7.29–7.20 (m, 2 H, ArH), 7.10–7.06 (m, 2 H, ArH, H-10), 4.79 (s, 2 H, H-7), 4.57 (s, 2 H, H-2 or H-17), 4.49 (s, 2 H, H-2 or H-17), 4.46 (s, 2 H, H-12), 3.83–3.77 (m, 4 H, OCH_2CH_2O), 3.71–3.68 (m, 2 H, OCH_2CH_2O), 3.63–3.60 (m, 2 H, OCH_2CH_2O), 2.90 (s, 6 H, NMe_2); MS (FD, 0 ma) m/z 425 (M^+).

Methyl 9-[(*N*,*N*-Dimethylamino)sulfonyl]-3,6,13,16-tetraoxa-9,23-diazatricyclo[16.3.1.1^{8,11}]tricosa-1(22),8-(23),10,18,20-pentaene-22-carboxylate (24). To a stirred suspension of 114 mg (4.97 mmol) of sodium hydride in 120 mL of THF was added dropwise, at ambient temperature, a solution of 730 mg (2.28 mmol) methyl 2,6-bis(bromomethyl)benzoate and 730 mg (2.28 mmol) of **3** in 120 mL of THF over 3 h. The reaction was stirred for 12 h at room temperature, quenched with several drops water, and concentrated under reduced pressure to yield an oily, brown solid. The oil was dissolved in CH_2Cl_2, filtered, and purified by flash chromatography (4% methanol–CH_2Cl_2) to yield 770 mg (61%) of **24** as a light yellow solid: IR (CCl_4) 2920, 1728, 1551, 1003, cm^{-1}; ^{1}H NMR δ 7.33–7.27 (m, 3 H, ArH), 7.13 (s, 1 H, H-10), 4.64 (s, 2 H, H-7), 4.55–4.48 (bs, 4 H, H-2, H-17), 4.38 (s, 2 H, H-12), 3.80 (s, 3 H, CO_2CH_3), 3.59 (m, 8 H, OCH_2CH_2O), 2.84 (s, 6 H, SO_2NMe_2); ^{13}C NMR δ 168.61, 144.79, 137.80, 136.82, 136.73, 132.01, 129.10, 128.58, 128.54, 118.33, 70.94, 70.92, 69.14, 69.07, 68.93, 68.70, 65.76, 64.52, 51.76, 37.97; mass spectrum (FD, ma), m/z 483 (M^+, 100).

Methyl 3,6,13,16-Tetraoxa-9,23-diazatricyclo[16.3.1.1^{8,11}]-tricosa-1(22),8,10,18,20-pentaene-22-carboxylate (4). A solution of 902 mg (1.87 mmol) of **24** in 50 mL of 10% sulfuric acid was heated to 60 °C for 12 h. The pH of the solution was carefully adjusted to pH = 5, at 0 °C, with saturated aqueous sodium bicarbonate. The solution was extracted four times with 100 mL of 10% isopropanol-chloroform. The organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield a yellow oil. Flash chromatography (4% methanol–CH_2Cl_2) yielded a light yellow solid, which was recrystallized from petroleum ether–ethyl acetate (3:1) to afford 506 mg (72%) of **4** as small off-white needles: mp 79–80 °C; IR (KBr) 3700–3000, 1725 cm^{-1}; ^{1}H NMR δ 7.39–7.25 (m, 3 H, ArH), 6.83 (s, 1 H, H-10), 4.84–4.68 (m, 4 H, $ArCH_2$), 4.49–4.45 (m, 2 H, $ImCH_2$), 4.37–4.31 (m, 2 H, $ImCH_2$), 3.94 (s, 3 H, CO_2CH_3), 3.7–3.6 (m, 8 H, OCH_2CH_2O); ^{13}C NMR δ 169.49, 146.36, 136.85, 136.72, 133.08, 129.74, 129.52, 127.90, 127.86, 126.29, 71.90, 71.59, 70.36, 70.16, 69.86, 68.95, 66.77, 63.33, 52.81; mass spectrum (FD, ma), m/z 376 (M^+, 100). Anal. Calcd for $C_{19}H_{24}N_2O_6 \cdot 2H_2O$: C, 55.32; H, 6.85; N, 6.79. Found: C, 55.18; H, 6.81; N, 6.59. X-ray analysis (see text and paragraph below).

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Registry No. **2**, 118599-61-4; **3**, 115912-73-7; **4**, 115912-74-8; **4**·2H_2O, 118599-85-2; **5**, 115960-26-4; **6**, 118599-62-5; **7**, 118599-63-6; **8**, 115912-72-6; **9**, 118599-64-7; **10**, 118599-65-8; **11a**, 13620-31-0; **11b**, 118599-66-9; **12**, 118599-67-0; **13**, 118599-68-1; **14a**, 14593-43-2; **14b**, 118599-69-2; **15a**, 60276-38-2; **15b**, 118599-70-5; **16a**, 118599-71-6; **16b**, 118599-72-7; **17a**, 118599-73-8; **17a**·HBr, 118599-75-0; **17b**, 118599-74-9; **17b**·2HCl, 118599-76-1; **18a**, 118599-78-3; **18b**, 118599-79-4; **19a**, 931-35-1; **19b**, 118599-77-2; **20b**, 118599-80-7; **21a**, 118599-81-8; **21b**, 118599-82-9; **22a**, 118599-83-0; **22b**, 118599-84-1; **23**, 118599-86-3; **24**, 118599-87-4; Me_2NSO_2Cl, 13360-57-1; $CH_2CH_2C(=NH)OCH_2CH_3$·HCl, 40546-35-8; 1-benzylimidazole, 4238-71-5; benzyl alcohol, 100-51-6; allyl bromide, 106-95-6; 2-(benzoyloxy)ethanol, 622-08-2; propionyl nitrile, 107-12-0; 1,2-diaminopropane, 78-90-0; 1,3-bis(bromomethyl)benzene, 626-15-3; methyl 2,6-bis(bromomethyl)benzoate, 56263-51-5.

Supplementary Material Available: Positional and thermal parameters from the X-ray analysis of compound **4** (5 pages). Order information is given on any current masthead page.

Reactivity of 1,3-Diaryl-2,4-bis(heteroarylimino)-1,3-diazetidines. Formation of N^1,N^2,N^3,N^4,N^5-Pentasubstituted Biguanides

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N^1,*N*^{3}-Di(Ar)-*N*^{2},*N*^{4}-bis(6-methyl-3-(methylthio)-5-oxo-4,5-dihydro-1,2,4-triazin-4-yl)-*N*^{5}-(*R*)-biguanides **2a–p** were obtained by reacting 1,3-di(Ar)-2,4-bis((6-methyl-3-(methylthio)-5-oxo-4,5-dihydro-1,2,4-triazin-4-yl)imino)-1,3-diazetidines **1** with several primary amines, piperidine, and 1,1-dimethylhydrazine. The structure of the biguanides was established by a careful ^{1}H and ^{13}C study. To assign unambiguously the NMR signals, NOE difference experiments of compounds **2b** (Ar = 4-Cl-C_6H_4, R = CH_3), **2l** (Ar = R = 4-Cl-C_6H_4), and **2m** (Ar = R = 4-H_3CO-C_6H_4) and 2-D heteronuclear ^{1}H–^{13}C correlation spectrum of **2l** were used. Compound **2a** (Ar = C_6H_5, R = CH_3) was analyzed by X-ray crystallography. Cell constants were 17.1116 (24), 10.4410 (9), and 16.8613 (22) Å; 107.98 (1)°; the space group was $P2_1/c$. Two intramolecular hydrogen bonds determine the conformation of the molecule.

The chemistry of 1,3-diaryl-2,4-bis(arylimino)-1,3-diazetidines, cyclodimers of *N*,*N*′-diarylcarbodiimides,[1] has been little explored; it has been briefly mentioned that these compounds on sequential treatment with phosgene

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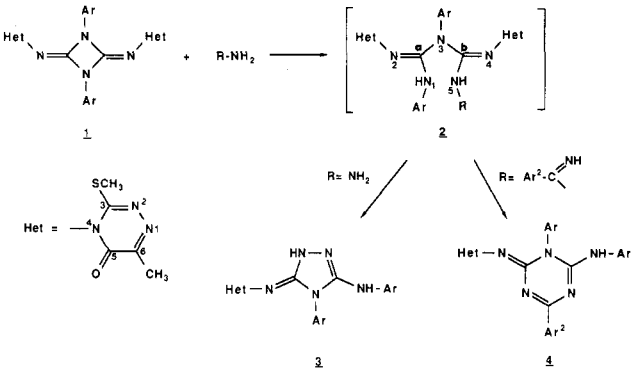
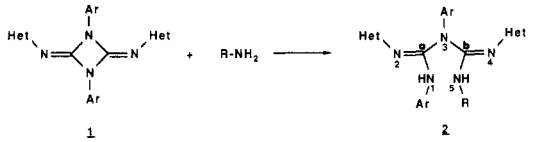
Scheme I



Scheme II



2	Ar	R
a	C_6H_5	CH_3
b	4-Cl-C_6H_4	CH_3
c	4-H_3CO-C_6H_4	CH_3
d	4-Cl-C_6H_4	CH_2=CH-CH_2
e	C_6H_5	H_2N-CH_2-CH_2
f	4-Cl-C_6H_4	H_2N-CH_2-CH_2
g	4-Cl-C_6H_4	HO-CH_2-CH_2
h	C_6H_5	CH_3-CH_2-OOC-CH_2

2	Ar	R
i	4-H_3CO-C_6H_4	C_6H_5-CH_2
j	C_6H_5	4-H_3CO-C_6H_4-CH_2
k	4-Cl-C_6H_4	4-H_3CO-C_6H_4-CH_2
l	4-Cl-C_6H_4	4-Cl-C_6H_4
m	4-H_3CO-C_6H_4	4-H_3CO-C_6H_4
n	4-Cl-C_6H_4	4-H_3CO-C_6H_4
o	C_6H_5	-CH_2-$(CH_2)_3$-CH_2-
p	4-Cl-C_6H_4	$(CH_3)_2$N

and aromatic amines yield perarylated diiminotriazinones.[2] Recently, we have reported[3] that the iminophosphorane derived from 4-amino-6-methyl-3-(methylthio)-5-oxo-4,5-dihydro[1,2,4]triazine, reacts with aryl isocyanates to yield the corresponding 1,3-diaryl-2,4-bis(heteroarylimino)-1,3-diazetidines **1**, which undergo hydrolytic cleavage to give [1,2,4]triazolo[5,1-c][1,2,4]triazine derivatives. In addition, compounds of type **1** undergo ring-opening reactions of the 1,3-diazetidine ring by the action of hydrazine and amidines to yield 3-(arylamino)-4-aryl-5-(heteroarylimino)-4,5-dihydro-1*H*-[1,2,4]triazoles **3**[4] and 6-(arylamino)-2-(heteroarylimino)-1,2-dihydro[1,3,5]triazines **4**,[5] respectively (Scheme I).

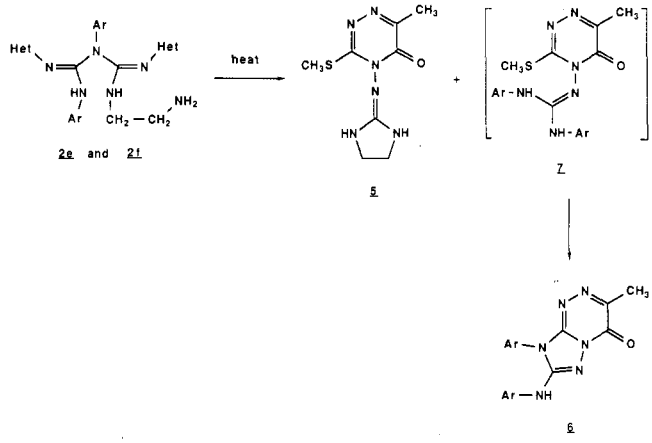
The formation of compounds **3** and **4** can be understood as an initial C–N endocyclic bond fission of the four-membered ring to give a biguanide as intermediate, which undergoes cyclization to give **3** or **4**. Thus, the 2,4-diimino-1,3-diazetidine ring was expected to be opened with a primary amine to give the N^1,N^2,N^3,N^4,N^5-pentasubstituted biguanide.[2,6] We now describe a new synthesis of pentasubstituted biguanides **2** based on the high reactivity of the four-membered ring in **1**, probably due to the release of strain energy, toward amino groups.

Results and Discussion

A. Preparation of N^1,N^2,N^3,N^4,N^5-Pentasubstituted Biguanides. The only method previously reported[2] for the preparation of pentasubstituted biguanides involves treatment of *N*,*N*′-diarylcarbodiimides with 0.5 mol of the corresponding arylamine. We have found that 1,3-diaryl-2,4-bis(heteroarylimino)-1,3-diazetidines **1** react with primary amines in dry methylene chloride at room temperature to give the N^1,N^3-diaryl-N^2,N^4-bis(heteroaryl)-N^5-substituted-biguanides **2** in 47–96% yield (Scheme II). The reaction appears to be quite general; it proceeds satisfactorily for aliphatic amines with or without functional groups, unsaturated amines, aromatic and arylmethanamines; good results have also been obtained with secondary amines, e.g. **2o**, and with 1,1-dimethylhydrazine, e.g. **2p**. Advantages of the present route to pentasubstituted biguanides **2** are unambiguous position of the substituents, good yields, mild and convenient reaction conditions, and the possibility for the preparation of pentasubstituted biguanides bearing three different types of substituents (heteroaromatic, aromatic, and aliphatic).

On the other hand, it has been reported[2] that pentaarylbiguanides by the action of carbonic acid derivatives undergo cyclization to give a six- or a four-membered ring. In our case, biguanides **2** did not react with diphenyl carbonate or *N*,*N*′-carbonyldiimidazole in refluxing toluene. At higher temperatures biguanides **2** decompose. However, when biguanides **2e** and **2f** were heated in refluxing dry toluene the 2-(heteroarylimino)imidazolidine **5** and the corresponding [1,2,4]triazolo[5,1-c][1,2,4]triazine **6** were formed in moderate yields. No reaction took place if the biguanide was heated in refluxing methylene chloride for a prolonged period of time. The conversion **2** → **5** + **6** probably involves initial formation of the imidazolidine ring by addition of the NH_2 group to the C=N bond, followed by elimination of N^1-(heteroaryl)-N^2,N^3-diarylguanidine **7**. The latter can then undergo cyclization and elimination of methanethiol to give **6**[7] (Scheme III).

Scheme III



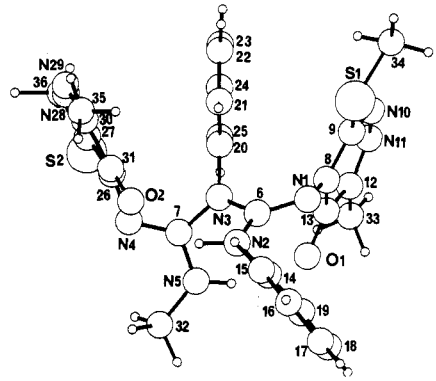


Figure 1. View[15] of the molecular conformation of compound **2a**·H_2O.

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Table I. Selected Geometrical Parameters (Å, deg)

S1–C9	1.744 (6)	S2–C27	1.733 (6)
S1–C34	1.788 (12)	S2–C36	1.795 (13)
O1–C13	1.237 (9)	O2–C31	1.231 (6)
N1–C6	1.302 (8)	N4–C7	1.294 (7)
N2–C6	1.341 (7)	N5–C7	1.340 (7)
N2–C14	1.415 (6)	N5–C32	1.453 (10)
N3–C6	1.410 (6)	N3–C7	1.414 (8)
N8–C9	1.370 (8)	N26–C27	1.385 (7)
N8–C13	1.372 (8)	N26–C31	1.371 (6)
N10–C9	1.297 (7)	N28–C27	1.309 (9)
N11–C12	1.299 (9)	N29–C30	1.302 (8)
N1–N8	1.409 (6)	N4–N26	1.409 (7)
N10–N11	1.380 (7)	N28–N29	1.375 (8)
C12–C13	1.447 (9)	C30–C31	1.453 (8)
C12–C33	1.488 (11)	C30–C35	1.472 (10)
N3–C20	1.440 (7)		
C34–S1–C9–N8	179.8 (5)	C36–S2–C27–N26	−173.0 (6)
C6–N1–N8–C9	127.9 (5)	C7–N4–N26–C27	125.0 (6)
N8–N1–C6–N2	165.2 (5)	N5–C7–N4–N26	166.9 (5)
H2–N2–C6–N3	−18 (5)	H5–N5–C7–N3	−18 (5)
C7–N3–C6–N2	−40.7 (7)	C6–N3–C7–N5	−45.9 (7)
C6–N3–C20–C25	129.0 (6)	C7–N3–C20–C21	126.4 (6)
C6–N2–C14–C15	129.9 (6)		
N2···O2	2.867 (6)	N5···O1	2.914 (8)
N2–H2	0.98 (7)	N5–H5	0.90 (8)
H2···O2	2.01 (7)	H5···O1	2.07 (8)
N2–H2···O2	145 (6)	N5–H5···O1	156 (6)
O3···N10	3.09 (2)	O3···N28 (−X, −Y, 1 − Z)	3.29 (2)
N10···O3···N28 (−X, −Y, 1 − Z)	139.4 (7)		

Although it has been reported[2] that pentaarylbiguanides dissociate and recombine on heating, causing scrambling of N-substituents, when biguanides **2a–d** and **2g–o** were heated in refluxing toluene they were recovered unchanged.

B. X-ray Diffraction Study of N^1,N^3-Diphenyl-N^2,N^4-bis(6-methyl-3-(methylthio)-5-oxo-4,5-dihydro-1,2,4-triazin-4-yl)-N^5-methylbiguanide (2a) (1 H_2O). The bond character distribution is well described by the bond distances shown in Table I, according to the atomic numbering given in Figure 1, with all sp^2 nitrogen atoms being planar.

The N^2–C^6–N^3–C^7–N^5 central part of the molecule has a helical conformation (see Figure 1), connecting both N–H to the oxygen atoms through intramolecular hydrogen bonds (N2–H2··O_2 and N5–H5··O1). The rest of the molecule surrounds this central part, with the rings nearly perpendicular to the axis of that helix. The two heterocycles are somewhat puckered (see Table I) and are situated as to give a pseudobinary axis to the molecule (see Figure 1). The hydrogen atoms of the water molecule, that could not be located, are implied in the hydrogen bonds involving this molecule.

C. ^{13}C and ^1H NMR Analyses of Biguanides 2a–p. Once the crystal structure determination of compound **2a** had proven that it was an N^1,N^2,N^3,N^4,N^5-pentasubstituted biguanide, we proceeded to assign the ^{13}C NMR signals to the different carbons. The chemical shifts of 3-SCH_3 (13.50–14.24), 6-CH_3 (17.41–17.69), C_3 (158.46–159.27), C_5 (147.01–151.48), and C_6 (152.67–153.79) of 6-methyl-3-(methylthio)-5-oxo-4,5-dihydro-1,2,4-triazin-4-yl substituents on N^2 and N^4 present small differences, which, in some cases, are only observed in the second significant figure. The assignment of these signals was straightforward on the basis of the multiplicity of signals and the averaged values of the coupling constants, in agreement with our previously published results:[3] C_3 (quartet) $^3J \sim 4$ Hz, C_5 (quartet) $^3J \sim 3$ Hz, C_6 (quartet) $^2J \sim 7$ Hz, 3-SCH_3 (quartet) $^1J \sim 143$ Hz, 6-CH_3 (quartet) $^1J \sim 130$ Hz.

Aryl groups on N^1 and N^3 have been differentiated on the basis of (i) the fully proton-decoupled ^{13}C NMR spectra of **2l** and **2m**, symmetrical biguanides, with the signals of the N^1-Ar being of double intensity as compared with those of N^3-Ar; (ii) the multiplicity of the phenyl signals in the normal ^{13}C NMR spectra with ^1H–^{13}C coupling constant values ($^1J \sim 160$ Hz, $^3J \sim 6$ Hz, $^2J \sim 1$ Hz) according to literature[8] and a ^3J coupling between $C_2(C_6)$ of the N^1-aryl substituent and N^1-H of nearly 3 Hz; (iii) the substituent chemical shifts (SCS) effects due to chlorine or methoxy groups on a phenyl derivative.[8] Thus, for instance, for compound **2a** the following values are found: N^1-Ar, C_1, 138.51, C_2 and C_6, 120.51, C_3 and C_5, 129.10, C_4, 124.26, and N^3-Ar, C_1, 134.51, C_2 and C_6, 122.93 and 122.97, C_3 and C_5, 128.94, C_4, 128.01 ppm.

Chart I

Substituent		δ (^{13}C)	δ (^1H)
	3-SCH_3	13.82	2.24
	6-CH_3	17.69	2.50
N^1-Ar	C_2-H_2(C_6-H_6)	122.05	7.56
	C_3-H_3(C_5-H_5)	129.17	7.30
N^3-Ar	C_2-H_2(C_6-H_6)	124.37	6.71
	C_3-H_3(C_5H_5)	129.38	7.05

The most interesting feature is the nonequivalence of the chemical shifts of ortho (C_2 and C_6) and meta (C_3 and C_5) carbons of the N^3-aryl group, this anisochrony being dependent on the nature of the substituents on the biguanide, ranging from accidentally equivalent in **2k** (Ar = 4-Cl-C_6H_4, R = 4-H_3OC-C_6H_4-CH_2), with C_2 and C_6 at 124.39 ppm and C_3 and C_5 at 129.00 ppm, to clearly different as in **2h** (Ar = C_6H_5, R = CH_3CH_2-O_2C-CH_2), where C_2 and C_6 appear at 122.82–123.08 ppm ($\Delta\delta$ = 0.26 ppm) and C_3 and C_5 appear at 128.83–129.14 ppm ($\Delta\delta$ = 0.31 ppm). Since the anisochrony did not vary when spectra were recorded at 50 °C but disappeared in the symmetrical biguanides **2l** (Ar = R = 4-Cl-C_6H_4) and **2m** (Ar = R = 4-H_3CO-C_6H_4), the reason for the nonequivalence must be the hindered rotation about the N^3 (sp^2)–C^{20} (sp^2) bond together with the intrinsic chirality of the molecule related to the spatial arrangement discussed before in the crystalline structure of **2a** (Figure 1).

Carbon atoms C_a and C_b of the C=N bonds have been assigned from fully proton-coupled spectra by their multiplicity (C_b is coupled with the R group; for instance, in compound **2a**, C_b is coupled with the *N*-methyl group with a $^3J = 3.6$ Hz) and appear at ~153 and ~156 ppm, respectively. Chemical shifts of other substituents do not deserve any particular comments, unless in the case of **2o** (Ar = C_6H_5, R = piperidine) where α- and β-carbons of the piperidine ring are anisochronous, another proof of the molecular chirality.

In order to assign the ^1H NMR signals, a heteronuclear 2D ^1H–^{13}C correlation spectrum of **2l** (Ar = R = 4-Cl-C_6H_4) was run, leading to the conclusion that in this biguanide there exist the relationships shown in Chart I.

Here again, multiplicity of the signals and SCS effects produced by introduction of a chlorine or a methoxy group[9] have been considered in assigning aryl groups.

H_2 and H_6 protons of N^3-aryl groups are anisochronous, and, in some cases, this nonequivalence was also observed for H_3 and H_5 protons as in **2b**, **2g**, and **2k**. The origin of this phenomenon has already been discussed in the ^{13}C NMR part.

Attention must be paid to the fact that in our previous work[3] the tentative assignment of protons in 1,3-bis(4-chlorophenyl)-2,4-bis(6-methyl-3-(methylthio)-5-oxo-4,5-

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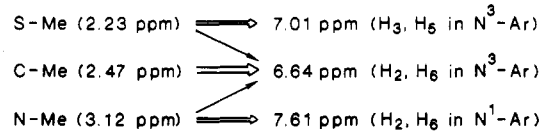
dihydro-1,2,4-triazin-4-ylimino)-1,3-diazetidine (**1b**) was wrong, the *p*-chlorophenyl groups were reversed. The error came from the ^{1}H NMR model chosen, *p*-chloroaniline instead of *p*-chloroacetanilide.

Assignment of N^1-H (~9.6 ppm), N^5-H (~7.8 ppm), and protons of the N^5-R substituent has been performed, taking into account the different multiplicity and SCS effects. In **2o**, similarly to what occurred in ^{13}C NMR, equatorial and axial α-protons of the piperidine ring are diastereotopic.

To confirm the unambiguous assignment of aromatic protons of biguanides **2**, we have carried out a series of NOE experiments. From the X-ray structure of compound **2a** (Figure 1) the following distances shorter than 5 Å can be found: S-Me/H_3,H_5 in N^3-Ar = 4.2 Å; S-Me/H_2,H_6 in N^3-Ar = 4.7 Å; C-Me/H_2,H_6 in N^3-Ar = 3.8 Å; C-Me/H_3,H_5 in N^3-Ar = 4.9 Å; N-Me/H_2,H_6 in N^3-Ar = 4.7 Å; N-Me/H_2,H_6 in N^1-Ar = 4.7 Å.

The experiments were performed on compounds **2b**, **2l**, and **2m**. Since they yielded identical results, only those concerning **2b** (Ar = 4-Cl-C_6H_4, R = CH_3) will be described:



Irradiation of the 2.23 ppm signal produces a clear increase of the 7.01 ppm signal and a somewhat lower increase of the 6.64 ppm signal. On irradiation of the ~2.47 ppm signals only the 6.64 ppm signal was affected. Irradiation of the *N*-methyl signal at 3.12 ppm modifies the intensities of the 7.61 and 6.64 ppm signals. These weak NOE effects, although observable only in a differential spectra, are useful to assign H_{ortho} (H_2 and H_6) and H_{meta} (H_3 and H_5) protons of both phenyl rings. Moreover, these experiments prove that the structure in the solid state (X-ray) and in solution (NMR) are very similar.

Conclusions

The pentasubstituted biguanides **2**, now readily accessible, present an unexpected and rather interesting structure. The five-membered pseudocycle, although formed exclusively by sp^2 atoms, is chiral as shown by the anisochrony of protons and carbon atoms. The chiral helicity is due to hydrogen bonds that fix the pseudocycle and to the five bulky substituents. The structure found in the solid state is representative of the behavior in solution, not only of the physicochemical aspects (NOE experiments) but also of the chemical reactivity. A simple examination of Figure 1 shows why biguanides **2** do not react with diphenyl carbonate to form a triazinone: the N^2–N^5 distance is too great to allow for the formation of an N–CO–N bridge.

Experimental Section

General Methods. All melting points were determined on a hot-plate melting point apparatus and are uncorrected. IR were obtained as Nujol emulsions or KBr disks on a Nicolet FT-5 spectrophotometer. ^{1}H NMR spectra were recorded on one of the following spectrometers: Varian FT-80 (80 MHz) or Varian XL-300 (300 MHz). ^{13}C NMR spectra were recorded on a Varian XL-300 (75 MHz): spectral width 16000 Hz, number of data points 65536 (memory size 64K), acquisition time 2.0 s (digital resolution 0.5 Hz per point), pulse width 5.0 μs, relaxation delay 1.3 s. Chemical shifts (δ) in ppm and coupling constants (J) in hertz were measured in deuteriochloroform referred to TMS as internal standard. ^{1}H and ^{13}C chemical shifts are accurate to 0.01 and 0.1 ppm, respectively. Coupling constants are accurate to 0.2 Hz for ^{1}H NMR and 0.5 Hz for ^{13}C NMR. These accuracies correspond to the experimental conditions used in each case. Two-dimensional spectra were recorded by using standard conditions.[10] Mass spectra were recorded on a Hewlett-Packard 5993C instrument. Microanalyses were performed on a Perkin-Elmer 240C instrument. Crystal and experimental data and refinement parameters are given in Table II.

Table II. Crystal Analysis Parameters at Room Temperature

Crystal Data	
formula	$C_{25}H_{27}N_{11}O_2S_2 \cdot H_2O$
crystal habit	transparent, colorless, triangular plate
crystal size (mm)	0.33 × 0.07
symmetry	monoclinic, $P2_1/c$
unit cell determination	least-squares fit from 77 reflexions ($\theta < 45°$)
unit cell dimensions	17.1116 (24), 10.4410 (9), 16.8613 (22) Å 90, 107.98 (1), 90°
packing: V (Å^3), Z	2865.4 (6), 4
D_c (g cm^{-3}), M, F(000)	1.381, 595.7, 1248
μ (cm^{-1})	20.50
Experimental Data	
technique	four circle diffractometer: Philips PW1100 bisecting geometry graphite oriented monochromator: Cu Kα $w/2\theta$ scans, scan width 1.6° detector apertures 1 × 1°, up θ_{max} 65° 1 min/reflex
number of reflexions	
independent	4878
observed	3019 ($I > 3\sigma(I)$ criterion)
standard reflexions	2 reflexiones every 90 min variation: no
max–min transmission factors	1.233–0.673
Solution and Refinement	
solution	direct methods
refinement	LS on F_{obsd} with 2 blocks
parameters	
number of variables	478
degrees of freedom	2541
ratio of freedom	6.3
H atoms	difference synthesis
final shift/error	0.27
w scheme	empirical as to give no trends in $\langle w\Delta^2F\rangle$ vs $\langle\|F_o\|\rangle$ and $\langle \sin\theta/\lambda\rangle$
max thermal value	$U11$(O3) = 0.34 (2) Å^2
final ΔF peaks	0.29 e Å^{-3}
final R and R_w	0.074, 0.079
computer and programs	Vax 11/750, XRAY76 System,[11] MULTAN80,[12] DIFABS[13]
scattering factors	Int. Tables for X-ray Crystallography[14]

Materials. 1,3-Diaryl-2,4-bis(heteroarylimino)-2,4-diazetidines **1** were prepared as described in the literature.[3]

Preparation of N^1,N^2,N^3,N^4,N^5-Pentasubstituted Biguanides 2. General Procedure. To a well-stirred solution of the appropriate 1,3-diaryl-2,4-bis(heteroarylimino)-1,3-diazetidine **1** (2 mmol) in 25 mL of dry CH_2Cl_2 was added the adequate amine (2 mmol). The resultant solution was stirred at room temperature

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(11) Stewart, J. M.; Machin, P. A.; Dickinson, C. W.; Ammon, H. L.; Heck, H.; Flack, H. The X-Ray system, 1976. Technical Report TR-446, Computer Science Center, University of Maryland.
(12) Main, P.; Fiske, S. J.; Hull, S. E.; Lessinger, L.; Germain, G.; Declercq, J. P.; Woolfson, M. M. Multan 80 System; 1980, University of York, England.
(13) Walker, N.; Stuart, D. Difabs. *Acta Crystallogr.* **1983**, *A39*, 158.
(14) *International Tables for X-Ray Crystallography*; Kynoch Press: Birmingham, England, 1974; Vol. IV.
(15) Allen, F. H.; Bellard, S.; Brice, M. D.; Cartwright, B. A.; Doubleday, A.; Higgs, H.; Hummelink, T.; Hummelink-Peters, B. G.; Kennard, O.; Motherwell, W. D. S.; Rogers, J. R.; Watson, D. G. *Acta Crystallogr.* **1979**, *B35*, 2331.

for 24 h, and the solvent was removed under reduced pressure at 25 °C. The residual material was slurried with 10 mL of cold ethanol. The separated solid was collected by filtration, air-dried, and recrystallized from ethanol to give **2**.

2a: yield 93%; mp 212–214 °C; yellow prisms; IR (Nujol) 3336, 3256, 1660, 1557, 1302 cm^{-1}; mass spectrum, *m/z* (relative intensity) 304 (19), 273 (29), 212 (15), 133 (100), 132 (24), 115 (39), 47 (61). Anal. Calcd for $C_{25}H_{27}N_{11}O_2S_2$: C, 51.98; H, 4.71; N, 26.67. Found: C, 51.79; H, 4.82; N, 26.62.

2b: yield 64%; mp 228–230 °C; yellow prisms; IR (Nujol) 3336, 3285, 1670, 1614, 1586, 1550, 1308, 1285 cm^{-1}; mass spectrum, *m/z* (relative intensity) 307 (10), 212 (10), 153 (16), 151 (9), 139 (7), 137 (11), 47 (100). Anal. Calcd for $C_{25}H_{25}Cl_2N_{11}O_2S_2$: C, 46.44; H, 3.90; N, 23.83. Found: C, 46.35; H, 3.75; N, 23.95.

2c: yield 83%; mp 212–213 °C; pale yellow prisms; IR (Nujol) 3324, 3080, 1665, 1546, 1506, 1246 cm^{-1}; mass spectrum, *m/z* (relative intensity) 334 (5), 303 (6), 212 (10), 163 (20), 147 (63), 134 (10), 47 (100). Anal. Calcd for $C_{27}H_{31}N_{11}O_4S_2$: C, 50.85; H, 4.90; N, 24.16. Found: C, 50.97; H, 5.13; N, 24.29.

2d: yield 73%; mp 218–220 °C; yellow prisms; IR (Nujol) 3296, 3115, 1665, 1613, 1574, 1557, 1308, 1291 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.30 (s, 2 CH_3S), 2.55 (s, 2 CH_3), 4.10–4.45 (m, 2 H, CH_2CH=CH_2), 5.20–5.70 (m, 2 H, CH_2=CH), 6.45–6.70 (m, 1 H, CH=CH_2), 6.80–8.20 (m, 8 H, Ar + N^5-H), 9.90 (s, N^1-H); mass spectrum, *m/z* (relative intensity) 362 (10), 307 (10), 238 (15), 192 (10), 152 (30), 127 (25), 111 (15), 47 (100). Anal. Calcd for $C_{27}H_{27}Cl_2N_{11}O_2S_2$: C, 48.21; H, 4.05; N, 22.91. Found: C, 48.28; H, 3.96; N, 22.83.

2e: yield 96%; mp 212–214 °C; yellow prisms; IR (Nujol) 3273, 3083, 1665, 1568, 1304 cm^{-1}; mass spectrum, *m/z* (relative intensity) 366 (10), 273 (10), 240 (60), 172 (22), 161 (47), 160 (34), 156 (35), 131 (20), 124 (100), 111 (28), 104 (27). Anal. Calcd for $C_{26}H_{30}N_{12}O_2S_2$: C, 51.47; H, 4.98; N, 27.70. Found: C, 51.35; H, 4.79; N, 27.83.

2f: yield 95%; mp 195–197 °C; yellow prisms; IR (Nujol) 3364, 3296, 3233, 1664, 1551, 1489, 1308, 1291 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.60–2.00 (m, 2 H, NH_2), 2.30 (s, 2 CH_3S), 2.55 (s, 2 CH_3), 3.90–4.20 (m, 2 H, CH_2NH_2), 4.40–4.90 (m, 2 H, CH_2NH), 6.47–7.03 (m, 4 H, N^3-Ar), 7.30–7.55 (m, 4 H, N^1-Ar), 7.64 (br s, N^5-H), 10.00 (br s, N^1-H); mass spectrum, *m/z* (relative intensity) 388 (11), 386 (20), 276 (10), 248 (15), 193 (8), 192 (64), 165 (27), 164 (40), 163 (57), 154 (31), 153 (20), 152 (100), 140 (22), 138 (69), 127 (39), 113 (24), 111 (77), 102 (20). Anal. Calcd for $C_{26}H_{28}Cl_2N_{12}O_2S_2$: C, 46.22; H, 4.18; N, 24.88. Found: C, 46.15; H, 4.23; N, 24.95.

2g: yield 91%; mp 202–204 °C; pale yellow prisms; IR (Nujol) 3336, 3296, 3200, 3120, 1665, 1602, 1585, 1563, 1546, 1302, 1291 cm^{-1}; mass spectrum, *m/z* (relative intensity) 309 (2), 307 (6), 197 (4), 195 (12), 172 (5), 156 (6), 152 (10), 127 (10), 111 (10), 47 (100). Anal. Calcd for $C_{26}H_{27}Cl_2N_{11}O_3S_2$: C, 46.15; H, 4.02; N, 22.77. Found: C, 46.16; H, 3.98; N, 22.62.

2h: yield 85%; mp 172–174 °C; yellow prisms; IR (Nujol) 3296, 3100, 1750, 1665, 1568, 1308, 1296, 1200 cm^{-1}; mass spectrum, *m/z* (relative intensity) 376 (17), 329 (16), 273 (38), 210 (20), 194 (12), 177 (23), 156 (11), 146 (24), 131 (76), 119 (28), 117 (23), 115 (52), 104 (13), 77 (50), 47 (100). Anal. Calcd for $C_{28}H_{31}N_{11}O_4S_2$: C, 51.76; H, 4.81; N, 23.71. Found: C, 51.63; H, 4.93; N, 22.63.

2i: yield 56%; mp 115–116 °C; yellow prisms; IR (Nujol) 3296, 3080, 1660, 1557, 1512, 1308, 1246 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.25 (s, 2 CH_3S), 2.50 (s, CH_3), 2.55 (s, CH_3), 3.70 (s, CH_3O), 3.90 (s, CH_3O), 4.73 (dd, 1 H), 4.90 (dd, 1 H), 6.5–7.9 (m, 13 H, Ar), 8.20 (t, N^5-H), 9.55 (s, N^1-H); mass spectrum, *m/z* (relative intensity) 410 (10), 303 (20), 264 (15), 238 (10), 157 (10), 147 (72), 133 (20), 121 (15), 106 (15), 91 (100), 47 (26). Anal. Calcd for $C_{33}H_{35}N_{11}O_4S_2$: C, 55.53; H, 4.94; N, 21.58. Found: C, 55.68; H, 5.09; N, 21.39.

2j: yield 83%; mp 181–183 °C; yellow prisms; IR (Nujol) 3358, 3279, 1659, 1597, 1580, 1552, 1512, 1302 cm^{-1}; mass spectrum, *m/z* (relative intensity) 273 (20), 136 (37), 121 (100), 115 (26), 77 (20), 47 (58). Anal. Calcd for $C_{32}H_{33}N_{11}O_3S_2$: C, 56.21; H, 4.86; N, 22.53. Found: C, 56.33; H, 5.03; N, 22.69.

2k: yield 90%; mp 217–218 °C; brown prisms; IR (Nujol) 3290, 3200, 3100, 1670, 1568, 1552, 1308, 1240 cm^{-1}; mass spectrum, *m/z* (relative intensity) 309 (10), 307 (18), 136 (15), 122 (10), 121 (100), 99 (15), 47 (62). Anal. Calcd for $C_{32}H_{31}Cl_2N_{11}O_3S_2$: C, 51.06; H, 4.15; N, 20.47. Found: C, 50.93; H, 4.28; N, 20.39.

2l: yield 47%; mp 222–224 °C; yellow prisms; IR (Nujol) 3250, 3188, 3100, 1664, 1602, 1568, 1552, 1308 cm^{-1}; mass spectrum, *m/z* (relative intensity) 309 (5), 307 (15), 264 (10), 262 (15), 153 (14), 129 (5), 127 (14), 113 (10), 111 (28), 47 (100). Anal. Calcd for $C_{30}H_{26}Cl_3N_{11}O_2S_2$: C, 48.49; H, 3.53; N, 20.73. Found: C, 48.53; H, 3.42; N, 20.66.

2m: yield 55%; mp 150–152 °C; colorless needles; IR (Nujol) 3279, 3239, 1659, 1563, 1512, 1303, 1251 cm^{-1}; mass spectrum, *m/z* (relative intensity) 303 (13), 254 (73), 239 (90), 147 (50), 123 (6), 107 (5), 106 (14), 47 (100). Anal. Calcd for $C_{33}H_{35}N_{11}O_5S_2$: C, 54.31; H, 4.83; N, 21.11. Found: C, 54.19; H, 4.70; N, 20.98.

2n: yield 64%; mp 218–220 °C; yellow prisms; IR (Nujol) 3245, 3200, 3100, 1664, 1608, 1568, 1308 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.25 (s, 2 CH_3S), 2.55 (s, 2 CH_3), 3.85 (s, CH_3O), 6.7–8.0 (m, 12 H, Ar), 9.70 (s, N^5-H), 10.00 (s, N^1-H); mass spectrum, *m/z* (relative intensity) 307 (10), 305 (10), 264 (8), 262 (14), 260 (5), 258 (17), 245 (7), 243 (17), 153 (18), 152 (5), 149 (9), 127 (8), 125 (20), 113 (7), 111 (21), 47 (100). Anal. Calcd for $C_{31}H_{29}Cl_2N_{11}O_3S_2$: C, 50.41; H, 3.96; N, 20.86. Found: C, 50.33; H, 4.08; N, 21.02.

2o: yield 95%; mp 226–228 °C; yellow prisms; IR (Nujol) 3233, 3182, 1676, 1653, 1596, 1551, 1308, 1274 cm^{-1}; mass spectrum, *m/z* (relative intensity) 358 (5), 311 (6), 310 (20), 282 (6), 273 (15), 266 (5), 212 (10), 202 (15), 187 (35), 172 (8), 156 (5), 131 (20), 118 (35), 104 (13), 91 (20), 84 (100), 77 (50), 47 (50). Anal. Calcd for $C_{29}H_{33}N_{11}O_2S_2$: C, 55.13; H, 5.26; N, 24.39. Found: C, 55.03; H, 5.12; N, 24.30.

2p: yield 61%; mp 182–184 °C; colorless prisms; IR (Nujol) 3245, 3137, 1682, 1620, 1574, 1495, 1308, 1093 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.23 (s, CH_3S), 2.24 (s, CH_3S), 2.46 (s, CH_3), 2.47 (s, CH_3), 2.73 (s, Me_2N), 6.58 (m, 1 H, N^3-Ar), 6.68 (m, 1 H, N^3-Ar), 7.02 (m, 2 H, N^3-Ar), 7.34 (m, 2 H, N^1-Ar), 7.62 (m, 2 H, N^1-Ar), 8.51 (s, N^5-H), 9.73 (s, N^1-H); mass spectrum, *m/z* (relative intensity) 366 (5), 276 (5), 210 (6), 172 (5), 156 (5), 152 (7), 111 (15), 69 (100). Anal. Calcd for $C_{26}H_{28}Cl_2N_{12}O_2S_2$: C, 46.22; H, 4.18; N, 24.88. Found: C, 46.05; H, 4.13; N, 24.76.

Thermal Treatment of Biguanides 2e and 2f. A well-stirred suspension of the appropriate biguanide **2e** or **2f** (3 mmol) in 50 mL of dry toluene was heated at reflux temperature for 48 h. After cooling, the separated solid was collected by filtration and treated with 10 mL of DMSO. The remaining solid was separated by filtration and recrystallized from ethanol to give **6**.[3] The filtrate was poured into 10 mL of cold water, and the precipitated solid was collected by filtration, washed with cold ethanol, and recrystallized from ethanol to give **5**: 0.30 g (43%); mp 296–298 °C; yellow crystals; IR (Nujol) 3319, 3160, 1662, 1626, 1598, 1513, 1289 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.30 (s, 3 H, CH_3S), 2.45 (s, 3 H, CH_3), 3.40 (s, 4 H, CH_2CH_2), 7.10 (s, 2 H, 2 NH); mass spectrum, *m/z* (relative intensity) 240 (M^+, 26), 157 (10), 152 (15), 128 (20), 125 (15), 124 (92), 111 (30), 98 (100), 84 (28), 70 (98), 47 (35). Anal. Calcd for $C_8H_{12}N_6OS$: C, 39.99; H, 5.03; N, 34.98. Found: C, 39.85; H, 4.97; N, 34.92.

Registry No. **1a**, 111969-38-1; **1b**, 111981-41-0; **1c**, 111969-40-5; **2a**, 118458-63-2; **2b**, 118458-64-3; **2c**, 118458-65-4; **2d**, 118458-66-5; **2e**, 118458-67-6; **2f**, 118458-68-7; **2g**, 118458-69-8; **2h**, 118458-70-1; **2i**, 118473-73-7; **2j**, 118458-71-2; **2k**, 118458-72-3; **2l**, 118458-73-4; **2m**, 118458-74-5; **2n**, 118458-75-6; **2o**, 118458-76-7; **2p**, 118458-77-8; **5**, 118458-78-9; **6e**, 96546-30-4; **6f**, 96546-28-0; H_2NCH_3, 74-89-5; H_2NCH_2CH=CH_2, 107-11-9; $H_2N(CH_2)_2NH_2$, 107-15-3; $H_2N(CH_2)_2OH$, 141-43-5; $H_2NCH_2CO_2CH_2CH_3$, 459-73-4; $H_2NCH_2C_6H_5$, 100-46-9; 4-$H_2NCH_2C_6H_4OCH_3$, 2393-23-9; 4-$H_2NC_6H_4Cl$, 106-47-8; 4-$H_3COC_6H_4NH_2$, 104-94-9; $H_2NN(CH_3)_2$, 57-14-7; piperidine, 110-89-4.

Supplementary Material Available: Tables of final atomic parameters, bond distances and angles, ^{13}C NMR data (chemical shifts and ^1H–^{13}C coupling constants), and ^1H NMR data (chemical shifts and ^1H–^1H coupling constants) (21 pages). Ordering information is given on any current masthead page.