Molecular Structure in the Solid State (X-Ray Crystallography) and in Solution (^{1}H and ^{13}C Nuclear Magnetic Resonance Spectroscopy) of 1,3-Diazetidines and Pentasubstituted Biguanides. X-Ray Molecular Structure of 2,4-Bis-(6-methyl-3-methylthio-5-oxo-4,5-dihydro-1,2,4-triazin-4-yl)-5,5-pentamethylene-1,3-diphenylbiguanide and 1,3-Bis-(*p*-chlorophenyl)-5-dimethylamino-2,4-bis-(6-methyl-3-methylthio-5-oxo-4,5-dihydro-1,2,4-triazin-4-yl)biguanide

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The molecular structures of a hexa- and a penta-substituted biguanide have been solved by X-ray crystallography: compound (**9c**) disubstituted at N(5) by (as) a piperidine ring, and compound (**11b**) monosubstituted at N(5) by a dimethylamino group. The X-ray structures can be used to explain the ^{1}H and ^{13}C NMR behaviour observed for these and related compounds. Consideration of the intramolecular hydrogen bonds between the NH and C=O groups is essential for the determination of the structure and spectroscopic properties of biguanides. In addition, the precursor diazetidines have also been studied by NMR spectroscopy: the *Z,Z*-isomer is always the most abundant, but minor quantities of the *E,E*-isomer can be observed.

In two previous papers, we have discussed the formation of (*Z,Z*)-1,3-diazetidine-2,4-diimines from iminophosphoranes and aryl isocyanates[1] and the reaction of the diazetidines with amines to yield N^1,N^2,N^3,N^4,N^5-pentasubstituted biguanides.[2] These papers dealt mainly with chemical aspects; physicochemical methods (X-ray and NMR) being used to establish the structure of these unexpected compounds.

We will now describe two new molecular structures of two biguanides and a careful ^{1}H and ^{13}C NMR study of a selected set of diazetidines and biguanides. As we will discuss afterwards, assignment problems in these series are by no means trivial. The synthetic sequence and the products' numbering schemes are shown in Scheme 1.

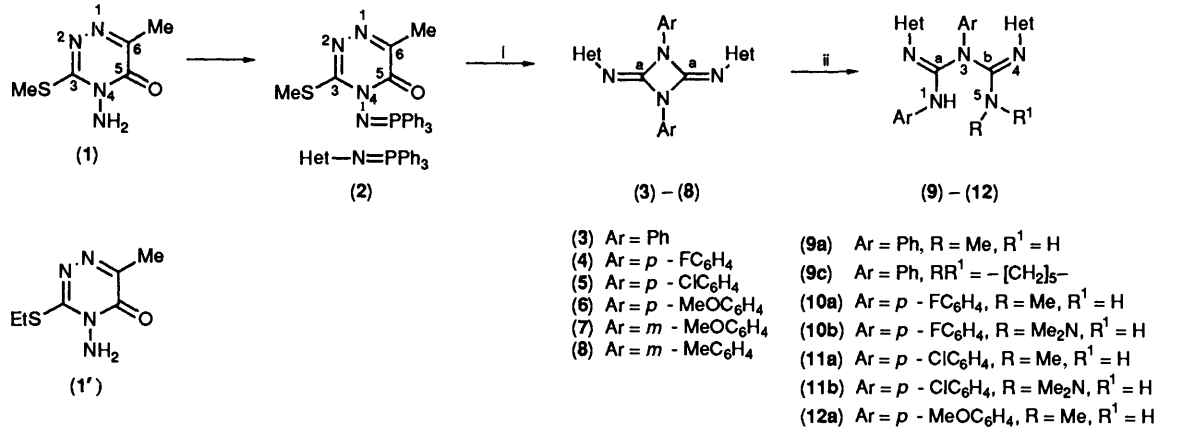
Ring opening of diazetidines by methylamine, 1,1-dimethylhydrazine, and piperidine yields biguanides series (**a**), (**b**), and (**c**), respectively. Compounds (**1'**), (**4**), (**8**), (**10a**), and (**10b**) have been prepared especially for this work; details of the remaining compounds can be found in the quoted references.[1,2]

Results and Discussion †

Crystal Structure of Biguanides (**9c**) *and* (**11b**).—Table 1 shows the selected geometrical parameters for both compounds, following the numbering system displayed in Figures 1 and 2.[3] Two independent molecules are present in compound (**9c**). The main differences between them are those concerning the conformation of the piperidine ring [see Figure 1(*a*, *b*) and Table 1], the puckering parameters[4] being Q = 0.559(6) and 0.565(6) Å and Θ = 179.4(7) and 3.7(6)° for molecules A and B, respectively. This is equivalent to a 180° rotation around C(7)–N(5). No significant differences have been found between the two compounds except for those involving intramolecular hydrogen bonds, which restrict the conformation of the molecules around the N(2)–C(6)–N(3)–C(7)–N(5) central part so as to give a pseudobinary axis through the C(20)···C(23) atoms in the case where two hydrogen bonds are present [compound (**11b**) and ref. 2]. This situation is also characterized by torsions N(8)–N(1)–C(6)–N(2) and N(5)–C(7)–N(4)–N(26) in compound (**11b**) and ref. 2, which are similar owing to the presence of H-bonds.

NMR Assignments of Starting Amine (**1**) *and Iminophosphorane* (**2**).—The use of compound (**1'**) and heteronuclear COSY experiments allowed us to assign all the signals of the protons and carbons of the heterocyclic parts of compounds (**1**) and (**2**) (Table 2). Carbon assignments were based on chemical shifts and ^{1}H–^{13}C coupling constants. Amongst the latter, the largest coupling showed by the SMe and SCH_2 carbons compared with that of the CMe and CH_2Me carbons is well documented.[5a] Carbon C(3) was unambiguously identified by its change of multiplicity in compounds (**1**) and (**1'**), and carbon C(6) by its large ^2J coupling constant and the absence of coupling with ^{31}P in compound (**2**). The signals of *C*-Me and *S*-

† Throughout this and the Experimental section, NMR spectroscopic data for (**9**)–(**12**) refer to the *crystallographic* numbering scheme and not the systematic scheme shown in Scheme 1.



Scheme 1. *Reagents:* i, ArNCO; ii, RR′NH.

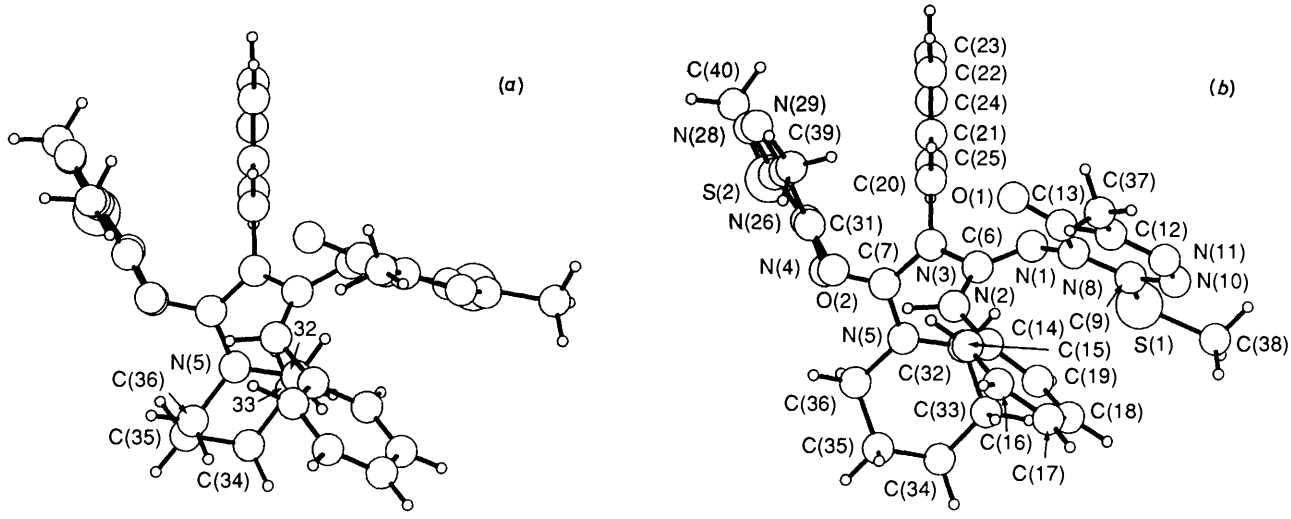


Figure 1. Molecular structure of compound (**9c**) with the numbering system used in the crystallographic work.

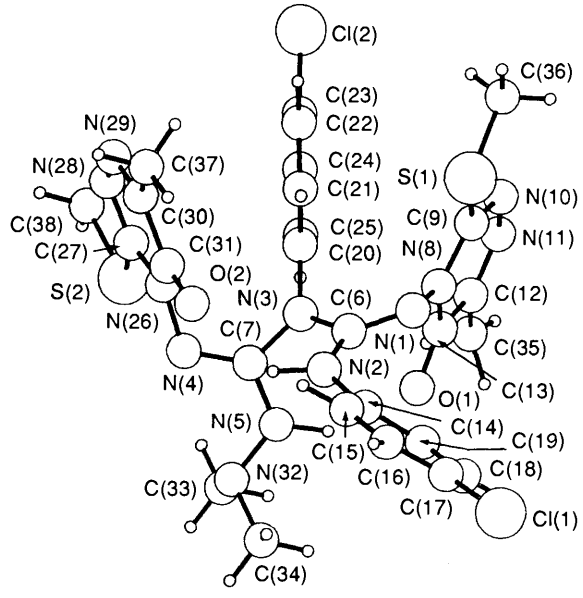


Figure 2. Molecular structure of compound (**11b**) with the numbering system used in the crystallographic work.

Me(Et) groups in the ^{1}H NMR spectra were assigned through 2D(^{1}H–^{13}C) experiments.

The most surprising result, which could have led to incorrect assignments, was that the formation of the iminophosphorane affects position 6 more than position 3. For instance, when the chemical shifts of compounds (**1**) and (**2**) are compared, the C(6) signal is shifted (2.7 ppm) to a greater extent than those of C(3) and C(5) (< 1.3 ppm). The same happens in the ^{1}H NMR spectra where the S–Me signal is unaffected whereas the C–Me signal is shifted by 0.2 ppm.

NMR Spectroscopy of (Z,Z)-1,3-*Diazetidine*-2,4-*diimines.*— The spectra of these compounds were only tentatively assigned[1] since they are of considerable complexity. Two aspects should be considered: (*i*) the assignment of the heterocyclic signals including the quaternary diazetidine carbon C(a); (ii) the assignment of the Ar signals with special attention paid to identification of the aryl groups near to (Ar-*Z*) and distant from (Ar-*E*) the heterocycles.

The first assignment was based on compound (**4**) which was prepared for this purpose. Heterocyclic carbons were identified by their ^{1}H–^{13}C coupling constants, including the absence of coupling for C(a). A COSY experiment identified the ^{1}H NMR signals of the C – Me and S–Me groups (the shielding of the C–Me protons being related to the proximity of Ar-*Z*; see later). The ^{13}C–^{19}F coupling constants are very characteristic of the relative positions of both nuclei in benzenes.[5b] It was possible to identify pairs of signals belonging to carbons *ipso* [C(1)], *ortho* [C(2) and C(6)], *meta* [C(3) and C(5)], and *para* [C(4)] (with regard to the diazetidine ring). The COSY experiment related

Table 1. Selected geometrical parameters.

Bond lengths (Å)

Compound	(9c) Mol. A	(9c) Mol. B	(11b)	Compound	(9c) Mol. A	(9c) Mol. B	(11b)
S(1)–C(9)	1.742(5)	1.750(6)	1.743(3)	S(2)–C(27)	1.752(6)	1.739(6)	1.724(4)
S(1)–Me	1.794(6)	1.801(6)	1.797(3)	S(2)–Me	1.791(7)	1.786(7)	1.795(7)
O(1)–C(13)	1.217(6)	1.219(6)	1.224(4)	O(2)–C(31)	1.229(6)	1.230(6)	1.221(5)
N(1)–C(6)	1.307(6)	1.293(6)	1.307(4)	N(4)–C(7)	1.287(6)	1.289(6)	1.308(4)
N(2)–C(6)	1.354(5)	1.359(7)	1.349(4)	N(5)–C(7)	1.352(7)	1.352(6)	1.331(4)
N(2)–C(14)	1.409(5)	1.414(5)	1.415(5)	N(5)–C(32)	1.457(6)	1.481(8)	
N(3)–C(6)	1.393(6)	1.409(5)	1.400(4)	N(5)–N(32)			1.413(4)
N(8)–C(9)	1.369(6)	1.376(6)	1.377(4)	N(3)–C(7)	1.412(7)	1.404(6)	1.416(4)
N(8)–C(13)	1.392(7)	1.378(7)	1.388(4)	N(26)–C(27)	1.363(6)	1.373(6)	1.377(5)
N(10)–C(9)	1.311(7)	1.302(6)	1.298(4)	N(26)–C(31)	1.380(7)	1.362(7)	1.385(5)
N(11)–C(12)	1.287(7)	1.302(7)	1.297(5)	N(28)–C(27)	1.297(8)	1.309(7)	1.301(4)
C(12)–C(13)	1.451(7)	1.454(6)	1.446(5)	N(29)–C(30)	1.307(8)	1.290(8)	1.292(6)
C(12)–Me	1.505(9)	1.492(9)	1.490(6)	C(30)–C(31)	1.448(8)	1.443(8)	1.457(5)
N(3)–C(20)	1.443(5)	1.456(6)	1.436(4)	C(30)–Me	1.506(9)	1.487(9)	1.487(8)

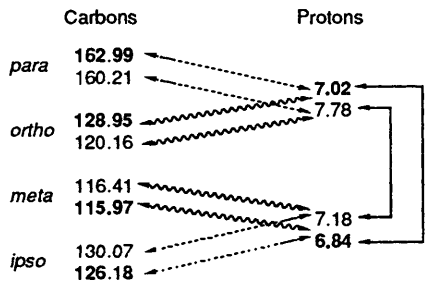
Bond angles (°)

Compound	(9c) Mol. A	(9c) Mol. B	(11b)
Me–S(1)–C(9)–N(8)	178.5(4)	−175.0(4)	−170.0(3)
Me–S(2)–C(27)–N(26)	−177.0(5)	−172.3(4)	−176.4(3)
C(6)–N(1)–N(8)–C(9)	135.7(4)	131.4(4)	129.9(3)
C(7)–N(4)–N(26)–C(27)	127.0(5)	126.6(5)	122.2(3)
N(8)–N(1)–C(6)–N(2)	−16.8(7)	−17.2(7)	164.6(3)
N(5)–C(7)–N(4)–N(26)	163.2(4)	165.7(4)	173.4(3)
C(7)–N(3)–C(6)–N(2)	−32.7(6)	−43.0(6)	−37.2(4)
H(2)–N(2)–C(6)–N(3)	−31(4)	−18(4)	−29(3)
C(32)/H(5)–N(5)–C(7)–N(3)	−36.4(7)	−30.9(7)	−20(4)
C(6)–N(3)–C(7)–N(5)	−44.9(6)	−48.1(6)	−49.9(4)
C(6)–N(3)–C(20)–C(25)	131.5(5)	125.6(5)	129.7(3)
C(7)–N(3)–C(20)–C(21)	130.3(5)	126.4(5)	125.8(3)
C(6)–N(2)–C(14)–C(15)	145.2(5)	136.3(5)	141.3(3)
C(36)/N(32)–N(5)–C(7)–N(3)	158.5(5)	174.4(4)	173.4(3)
N(5)–C(32)–C(33)–C(34)	−55.3(7)	58.2(7)	
C(32)–C(33)–C(34)–C(35)	54.3(7)	−57.7(7)	
C(33)–C(34)–C(35)–C(36)	−54.0(8)	54.6(8)	
C(34)–C(35)–C(36)–N(5)	54.6(7)	−53.1(7)	
C(35)–C(36)–N(5)–C(32)	−57.2(6)	55.1(6)	
C(36)–N(5)–C(32)–C(33)	57.9(6)	−57.5(6)	
N(2)···O(2)	2.843(5)	2.746(6)	2.854(4)
N(2)–H(2)	0.90(6)	0.89(5)	0.95(5)
H(2)···O(2)	2.00(6)	1.88(5)	2.01(5)
N(2)–H(2)···O(2)	156(6)	164(4)	151(4)
N(5)···O(1)			2.909(4)
N(5)–H(5)			0.92(5)
H(5)···O(1)			2.05(5)
N(5)–H(5)···O(1)			154(4)
O(3)···N(10)	3.12(2)		
O(4)···N(11)	2.89(2)		

protons of the AA′BB′X systems to their linked carbons (↜⇝) (Scheme 2).

An homonuclear COSY experiment (⟷) showed the relationship between aromatic protons: the δ_H 6.84 and 7.02 multiplets, on one hand, and the δ_H 7.18 and 7.78 multiplets, on the other, belong to the same Ar substituent. A COLOC experiment, using a value of J 7 Hz, related carbons and protons separated by three bonds (C–C–C–H) (⟵ - - - ⟶), allowing us to assign the *ipso* and *para* carbons.

For all the remaining compounds of Table 3, COSY (^{1}H–^{1}H) and (^{1}H–^{13}C) spectra were obtained enable us to assign the remaining signals. Thus, the signals belonging to each Ar



Scheme 2.

Table 2. Chemical shifts, coupling constants (Hz), and 2D correlations (⟿) of starting materials in $CDCl_3$.

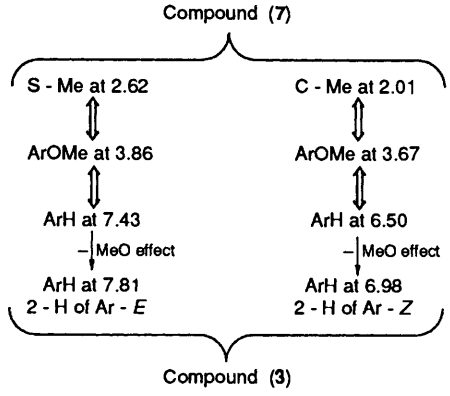
Compound	nucleus	C-Me	S-Me(Et)		NH_2	C-3	C-5	C-6
(1)	^1H	2.47	2.59		4.88			
	^{13}C	17.33 (^1J 129.8)	14.20 (^1J 142.1)			160.38 (^3J 3.5)[a]	152.57 (^3J 2.9)	154.11 (^2J 7.1)
(1′)	^1H	2.46	1.42 (CH_3)	3.22 (CH_2)	4.89			
	^{13}C	17.06 (^1J 130.0)	15.31 (^1J 128.5, ^3J 3.0)	25.33 (^1J 143.4, ^3J 4.5)		159.74 (^3J 3.7)[b]	152.41 (^3J 2.9)	153.71 (^2J 7.2)
(2)	^1H[c]	2.26	2.52					
	^{13}C	17.52 (^1J 129.6)	14.88 (^1J 141.9)			161.67 (^3J 3.7, ^3J 11.3[d])	153.52 (^3J 3.0, ^3J 3.8[d])	151.38 (^2J 7.1)

[a] Quartet (SMe). [b] Triplet (SEt). [c] The Ph_3P protons appear between δ 7.4–7.9. [d] Couplings with ^{31}P.

residue were identified (normal *vs.* bold characters, respectively, in Scheme 2), but which residue was Ar-*Z* and which was Ar-*E* remained to be determined. To solve this, NOESY and NOE differential spectra were recorded.

Unfortunately, for both compounds (**3**) and (**4**), these experiments were inconclusive. In all probability the *ortho* and *meta* protons of the Ar residues are mutually too close together to enable us to observe an NOE effect when the methyl groups of the heterocycles are irradiated.[6] To avoid this problem, compounds (**7**) and (**8**) with a substituent, MeO or Me, in the *meta* position were analysed. If the molecular geometry of compound (**5**), determined by X-ray crystallography,[1] is maintained in the *meta* analogues (**7**) and (**8**), the *C*-methyl group of the heterocycle would be much closer to R^3-*Z* than to R^3-*E*, while the reverse is true for the *S*-methyl group. An examination of the off-diagonal spots in the NOESY spectra showed that this is clearly the case in compound (**7**).

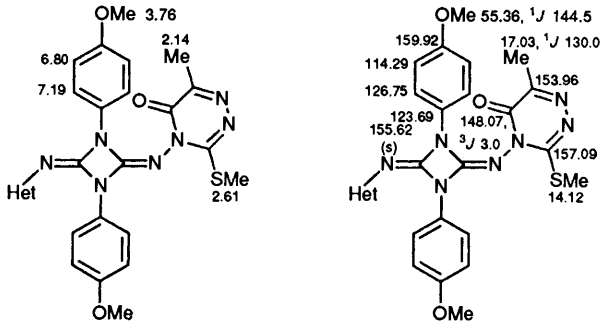
The following sequence of experiments allowed us to identify the Ar-*Z* and Ar-*E* substituents for all compounds mentioned in Table 3 (Scheme 3).



Scheme 3. (⇔ NOESY).

Thus, from these results concerning the structure of the 1,3-diazetidine-2,4-diimines in solution, the following conclusions can be drawn:

(i) The most abundant compound is always the *Z,Z*-isomer, but in some spectra signals corresponding to the *E,E*-isomer can be seen (signals for only one aryl group). For instance, in the case of compound (**6**), we have identified all the signals of the minor isomer.



(6)

^1H and ^{13}C NMR data for compound (**6**).

The values for the nuclei of the Ar residue in the *E,E*-isomer are intermediate between those of Ar-*Z* and Ar-*E* in the *Z,Z*-isomer. They are very near the averaged values for protons and carbons of all positions, except for the *ortho* signals (2 and 6) where the chemical shifts of Ar-*Z* are abnormal.

(ii) In the *Z,Z*-isomer, the Ar-*Z* group cannot rotate freely, but due to the 'symmetry' of its environment (see Figure 3)[1] the *ortho* and *meta* protons and carbons are isochronous. Reciprocally, when Ar-*Z* is *para* substituted, both Het residues are also equivalent.

(iii) The spatial relationships depicted in Figure 3 explain why the *C*-Me groups appear shielded in *Z,Z*-diazetidines (**3**)–(**8**) (averaged value of Table 3, δ 2.00) compared with the starting amine (**1**) (δ 2.47, Table 2) and with the *E,E*-isomer [δ 2.14; structure (**6**)] while the S-Me groups are rather insensitive to these changes (δ 2.61 ± 0.02). Reciprocally, the proximity of both heterocycles shielded all the protons (C–H, C–Me, C–OMe) of Ar-*Z*. This was particularly important for the *ortho* protons.

NMR Spectroscopy of Biguanides.—Contrary to that for diazetidines,[1] the ^1H and ^{13}C NMR study of the biguanides had been carefully carried out in our previous work.[2] The most striking observation was that *ortho* and/or *meta* protons and carbons of the N(3)-Ar residue are anisochronous in these compounds due both to restricted rotation and to chirality of

Table 3. ^1H and ^{13}C-values for (*Z*,*Z*)-1,3-diazetidine-2,4-diimines in $CDCl_3$.

No.	Nucleus	C-Me	S-Me	C-3	C-5	C-6	C-a	Ar-*E* 1	2	3	4	5	6	Ar-*Z* 1	2	3	4	5	6
(3)	^1H	1.95	2.63						7.81	7.47	7.27	7.47	7.81		6.98	7.14	7.24	7.14	6.98
	^1H[a]	1.97	2.59						7.84	7.60	7.37	7.60	7.84		7.10	7.25	7.33	7.25	7.10
	^{13}C	17.02 (^1J 130.0)	14.33 (^1J 143.5)	157.24 (^3J 4.2)	148.10 (^3J 3.1)	154.15 (^2J 7.2)	153.05 (s)	134.10	118.01	129.39	125.60	129.39	118.01	130.31	126.56	128.79	130.29	128.79	126.56
(4)	^1H	2.05	2.63						7.78 ($^3J_{HH}$ 9.01, $^3J_{HF}$ 8.30, $^4J_{HH}$ 2.26, $^4J_{HF}$ 4.53)	7.18		7.18	7.78		7.02 ($^3J_{HH}$ 8.95, $^3J_{HF}$ 7.79, $^4J_{HH}$ 2.27, $^4J_{HF}$ 4.58)	6.84		6.84	7.02
	^{13}C	17.06 (^1J 130.1)	14.35 (^1J 143.5)	157.15 (^3J 4.2)	148.13 (^3J 3.1)	154.18 (^2J 7.1)	153.07 (s)	130.7 (^4J 2.8)	120.16 (^3J 8.2)	116.41 (^2J 22.9)	160.21 (^1J 246.4)[b]	116.41	120.16	126.18 (^4J 3.6)	128.95 (^3J 9.1)	115.97 (^2J 23.0)	162.99 (^1J 254.5)[b]	115.97	128.95
(5)	^1H	1.96	2.62						7.75	7.44		7.44	7.75		6.92	7.11		7.11	6.92
	^{13}C	17.01	14.33	157.17	148.08	154.32	152.56	132.58	119.43	128.01	129.78	128.01	119.43	128.72	129.69	129.13	132.49	129.13	129.69
(6)	^1H	2.03	2.60						7.69	6.98	3.82 (OMe)[c]	6.98	7.69		6.93	6.59	3.69 (OMe)[c]	6.59	6.93
	^{13}C	16.89 (^1J 129.9)	14.12 (^1J 143.3)	157.09 (^3J 4.2)	148.03 (^3J 3.1)	153.96 (^2J 7.1)	154.02 (s)	126.95	120.02	114.42	157.28	114.42	120.02	122.30	127.98	113.70	160.54	113.70	127.98
(7)	^1H[d]	2.01	2.62						7.44	3.86 (OMe)[e]	6.83	7.38	7.42		6.52	3.67 (OMe)[f]	6.79	7.02	6.56
	^{13}C	16.98 (^1J 130.0)	14.25 (^1J 143.3)	157.08 (^3J 4.1)	148.00 (^3J 3.0)	154.19 (^2J 7.0)	153.01 (s)	134.98	103.75	160.17	111.52	130.20	110.11	131.13	111.25	159.46	116.83	129.39	118.31
(8)	^1H	1.98	2.62						7.63	2.43 (Me)[g]	7.08	7.38	7.63		6.78	2.17 (Me)[h]	7.03	7.03	6.78
	^{13}C	16.95 (^1J 129.9)	14.22 (^1J 143.4)	157.11 (^3J 4.2)	148.01 (^3J 3.0)	154.06 (^2J 7.2)	153.26 (s)	133.92	118.42	139.42	126.31	129.09	115.07	130.72	126.70	139.17	128.45	130.14	123.09

[a] In [$^2H_6$]acetone. [b] These couplings constants involving Ar-*Z* and Ar-*E* are ^{13}C–^{19}F couplings. [c] In the ^{13}C NMR spectrum, the methoxy group appears at δ_C 55.32 (^1J 144.0) and 55.39 (^1J 144.7). [d] The ^1H chemical shifts and proton–proton coupling constants of compound (7) have been calculated using the PANIC program (RMS error 0.05 Hz); Ar-*E*: $J_{2,4}$ 2.44, $J_{2,6}$ 2.06, $J_{4,5}$ 8.40, $J_{4,6}$ 0.87, $J_{5,6}$ 8.15; Ar-*Z*: $J_{2,4}$ 2.41, $J_{2,6}$ 2.10, $J_{4,5}$ 8.49, $J_{4,6}$ 0.87, $J_{5,6}$ 7.82 Hz. [e] In ^{13}C NMR spectrum this methoxy group appears at δ_C 55.35 (^1J 144.5). [f] In ^{13}C NMR spectrum, this methoxy group appears at δ_C 55.25 (^1J 144.5). [g] In ^{13}C NMR spectrum, this methyl group appears at δ_C 21.45. [h] In ^{13}C NMR spectrum, this methyl group appears at δ_C 20.60.

Table 4. ^1H- and ^{13}C-values of biguanides in $CDCl_3$.

No.	Nucleus	C-Me	S-Me	C-3	C-5	C-6	C-a	C-b	Ar-2 1	2	3	4	5	6
(9a)	^1H[a]	2.45	2.17							7.684	7.424	7.175	7.424	7.684
		2.47	2.18											
	^{13}C	17.63	13.59	158.91	150.76	152.95	153.03	156.38	138.51	120.51	129.10	124.26	129.10	120.51
		17.69	13.64	159.23	151.48	153.13	(s)	(^3J 3.6)						
(9c)	^1H	2.58	2.21							7.1	7.1	7.02	7.1	7.1
		2.04	2.46											
	^{13}C	17.41	13.50	159.00	151.44	153.66	153.08	158.22	139.40	124.82	129.06	126.60	129.06	124.82
		17.83	14.20	157.85	147.01	153.79	(s)	(br)						
(10a)	^1H	2.46	2.21							7.63	7.07		7.07	7.63
		2.47	2.22							($^3J_{HH}$ 9.0, $^3J_{HF}$ 8.5, $^4J_{HH}$ 2.3, $^4J_{HF}$ 4.6)				
	^{13}C	17.63	13.65	158.67	150.70	152.88	153.04	156.32	134.32	122.23	115.76	159.37	115.76	122.23
		17.63	13.69	159.09	151.43	153.17	(s)	(^3J 3.6)	(^4J 2.8)	(^3J 7.9)	(^2J 22.5)	(^1J 244.2)		
(10b)	^1H	2.46	2.22							7.64	7.08		7.08	7.64
		2.46	2.23							($^3J_{HH}$ 9.1, $^3J_{HF}$ 8.6, $^4J_{HH}$ 2.2, $^4J_{HF}$ 4.7)				
	^{13}C	17.35	13.49	158.57	150.70	152.78	152.64	154.22	134.18	121.75	115.72	159.23	115.72	121.75
		17.39	13.53	158.94	150.49	152.87	(s)	(^2J 6.6)	(^4J 2.7)	(^3J 7.9)	(^2J 22.7)	(^1J 244.3)		
(11a)	^1H	2.46	2.23							7.61	7.33		7.33	7.61
		2.48	2.23											
	^{13}C	17.57	13.70	158.46	150.54	152.83	152.77	156.05	136.84	121.63	129.03	129.32	129.03	121.63
		17.61	13.74	158.95	151.40	152.97	(s)	(^3J 3.5)						
(11b)	^1H	2.46	2.23							7.62	7.34		7.34	7.62
		2.47	2.24											
	^{13}C	17.48	13.64	158.40	150.71	152.78	152.31	154.01	136.73	121.22	129.04	129.27	129.04	121.22
		17.44	13.67	158.86	150.39	152.88	(s)	(^2J 6.7)						
(12a)	^1H[b]	2.45	2.18							7.60	6.92		6.92	7.60
		2.47	2.19											
	^{13}C[c]	17.58	13.58	159.02	150.97	152.85	153.52	156.78	131.67	122.24	114.24	156.47	114.24	122.24
		17.58	13.61	159.25	151.50	153.03	(s)	(^3J 3.6)						

[a] Couplings constants, Ar-2, $J_{2,3} = J_{4,5}$ 8.21, $J_{2,4} = J_{4,6}$ 1.12, $J_{2,5} = J_{3,6}$ 0.53, $J_{2,6}$ 2.08, $J_{3,4} = J_{4,5}$ 7.45, $J_{3,5}$ 1.84; Ar-3, $J_{2,3}$ 7.88, $J_{2,4}$ 55.49. Italicized values indicate the signals of Ar-3 which split.

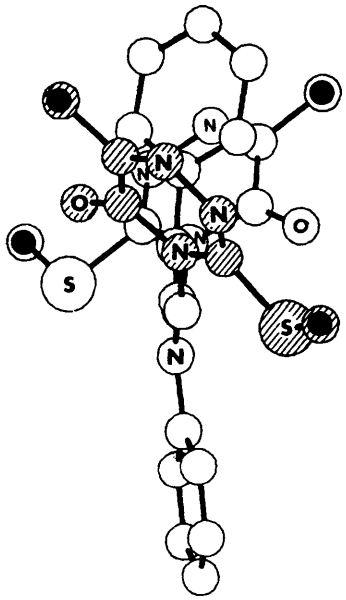


Figure 3. A lateral view (*ca.* 90° from the previous figures) of a diazetidine (black circles, methyl groups).

the biguanide [helical conformation of the N(3)–C(a)–N(3)–C(b)–N(5) central part]. However, some problems remained unsolved:

(i) If the identification of N(2)–Ar and N(3)–Ar signals was successfully achieved using a symmetric compound with N(5) bearing the same Ar residue as N(2), the assignment of *ortho* and *meta* nuclei in both aryl groups was based only on substituent effects.

(ii) On changing R from methyl (**a** series) to dimethylamino (**b** series) why does the splitting of some signals in the ^1H NMR spectrum change and do these changes involve the *ortho* and *meta* positions of the N(3)–Ar residue or the N(2)–Ar and N(3)–Ar residues?

(iii) Why, when RR′ $= -[CH_2]_5-$ (piperidine, **c** series), are some signals broadened in the ^1H NMR spectrum (those of the piperidine ring) and why, in the ^{13}C NMR spectrum, are the signals corresponding to the aryl residues considerably shifted without splitting?

These questions had to be answered first and so we decided:

(i) To record the NMR spectra of series (**9**) and (**10**) and to use the coupling with the *para* substituent, H or F, to assign the remaining signals.

(ii) To determine the X-ray structure of compound (**11b**) and to use the *p*-fluoro derivative (**10b**) for NMR purposes.

(iii) To determine the X-ray structure of the piperidine derivative (**9c**).

Table 4 summarizes the NMR results obtained. Homo- and hetero-nuclear COSY experiments will not be discussed, and we will only, as an illustration, comment that the anisochronous protons and carbons of compound (**11b**) are related in the following manner: 6.58 ⟿ 123.79 and 6.68 ⟿ 124.20. The only rigorous analysis of the spin systems was carried out on compound (**9a**). For the remaining compounds the values of Table 4 correspond to first-order analysis of the 200 *and* 300 MHz spectra and to heteronuclear COSY experiments.

The data in Table 4 shows that:

Ar-3						NH		N(5)-R
1	2	3	4	5	6	2	5	
	6.825	*7.088*	7.045	*7.114*	6.820	9.55 (s)	7.49 (^3J 4.9)	Me 3.13 (^3J 4.9)
134.51	*122.93*	128.94	128.01	128.94	*122.97*			Me 30.00
	6.89	7.08	6.95	7.08	6.89	9.71 (s)		piperidine 4.08 (α, eq), 3.37 (α, ax), 1.89 (β) 4.27 (α, eq), 3.72 (α, ax), 1.71 (β)
136.05	121.35	128.33	125.51	128.33	121.35			piperidine 48.74 (α), 25.25 (β), 24.74 (γ) 49.09 (α), 27.59 (β)
	6.76	6.69		6.72	6.75	9.53 (s)	7.50 (^3J 4.8)	Me 3.13 (^3J 4.8)
130.54 (^4J 3.1)	*124.83* (^3J 8.7)	116.00 (^2J 23.3)	161.17 (^1J 249.5)	116.00	*124.88*			30.00
	6.64	6.75		6.75	*6.75*	9.62 (s)	8.50 (s)	Me_2N 2.73
130.06 (^4J 3.1)	*124.35* (^3J 8.7)	115.99 (^2J 23.2)	161.12 (^1J 250.5)	115.99	*124.78*			Me_2N 47.09
	6.64	*7.00*		*7.03*	6.64	9.63 (s)	7.52 (^3J 4.7)	Me 3.12 (^3J 4.7)
132.83	*124.23*	129.03	133.63	129.03	*124.31*			Me 30.00
	6.58	7.02		7.02	*6.68*	9.73 (s)	8.52 (s)	Me_2N 2.73
132.36	*123.79*	129.04	133.78	129.04	*124.20*			Me_2N 47.13
	6.62	*6.49*		*6.52*	6.62	9.35 (s)	7.46 (^3J 4.8)	Me 3.12 (^3J 4.8)
127.43	124.51	*114.06*	158.80	*114.20*	124.51			Me 29.91

1.11, $J_{2,5}$ 0.49, $J_{2,6}$ 2.71, $J_{3,4}$ 7.50, $J_{3,5}$ 1.85, $J_{3,6}$ 0.53, $J_{4,5}$ 7.48, $J_{4,6}$ 1.13, $J_{5,6}$ 8.13 Hz. [b] MeO groups at δ 3.64 and 3.81. [c] MeO groups, both at δ

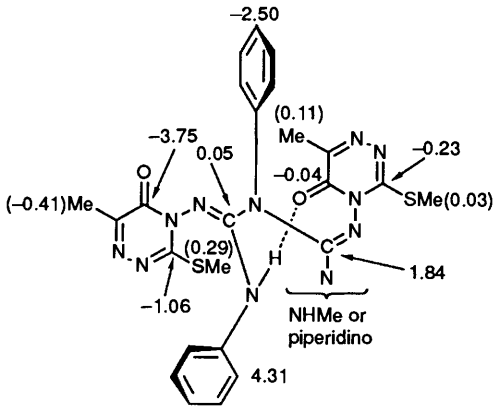


Figure 4.

(i) The assignment of protons in series (**9**) and (**10**) results from analysis of the spectra and from that of the corresponding carbons from heteronuclear COSY experiments and ^{13}C–^{19}F coupling constants [series (**10**)]. Thus, all the data in Table 4 are unambiguous.

(ii) It is clear that it is always the signals of Ar-3 which split. When the substituent on N(5) is a methyl group (**a** series) the splitting affects *meta* protons H(3) and H(5) (δ 0.03) whereas when the substituent is a dimethylamino group (**b** series) the *ortho* protons H(2) and H(6) split off (δ 0.10).

The proton chemical shift of the N(2)–H signals changes by 0.1 ppm between the *p*-fluoro and *p*-chloro series and between the methyl and dimethylamino series, and that of N(5)–H does so by 1.0 ppm between the methyl and dimethylamino series.

Comparison of the ^{13}C NMR spectra of compounds (**10a**), (**10b**), (**11a**), and (**11b**) shows some interesting features. Carbon C(b) is coupled with the methyl group ($^3J \simeq 3.6$ Hz) but not with the N(5)–H proton (**a** series), whereas in the **b** series the only coupling observed is with the N(5)–H proton ($^2J \simeq 6.6$ Hz). The effect of replacement of a methyl group by a dimethylamino group [Δδ = δ (**b**) − (**a**)] is important only for C(b) (Δδ − 2.1 ppm), but it is worth noting that of the four *ortho* and *meta* carbons of N(3)–Ar *one* of the anisochronous *ortho* carbons C(2) is shifted much more (Δδ ≃ −0.48 ppm) than are the other three (Δδ ≃ −0.05 ppm).

(iii) Both the ^1H and the ^{13}C NMR spectra of compound (**9c**) show large differences compared with those of other biguanides (Table 4). In the ^1H spectrum, the most striking difference concerns the chemical shifts of the Het residues. One of them is quite normal (*C*-Me at δ 2.58, S-Me at δ 2.21) whereas the other is very different (*C*-Me at δ 2.04, S-Me at δ 2.46) and resembles values for the diazetidines given in Table 3. The signals of the Ar-2 protons are slightly broadened. In the ^{13}C spectrum, besides the S-Me signals at δ_C 14.20 (still of the diazetidine type) one of the phenyl groups [that on N(2)] has all its signals slightly broadened (^3J coupling constants cannot be measured) whereas the other phenyl group [that on N(3)] shows well resolved signals. Finally, the piperidine signals, both in the ^1H and the ^{13}C spectra, are broad but this did not prevent us from observing that α and β signals are split. In summary, these spectra show compound (**9c**) to be a very different biguanide which retains a chiral element but where hindered rotations have most effect on the piperidine rather than on the Ar groups.

Relationships between the Molecular Structure of Biguanides

Table 5. Crystal-analysis parameters at room temperature.

Crystal data	(**9c**)	(**11b**)
Formula	$2(C_{29}H_{33}H_{11}O_2S_2)\cdot C_2H_6O$	$C_{26}H_{28}Cl_2N_{12}O_2S_2$
Crystal habit	Transparent plate	Yellow transparent prism
Crystal size/mm	0.33 × 0.20 × 0.07	0.40 × 0.27 × 0.17
Symmetry	Triclinic, $P\bar{1}$	Monoclinic, $P2_1/c$
Unit-cell determination	Least-squares fir from 88 reflections ($\theta < 45°$)	Least-squares fit from 97 reflections ($\theta < 45°$)
Unit-cell dimensions	21.695 2(11), 13.104 3(5), 12.219 7(5) Å 98.154(4), 102.748(4), 77.327(5)°	15.734 9(8), 12.201 0(3), 16.944 3(7) Å 103.377(3)
Packing V/Å^3, Z	1 309.9(3), 2	3 164.7(2), 4
D_c/g cm^{-3}, M, F(000)	1.322, 1 309.61, 1 380	1.418, 675.61, 1 400
μ/cm^{-1}	18.19	34.75
Experimental data		
Technique	Four-circle diffractometer Bisecting geometry Graphite-oriented monochromator: Cu-K_α $\omega/2\theta$ scans, scan width 1.6° Detector apertures 1.0 × 1.0°	
Total measurements	Up to 60° in θ	Up to 65° in θ
Speed	1 min/reflec.	1 min/reflec.
Number of reflections		
Independent	9 801	5 387
Observed	6 106 [$3\sigma(I)$ criterion]	3 722 [$3\sigma(I)$ criterion]
Standard reflections	2 reflections every 90 min No variation	
Max-min transmission factors	1.271–0.650 (DIFABS[8])	1.235–0.807 (DIFABS[8])
Solution and refinement		
Solution	Direct methods	Direct methods
Refinement	LS on F_{obs}, 7 blocks	LS on F_{obs}, 2 blocks
Parameters	1 074 (see text)	509
Number of variables	5 032	3 213
Degrees of freedom	5.7	7.3
Ratio of freedom	Difference synthesis	Difference synthesis
H Atoms	0.22	0.34
Final shift/error	Empirical as to give no trends in $\langle w\Delta^2F\rangle$	*vs.* $\langle\lvert F_{obs}\rvert\rangle$ or $\langle\sin\theta/\lambda\rangle$
Weighting scheme	U[C42] 0.255(9) Å^2	U_{11}[C37] 0.155(6) Å^2
Max. thermal value	0.74 e Å^{-3} near O(3)	0.38 e Å^2
Final ΔF peaks	0.060, 0.068	0.043, 0.051
Final R and R_w		
Computer and programs	VAX 11/750, XRAY76 System,[9] Multan80[10]	
Scattering factors	Int. Tables for X-Ray Crystallography[11]	

(**9c**) *and* (**11b**) *in the Solid State and their NMR Behaviour in Solution.*—The structures of biguanides (**9a**)[2] and (**11b**) (Figure 2) are almost identical: the torsion angles which characterize the central pseudo-five-membered ring [N(2)–C(6)–N(3)–C(7)–N(5)], the Het residues [N(1)–N(8) and N(4)–N(26)], and the aryl group on N(3) [N(3)–C(20)] are very close (less than 4° difference). Only the aryl group on N(2) has a different conformation, which changes from C(6)–N(2)–C(14)–C(15) 129.9° in compound (**9a**)[2] to 141.3° in compound (**11b**) (Table 1), but it is difficult to decide if this modification, concerning as it does a non-hindered aryl group, is of crystal-packing origin or if it is an effect of the nearby N(5)-dimethylamino group.

Thus, if the differences in the NMR spectrum, which relate to *ortho* signals of N(3)–Ar and the coupling between C(b) and N(5)–H, do not correspond to a conformational effect, the only other possible explanation is an electronic effect. The replacement of a methyl group on N(5) by a dimethylamino group increases the acidity of N(5)–H,[7] which in turn becomes more tightly bonded to O(1). The strengthening of the intramolecular hydrogen bond (IMHB) explains why the N(5)–H does not exchange with the solvent and why coupling with C(b) is observed in ^{13}C NMR spectrum. The Het residue on N(1) [to which O(1) belongs] is modified by the IMHB and it, in turn, probably modifies the neighbouring N(3)–Ar.

The molecular structures (two independent molecules in the unit cell) of compound (**9c**) (Figure 1) are very different from those of the biguanides (**9a**) and (**11b**): the IMHB N(5)–H···O(1)=C(13) is broken and this results in a dramatic modification of the structure.

The Het residue on N(1) changes its configuration about the N(1)–C(6) double bond from *Z* in compound (**11b**) [N(8)–N(1)–C(6)–N(2) 164.6°] to *E* in compound (**9c**) [N(8)–N(1)–C(6)–N(2) −17.0°, $\Delta\varphi$ 181.6°]. The breaking of one of the IMHBs considerably modifies the signals belonging to the Het residue on N(1), whereas the other Het residue, that on N(4), still hydrogen-bonded to N(2)–H, is much less affected. In Figure 4 are gathered the more significant $\Delta\delta$-values in ppm [$\Delta\delta$ δ(**9c**) − δ(**9a**); in parentheses, ^{1}H NMR; otherwise, ^{13}C NMR].

The carbons of the carbonyl groups C(5), of compound (**9c**) appear at δ_C 151.4 (IMHB) and δ_C 147.0, similar to those of diazetidines (Table 3) where no IMHB exists. The aryl group on N(2) presents signals slightly broadened due to a 'slow' rotation about the N(2)–C(14) bond (Figure 1). The situation is very different from that found in 'normal' biguanides, such as

Table 6. Final atomic co-ordinates for compound (**9c**).

Atom	*x*	*y*	*z*	Atom	*x*	*y*	*z*
S(1)A	0.330 75(6)	0.546 02(11)	0.663 13(11)	O(1)B	0.834 32(18)	0.783 76(29)	0.707 53(30)
S(2)A	−0.022 44(7)	0.924 48(13)	0.835 20(13)	O(2)B	0.631 78(18)	0.802 68(29)	0.578 66(36)
O(1)A	0.330 27(17)	0.898 60(28)	0.859 65(33)	N(1)B	0.821 96(17)	0.827 62(29)	0.489 22(33)
O(2)A	0.195 56(18)	0.952 68(28)	1.042 97(31)	N(2)B	0.743 44(18)	0.724 26(28)	0.498 82(37)
N(1)A	0.270 94(17)	0.727 99(29)	0.768 85(31)	N(3)B	0.714 53(17)	0.897 47(27)	0.460 40(32)
N(2)A	0.276 52(19)	0.765 73(30)	0.969 20(31)	N(4)B	0.599 45(18)	0.931 25(33)	0.403 08(34)
N(3)A	0.179 74(17)	0.788 90(28)	0.841 54(29)	N(5)B	0.660 39(20)	0.834 31(34)	0.283 74(36)
N(4)A	0.098 54(20)	0.841 34(33)	0.954 51(35)	C(6)B	0.764 88(22)	0.810 43(33)	0.484 17(38)
N(5)A	0.161 16(22)	0.678 08(32)	0.960 35(35)	C(7)B	0.656 33(22)	0.889 11(34)	0.385 22(40)
C(6)A	0.246 57(21)	0.758 35(33)	0.859 56(37)	N(8)B	0.872 58(17)	0.754 08(28)	0.544 96(33)
C(7)A	0.144 44(23)	0.773 25(37)	0.919 94(40)	C(9)B	0.923 46(22)	0.711 59(36)	0.491 83(42)
N(8)A	0.337 11(17)	0.727 08(30)	0.785 42(31)	N(10)B	0.975 37(19)	0.649 38(33)	0.537 70(37)
C(9)A	0.373 47(22)	0.640 72(38)	0.737 19(39)	N(11)B	0.979 62(21)	0.623 86(35)	0.644 83(39)
N(10)A	0.435 78(20)	0.628 86(36)	0.744 54(38)	C(12)B	0.933 49(25)	0.664 30(39)	0.699 70(44)
N(11)A	0.466 27(21)	0.707 31(41)	0.806 63(43)	C(13)B	0.876 25(23)	0.739 15(37)	0.655 79(42)
C(12)A	0.432 98(25)	0.792 98(45)	0.845 93(47)	C(14)B	0.778 65(22)	0.620 29(35)	0.507 14(42)
C(13)A	0.363 33(24)	0.815 07(41)	0.832 32(42)	C(15)B	0.769 66(28)	0.566 20(42)	0.590 06(50)
C(14)A	0.336 99(22)	0.707 47(37)	1.015 99(38)	C(16)B	0.801 74(34)	0.461 54(49)	0.597 88(61)
C(15)A	0.375 99(26)	0.756 82(41)	1.104 28(43)	C(17)B	0.842 07(32)	0.414 01(46)	0.525 59(66)
C(16)A	0.434 67(26)	0.700 64(48)	1.154 28(48)	C(18)B	0.851 29(28)	0.469 03(43)	0.444 64(56)
C(17)A	0.455 30(26)	0.597 66(47)	1.116 45(47)	C(19)B	0.818 80(25)	0.570 16(38)	0.433 78(46)
C(18)A	0.416 20(26)	0.548 95(39)	1.028 66(44)	C(20)B	0.723 26(20)	1.001 13(33)	0.514 51(38)
C(19)A	0.357 13(23)	0.603 75(37)	0.979 22(40)	C(21)B	0.740 07(23)	1.015 25(38)	0.630 11(42)
C(20)A	0.145 76(21)	0.838 32(34)	0.741 25(36)	C(22)B	0.747 37(27)	1.114 28(44)	0.682 25(46)
C(21)A	0.167 12(24)	0.921 38(39)	0.712 94(44)	C(23)B	0.738 12(31)	1.196 33(42)	0.617 60(57)
C(22)A	0.135 34(27)	0.968 71(45)	0.616 52(53)	C(24)B	0.722 21(31)	1.181 22(42)	0.502 35(57)
C(23)A	0.081 78(27)	0.934 62(51)	0.551 44(50)	C(25)B	0.714 46(24)	1.082 53(39)	0.449 63(42)
C(24)A	0.060 08(25)	0.854 12(46)	0.580 85(44)	N(26)B	0.596 65(18)	0.965 73(32)	0.517 67(34)
C(25)A	0.092 76(23)	0.803 37(37)	0.676 46(41)	C(27)B	0.567 29(22)	1.068 51(40)	0.538 74(43)
N(26)A	0.095 89(19)	0.945 55(31)	0.934 18(33)	N(28)B	0.556 44(22)	1.108 37(38)	0.638 74(43)
C(27)A	0.038 56(26)	0.998 04(43)	0.879 26(45)	N(29)B	0.576 56(24)	1.045 45(43)	0.726 33(41)
N(28)A	0.027 84(26)	1.096 31(42)	0.861 80(42)	C(30)B	0.602 04(27)	0.947 61(50)	0.707 71(51)
N(29)A	0.076 81(30)	1.151 35(39)	0.904 15(46)	C(31)B	0.611 05(23)	0.897 27(42)	0.597 90(47)
C(30)A	0.130 93(32)	1.106 45(44)	0.964 53(50)	C(32)B	0.714 76(28)	0.829 20(46)	0.226 83(48)
C(31)A	0.145 26(25)	0.997 11(39)	0.986 32(42)	C(33)B	0.727 53(34)	0.723 32(50)	0.161 37(53)
C(32)A	0.181 17(26)	0.579 88(40)	0.893 66(47)	C(34)B	0.668 40(42)	0.702 94(52)	0.075 67(55)
C(33)A	0.128 78(30)	0.515 64(46)	0.868 43(53)	C(35)B	0.613 05(36)	0.711 16(49)	0.135 68(53)
C(34)A	0.110 29(38)	0.497 03(52)	0.977 77(64)	C(36)B	0.600 88(29)	0.815 27(49)	0.206 79(52)
C(35)A	0.092 41(33)	0.600 83(53)	1.046 02(55)	C(37)B	0.938 44(34)	0.634 53(58)	0.815 16(55)
C(36)A	0.145 15(32)	0.664 72(44)	1.067 83(46)	C(38)B	0.984 47(29)	0.667 35(54)	0.312 04(57)
C(37)A	0.467 80(32)	0.877 06(58)	0.910 66(73)	C(39)B	0.622 67(43)	0.883 16(73)	0.805 03(69)
C(38)A	0.394 41(31)	0.452 00(50)	0.612 64(57)	C(40)B	0.521 05(40)	1.270 12(51)	0.493 40(69)
C(39)A	0.182 83(37)	1.168 51(53)	1.015 99(66)	C(41)	0.618 55(80)	0.568 94(140)	0.730 34(144)
C(40)A	−0.085 39(34)	1.018 63(68)	0.762 70(62)	C(42)	0.660 18(117)	0.474 68(210)	0.734 55(211)
S(1)B	0.913 03(6)	0.746 07(11)	0.354 77(11)	O(3)	0.556 78(78)	0.512 75(132)	0.647 16(143)
S(2)B	0.545 78(7)	1.142 86(11)	0.424 24(13)	O(4)	0.603 13(108)	0.632 79(183)	0.822 15(204)

compound (**9a**), where the resolved signals are very narrow (very high rotational barriers). The piperidine ring shows anisochrony of pairs of signals belonging to α and β positions. Thus, the diastereotopy of the central pseudo-cycle remains with only one IMHB; this, and hindered rotation due to the proximity of N(2)–Ar, explains both the anisochrony and the broadening observed for the piperidine signals (mainly in the 300 MHz ^{1}H NMR spectrum).

Experimental

M.p.s were determined with a Kofler hot-stage microscope and are uncorrected. Spectral studies were performed with the following instruments: IR, Nicolet FT-5DX; ^{1}H and ^{13}C NMR, Bruker AC-200 (UNED), AC-250 (Montpellier), and Varian XL-300 (CSIC) ($SiMe_4$ internal reference; all chemical shifts expressed as δ-values); mass (70 eV), Hewlett-Packard 5993C. Combustion analyses were performed with a Perkin-Elmer 240C instrument.

Crystal-structure Determination of Compounds (**9c**) *and* (**11b**).—The crystallographic analysis is summarized in Table 5. The oxygen atom of the ethanol molecule [compound (**9c**)] appears to be disordered, the population parameters being 0.62(2) and 0.38(2) for the O(3) and O(4) atoms, respectively. A model of disorder for the other atoms in the ethanol molecule could not be properly fitted. The hydrogen atoms of the molecule cannot be located. The final atomic co-ordinates are presented in Tables 6 and 7.*

Bidimensional NMR Experiments and Spectral Analyses.—^{1}H and ^{13}C chemical shifts (δ) are given with an accuracy of ±0.01 and ±0.1 ppm, respectively. Coupling constants (*J*) were measured with a digital resolution of 0.2 for ^{1}H NMR and 0.6

* *Supplementary data available* (see section 5.6.3 of Instructions for Authors, January issue): Lists of thermal components, hydrogen parameters, and bond distances and angles have been deposited at the Cambridge Crystallographic Data Centre.

Table 7. Final atomic co-ordinates for compound (**11b**).

Atom	*x*	*y*	*z*
Cl(1)	0.710 11(7)	0.375 51(13)	0.017 46(9)
Cl(2)	−0.084 54(6)	0.417 42(9)	0.109 15(6)
S(1)	0.196 16(6)	0.314 37(8)	−0.028 11(5)
S(2)	0.172 60(6)	0.540 51(8)	0.409 07(6)
O(1)	0.355 95(19)	0.192 06(21)	0.242 25(16)
O(2)	0.339 45(17)	0.663 89(20)	0.213 78(17)
N(1)	0.333 94(17)	0.330 57(22)	0.109 34(16)
N(2)	0.421 14(17)	0.469 01(22)	0.174 48(17)
N(3)	0.299 87(16)	0.424 43(20)	0.223 37(15)
N(4)	0.317 41(17)	0.536 39(23)	0.344 63(16)
N(5)	0.405 98(18)	0.389 12(23)	0.338 36(17)
C(6)	0.351 02(19)	0.403 09(25)	0.167 65(19)
C(7)	0.340 79(20)	0.455 39(26)	0.303 73(19)
N(8)	0.274 24(16)	0.248 79(21)	0.119 54(15)
C(9)	0.204 69(20)	0.228 01(25)	0.055 28(18)
N(10)	0.147 85(19)	0.151 00(24)	0.055 64(17)
N(11)	0.156 51(21)	0.087 38(25)	0.124 06(19)
C(12)	0.222 98(26)	0.100 27(29)	0.184 86(22)
C(13)	0.290 79(24)	0.180 95(27)	0.187 13(20)
C(14)	0.493 07(19)	0.445 90(26)	0.140 22(18)
C(15)	0.531 55(22)	0.530 52(29)	0.106 84(22)
C(16)	0.599 10(24)	0.510 47(34)	0.070 52(24)
C(17)	0.628 73(21)	0.404 52(35)	0.068 61(21)
C(18)	0.594 19(21)	0.319 70(31)	0.105 00(22)
C(19)	0.526 66(21)	0.340 77(28)	0.141 67(21)
C(20)	0.206 30(19)	0.422 50(24)	0.197 09(17)
C(21)	0.166 53(20)	0.480 96(25)	0.128 45(18)
C(22)	0.077 09(21)	0.480 07(28)	0.102 54(19)
C(23)	0.028 19(20)	0.419 56(28)	0.144 56(20)
C(24)	0.066 61(21)	0.360 30(29)	0.213 01(20)
C(25)	0.156 55(20)	0.361 96(26)	0.239 42(19)
N(26)	0.254 32(17)	0.606 76(21)	0.298 05(16)
C(27)	0.178 10(22)	0.617 91(27)	0.324 03(21)
N(28)	0.114 48(21)	0.681 51(26)	0.288 08(20)
N(29)	0.124 03(23)	0.741 13(26)	0.221 76(20)
C(30)	0.195 89(27)	0.737 17(29)	0.197 30(22)
C(31)	0.270 62(23)	0.669 70(26)	0.235 11(20)
N(32)	0.459 55(20)	0.414 64(26)	0.415 26(19)
C(33)	0.548 63(33)	0.384 10(56)	0.415 99(43)
C(34)	0.427 13(45)	0.357 10(47)	0.478 47(31)
C(35)	0.230 10(48)	0.029 28(47)	0.257 65(29)
C(36)	0.089 75(34)	0.274 49(42)	−0.085 27(30)
C(37)	0.202 21(64)	0.802 42(52)	0.124 76(39)
C(38)	0.063 36(39)	0.572 42(61)	0.416 53(48)

Hz for ^{13}C NMR spectra. The data-acquisition parameters for the heteronuclear (^1H–^{13}C) 2D-correlation experiments performed on a Bruker AC-200 were: F_1 domain (SI1 256W, SW1 1 000 Hz, relaxation delay D1 2s); F_2 domain (SI2 2K, SW2 10 000 Hz), number of transients per FID, NS 128; number of preparatory dummy transients per FID, DS 2. For (^1H–^1H) COSY and NOESY in the same instrument they were: F_1 domain (SI1 1K, SW1 900 Hz, relaxation delay D1 1s);n F_2 domain (SI2 2K, SW2 1 800 Hz), number of transients per FID, NS 32; number of preparatory dummy transients per FID, DS 2. All parameters were processed with a sine-bell window.

Analysis of the ^1H NMR spectrum of compound (**9a**) (two phenyl groups, one appearing as an ABB'CC' system and the other as an ABCDE system) was carried out using the PANIC software from Bruker (RMS error < 0.07).

4-*Amino*-3-*ethylthio*-6-*methyl*-1,2,4-*triazin*-5(4H)-*one* (**1'**) was prepared by the same method described[12] for the preparation of compound (**1**), but using ethyl bromide as the alkylating agent, in 45% yield, as white prisms from ethanol, m.p. 118–121 °C (Found: C, 38.8; H, 5.3; N, 30.2. $C_6H_{10}N_4OS$ requires C, 38.70; N, 5.41; N, 30.08%); ν_{max}(Nujol) 3 300s, 3 200s, 1 670vs, 1 635s, 1 540s, 1 485vs, 1 430m, 1 345s, 1 315m, 1 280s, 1 250vs, 1 160s, 1 095s, 1 000m, 970s, and 765vs cm^{-1}.

1,3-*Diaryl*-2,4-*bis*[(6-*methyl*-3-*methylthio*-5-*oxo*-4,5-*dihydro*-1,2,4-*triazin*-4-*yl*)*imino*]-1,3-*diazetidines* (**3**)–(**8**) were prepared by a previously reported method[1] from 6-methyl-3-methylthio-4-triphenylphosphoranylideneamino-1,2,4-triazin-5(4*H*)-one (**2**) and the appropriate aryl isocyanate.

Compound (**4**) (Ar = 4-F-C_6H_4), 59% yield, as prisms from dichloromethane–diethyl ether, m.p. 175–177 °C (Found: C, 49.6; H, 3.4; N, 23.9. $C_{24}H_{20}F_2N_{10}O_2S_2$ requires C, 49.48; H, 3.46; N, 24.04%); ν_{max}(Nujol) 1 698vs, 1 630vs, 1 602vs, 1 506vs, 1 331s, 1 308s, 1 228vs, 1 155m, 1 109m, 1 064m, 985m, 837s, and 752m cm^{-1}; *m/z* (%) 291 (68), 230 (37), 149 (13), 137 (29), 136 (21), 135 (53), 121 (52), 115 (90), 95 (20), 83 (65), 69 (41), and 47 (100).

Compound (**8**) (Ar = 3-MeC_6H_4), 75% yield, as prisms, m.p. 186–188 °C (Found: C, 54.2; H, 4.6; N, 24.3. $C_{26}H_{26}N_{10}O_2S_2$ requires C, 54.34; H, 4.56; N, 24.37%); ν_{max}(Nujol) 1 698vs, 1 631vs, 1 495s, 1 330s, 1 318s, 1 303vs, 1 218vs, 1 168m, 1 069m, 788m, 749m, 714m, and 692m cm^{-1}; *m/z* (%) 288 (8), 286 (60), 233 (15), 222 (94), 177 (5), 156 (6), 145 (13), 133 (54), 132 (36), 131 (37), 117 (30), 116 (28), 115 (100), 105 (22), 104 (50), 91 (42), 78 (30), and 47 (67).

N^1,N^3-*Diaryl*-N^2,N^4-*bis*-(6-*methyl*-3-*methylthio*-5-*oxo*-4,5-*dihydro*-1,2,4-*triazin*-4-*yl*)-N^5-*substituted biguanides* (**9**)–(**12**) were prepared following the method[2] described in the literature.

Compound (**10a**) (Ar = 4-FC_6H_4, R = Me, R' = H) 38% yield, as prisms from ethanol, m.p. 224–226 °C (Found: C, 49.0; H, 4.1; N, 25.0. $C_{25}H_{25}F_2N_{11}O_2S_2$ requires C, 48.93; H, 4.11; N, 25.11%); ν_{max}(Nujol) 3 380m, 3 250m, 1 663vs, 1 618s, 1 582vs, 1 558vs, 1 504vs, 1 411s, 1 307s, 1 286s, 1 217s, 1 154m, 1 074m, 969m, 840s, 781m, and 754m cm^{-1}; *m/z* (%) 355 (5), 300 (6), 230 (17), 212 (29), 151 (71), 136 (92), 135 (34), 122 (27), 115 (31), 111 (56), 110 (68), 109 (45), 95 (55), 83 (77), 69 (83), and 47 (100).

Compound (**10b**) (Ar = 4-FC_6H_4, R = Me_2N, R' = H) 54% yield, as prisms from dichloromethane–diethyl ether, m.p. 185–187 °C (Found: C, 48.7; H, 4.4; N, 26.1. $C_{26}H_{28}F_2N_{12}O_2S_2$ requires C, 48.59; H, 4.39; N, 26.15%); ν_{max}(Nujol) 3 250m, 3 225m, 1 661vs, 1 614s, 1 585vs, 1 550vs, 1 509vs, 1 304s, 1 286s, 1 228s, 1 210s, 1 158m, 1 076m, 968m, 838m, and 757m cm^{-1}; *m/z* (%) 353 (5), 303 (5), 260 (10), 235 (6), 230 (8), 193 (15), 157 (18), 136 (19), 135 (16), 116 (22), 110 (35), 95 (30), 83 (30), and 69 (100).

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