

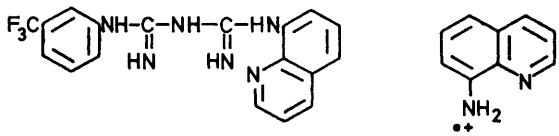
lack of noticeable splitting of $CF_3^+$ from the nucleus; the peak of *m/e* 69 was proved by high resolution measurement and peak matching (with introduction of perfluorokerosene) to have the elemental composition $C_2H_3N_3$. The surprising lack of formation of $CF_3$ ions by cleavage from a benzene ring was also shown by *m*-trifluoromethylaniline and *p*-trifluoromethyltoluene, which yielded no ions of *m/e* 69 in either case.

The mass spectra of 1-(2-bromo-5-trifluoromethylphenyl)biguanide and its 2-chloro-analogue both showed

an intense peak due to the ion resulting from extrusion of HBr from $ArNH_2^{+\cdot}$.

The mass spectrum of 1-isopropyl-5-(3-trifluoromethylphenyl)biguanide shows no molecular ion at 70 eV (although such an ion is distinct at 8 eV), and the base peak corresponds to loss of propene ($C_3H_6$). How ever, when there is no hydrogen available at N-1, *e.g.* in the case of 1,1-diethyl-5-(3-trifluoromethylphenyl)biguanide, the molecular ion (at 70 eV) reappears, although the base peak (*m/e* 141) still corresponds to a fragmentation species. This is also the case with symmetrical 1,5-diarylbiguanides such as 1,5-bis-(3-trifluoromethylphenyl)-biguanide, for which the base peak corresponds to the fragmentation ion $ArNH{\cdot}C(:NH){\cdot}NH{\cdot}C{\equiv}NH^{+\cdot}$.

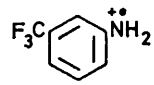
The behaviour of 1-(8-quinolyl)-5-(3-trifluoromethylphenyl)biguanide (X) exemplifies the fragmentation of unsymmetrical 1,5-diarylbiguanides; here, electron impact produced both aryl species and both of the two possible arylamine ions (XI) and (XII).



(X)



(XI)



(XII)

Several of the fluorinated 1-arylbiguanides investigated possess pharmacological properties which are highly dependent upon their structure: compounds (I) and (II), for instance, exhibit anti-inflammatory activity as well as the reported hypoglycaemia-inducing and anorexigenic effects; substitution of the $NH_2$ group in compound (I) with an isopropyl radical maintains anti-inflammatory activity but drastically reduces the hypoglycaemic potency. The highly fluorinated aminotriazine (VIII) displays fungistatic activity, completely inhibiting the *in vitro* growth of *Microsporum canis* and *Trichophyton mentagrophytes* at a concentration of 10 μg $ml^{-1}$.

## EXPERIMENTAL

1-(2,3,4,5-*Tetrafluorophenyl*)*biguanide*.—A solution of 2,3,4,5-tetrafluoroaniline hydrochloride (15 g) and freshly recrystallised cyanoguanidine (8 g) in hot water was heated under reflux for 2 h; the precipitate formed on cooling gave 1-(2,3,4,5-*tetrafluorophenyl*)*biguanide hydrochloride* (15 g), m.p. 242—243° (from water) (Found: C, 33·5; H, 2·8. $C_8H_8ClF_4N_5$ requires C, 33·6; H, 2·8%); basification with aqueous sodium hydroxide afforded the free base, which crystallised from water as needles of a *hydrate*, double m.p. 95° and 153° (Found: C, 36·3; H, 3·2. $C_8H_9F_4N_5O$ requires C, 36·0; H, 3·4%).

1-(p-*Trifluoromethylphenyl*)*biguanide*.—Similarly prepared from *p*-trifluoromethylaniline, this *base* formed needles, m.p. 142° (from water) (Found: C, 44·4; H, 4·4. $C_9H_{10}F_3N_5$ requires C, 44·1; H, 4·1%). The corresponding hydrochloride has been described by Shapiro *et al.*[2]

1-(3,5-*Bistrifluoromethylphenyl*)*biguanide*.—Prepared from 3,5-bistrifluoromethylaniline hydrochloride, this base crystallised as a *hydrate*, m.p. 113° (decomp. >95°) (Found: C, 36·3; H, 3·8; N, 21·2. $C_{10}H_{11}F_6N_5O$ requires C, 36·3; H, 3·6; N, 21·1%); the corresponding hydrochloride was unstable and easily dissociated in water.

1-(2-*Chloro*-5-*trifluoromethylphenyl*)*biguanide*.— Prepared from 2-chloro-5-trifluoromethylaniline hydrochloride, the *hydrochloride* of this base crystallised as prisms, m.p. 226° (from water) (Found: C, 34·5; H, 3·0. $C_9H_{10}Cl_2F_3N_5$ requires C, 34·2; H, 3·2%); the free *base* formed needles, m.p. 181° (from water) (Found: H, 3·1%; $M^+$, 270. $C_9H_9ClF_3N_5$ requires H, 3·3%; *M*, 279·5).

1-(2-*Bromo*-5-*trifluoromethylphenyl*)*biguanide*.— The *hydrochloride* formed needles, m.p. 232—233° (from water) (Found: C, 30·3; H, 2·8. $C_9H_{10}BrClF_3N_5$ requires C, 30·0; H, 2·8%); *base*, prisms, m.p. 202—203° (from aqueous ethanol) (Found: C, 33·2; H, 2·7. $C_9H_9BrF_3N_5$ requires C, 33·3; H, 2·8%).

1-*Isopropyl*-5-(3-*trifluoromethylphenyl*)*biguanide*.—A mixture of 1-cyano-3-(3-trifluoromethylphenyl)guanidine [3] (10 g), copper sulphate pentahydrate (9 g), and isopropylamine (12 g) in aqueous ethanol (1 : 1; 35 ml) was heated under reflux for 2 h with stirring, and the ethanol was then distilled off *in vacuo*. The violet precipitate was dissolved in hot hydrochloric acid, an aqueous solution (30 ml) of sodium sulphide (15 g) was added, and the precipitate of copper sulphide was filtered off. Basification of the filtrate with aqueous sodium hydroxide afforded the *biguanide* as needles (3 g), m.p. 178° (from aqueous ethanol) (Found: C, 50·1; H, 5·7. $C_{12}H_{16}F_3N_5$ requires C, 50·2; H, 5·6%). The *hydrochloride*, obtained by treating the base with hot dilute hydrochloric acid, crystallised as prisms, m.p. 204° (from water) (Found: C, 44·8; H, 5·2; N, 21·9. $C_{12}H_{17}ClF_3N_5$ requires C, 44·5; H, 5·3; N, 21·6%).

The 1,5-disubstituted biguanides listed in Table 2 were prepared in the same way unless otherwise stated.

1-(4-*Hydroxy*-6-*methyl*-2-*pyrimidyl*)-3-(m-*trifluoromethylphenyl*)*guanidine* (V).—Obtained from condensation of 1-(3-trifluoromethylphenyl)biguanide with ethyl acetoacetate [8] in ethanol in almost quantitative yield, this *guanidine* formed microprisms, m.p. 269—270° (from benzene–ethanol) (Found: C, 50·2; H, 4·0; N, 22·3. $C_{13}H_{12}F_3N_5O$ requires C, 50·2; H, 3·9; N, 22·5%); *hydrochloride*, prisms, m.p. 280—290° (decomp. >215°) (from water) (Found: C, 44·7; H, 3·8; N, 19·8. $C_{13}H_{13}ClF_3N_5O$ requires C, 44·9; H, 3·8; N, 20·1%).

2-*Amino*-4-*methyl*-6-(3-*trifluoromethylanilino*)-s-*triazine* (VI).—Similarly prepared by use of ethyl acetate, this *triazine* formed microprisms, m.p. 162—163° (from benzene–acetone) (Found: C, 49·0; H, 3·7. $C_{11}H_{10}F_3N_5$ requires C, 49·1; H, 3·8%); *hydrochloride*, microprisms, m.p. 217—218° (decomp. >160°) (from ethanol–ether) (Found: N, 22·6. $C_{11}H_{11}ClF_3N_5$ requires N, 22·9%). *Ethyl* 4-*amino*-6-(3-*trifluoromethylanilino*)-s-*triazine*-2-*carboxylate* (VII) was similarly obtained from ethyl oxalate in boiling ethanol as pale yellow prisms, m.p. 202° (from chloroform) (Found: C, 47·4; H, 3·6; N, 21·6. $C_{13}H_{12}F_3N_5O_2$ requires C, 47·7; H, 3·7; N, 21·4%); *hydrochloride*, bright microprisms, dissociating at 185° (Found: C, 42·8; H, 3·3. $C_{13}H_{13}ClF_3N_5O_2$ requires C, 42·7; H, 3·6%). 2-*Amino*-4-*trifluoromethyl*-6-(3-*trifluoromethylanilino*)-s-*triazine* (VIII), prepared from

ethyl trifluoroacetate, formed microprisms, m.p. 148° (Found: N, 21·5. $C_{11}H_7F_6N_5$ requires N, 21·7%).

1-(p-*Chlorophenyl*)-5-*isopropylbiguanide*.—To a suspension of sodium hydride (0·12 mol) in anhydrous tetrahydrofuran (20 ml), a solution of 1-(*p*-chlorophenyl)biguanide (0·1 mol) in anhydrous dimethoxyethane (20 ml) was added in portions with stirring, during 30 min, and the mixture was then heated at 50—60° to complete the formation of the sodio-derivative. After cooling, a solution of isopropyl iodide (0·15 mol) in tetrahydrofuran (30 ml) was added, and the mixture was heated at 60—70° for 12 h. The precipitate of sodium iodide was filtered off, the solvents were distilled off *in vacuo*, and the residue was taken up in ether and washed with water to remove unchanged 1-(*p*-chlorophenyl)-biguanide. The organic layer was extracted with hydrochloric acid (2N) and made basic with aqueous sodium hydroxide, and the 5-isopropyl derivative was taken up in ether and converted into its hydrochloride, leaflets, m.p. and mixed m.p. with an authentic sample, 243—244° (from aqueous ethanol); yield 45%.

*Mass Spectra*.—Spectra were determined with an Atlas CH-4 spectrometer and an A.E.I. MS9 high resolution spectrometer (70 eV) in the mass spectrometry department at Gif-sur-Yvette. The elemental compositions of the ions discussed (Table 1; MS 9 instrument) were checked with a Thomson TSN-218 high resolution spectrometer (mass spectrometry dept., Muséum National d'Histoire Naturelle, Paris); the same instrument was used for the peak-matching experiments with perfluorokerosene (used as a generator of $CF_3$ ions). The substances were inserted directly, and to avoid decomposition in the spectrometer source the ionisation temperatures used (approximately the m.p.s of the substances) were those at which no appreciable thermal decomposition had been observed.

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