23-8; (±)-17, 70503-69-4; 1-(4-methoxyphenyl)-1-hydroxycyclohex-4-one ethylene ketal, 67019-51-6; cyclohexane-1,4-dione monoethylene ketal, 4746-97-8; 4-bromoanisole, 104-92-7; 4-(benzyloxy)cyclohexanone, 2987-06-6; 4-bromoveratrole, 2859-78-1; benzyl bromide, 100-39-0; 4-hydroxycyclohexanone ethylene ketal, 22428-87-1; *N*-methylhydroxyamine hydrochloride, 4229-44-1; 4-hydroxycyclohexaone, 13482-22-9; 4-oxocyclohexanyl 2-tetrahydropyranyl ether, 60739-53-9.

Effect of Substituents on the 3-Azidobenzo-*as*-triazine/Tetrazolo[5,1-*c*]benzo-*as*-triazine/Tetrazolo[1,5-*b*]benzo-*as*-triazine Equilibrium[1]

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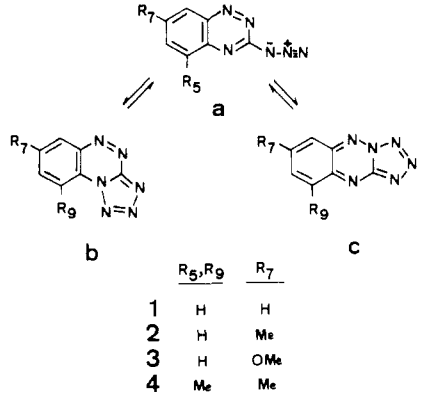
With the aim of gaining insight into the title equilibrium, some derivatives were synthesized and investigated by NMR and IR spectroscopy. The general statement that electron-donating groups and polar solvents stabilize tetrazole vs. azide forms is again confirmed. However, while the angular tetrazole tautomer **2b** is favored by a methyl group at position 7, a methoxy group at this position induces a surprising change, the linear tetrazole tautomer **3c** becoming the major one in acetone and in dimethyl sulfoxide. Likewise, **4c** predominates over **4b**, a fact that may be related to the steric hindrance between the methyl group at position 9 and the tetrazole ring in **4b**. 1-Oxido derivatives of **2a–4a** (**11a–13a**), also investigated, are true azides in chloroform, but in dimethyl sulfoxide the angular tetrazole form curiously appears to be predominant in 11 and is observed in 12 and 13 as well.

In 1973 Messmer et al. reported[2] that the product arising from the reaction of 3-hydrazinobenzo-*as*-triazine with nitrous acid, presumably 3-azidobenzo-*as*-triazine (**1a**),



	R_5,R_9	R_7
1	H	H
2	H	Me
3	H	OMe
4	Me	Me

showed no azide band in the solid state. Mainly on the basis of electronic spectra, the tetrazolo[5,1-*c*]benzo-*as*-triazine structure (angular structure **1b**) was proposed for the tetrazole form which seems to be the exclusive tautomer in the solid state and is also present in polar solvents. Taking into account that 5(and/or 6)-substituted 3-azido-*as*-triazines cyclize on N-2, affording tetrazolo-[1,5-*b*]-*as*-triazines, Paudler et al. suggested shortly afterward[3] that the tetrazolo[1,5-*b*]benzo-*as*-triazine linear structure (**1c**) should not have been ruled out by Messmer et al.[2] This group has very recently reinvestigated the problem and reached the conclusion that the structure they had proposed (**1b**) is actually predominant, both in the solid state and in Me_2SO solution, although **1a** and **1c** are also present (**1a**/**1b**/**1c** ratio equal to 25/65/10) in this solvent.[4]

With only a few ternary azide–tetrazole equilibria having been in fact observed,[5] it seemed interesting to us to study the present case in more detail, because a knowledge of the factors influencing the relative stabilization of one tetrazole tautomer vs. the other, and/or both over the azide, could be of great value in attacking the study of (or to account for the results obtained in) more complex related polyaza aromatic systems.[6] As it is well-established that electron-withdrawing substituents disfavor tetrazole forms,[5] only electron-donating groups were considered in this first approach.

Results and Discussion

The synthesis of the 7-methyl, 7-methoxy, 5,7 (or 7,9)-dimethyl derivatives of 1 (**2–4**, respectively) was first tried by means of the intramolecular cyclization[1] of the corresponding 2-(hydroxyphenyl)-1-azo-5′-tetrazolo derivatives, but only decomposition products were obtained, so that we directed our attention to a more formal step-by-step synthetic sequence.[7] Thus, heating of the ap-

(1) "Diazo-, Azo-, and Azidoazoles. 8." For the preceding paper in this series, see: S. Castillón, E. Meléndez, and J. Vilarrasa, *J. Heterocycl. Chem.*, **19**, 61 (1982).

(2) A. Messmer, G. Hajós, P. Benkő, and L. Pallos, *J. Heterocycl. Chem.*, **10**, 575 (1973).

(3) M. M. Goodman, J. L. Atwood, R. Carlin, W. Hunter, and W. W. Paudler, *J. Org. Chem.* **41**, 2860 (1976).

(4) A. Messmer, G. Hajós, J. Tamás, and A. Neszmélyi, *J. Org. Chem.*, **44**, 1823 (1979).

(5) For reviews, see: (a) R. N. Butler, *Adv. Heterocycl. Chem.*, **21**, 323 (1977); (b) V. Y. Pochinok, L. F. Avramenko, P. S. Grigorenko, and V. N. Skopenko, *Russ. Chem. Rev. (Engl. Transl.)*, **44**, 1028 (1975); (c) M. Tisler, *Synthesis*, 123 (1973); (d) S. Patai, Ed., "The Chemistry of the Azido Group", Wiley-Interscience, London, 1971.

(6) For instance (naphthotetrazolotriazines), see: J. Vilarrasa and R. Granados, *J. Heterocycl. Chem.*, 11, 867 (1974).

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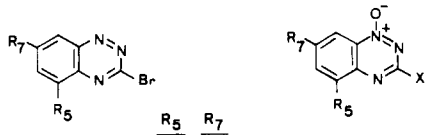
Table I. ^{1}H NMR Spectral Data of 2

compd[a]	parameter	solvent: $CDCl_3$	acetone-d_6	Me_2SO-d_6
2a	δ(H-5)	7.80	8.05	8.04
	δ(H-6)	7.80	8.05	8.04
	δ(H-8)	8.20	8.18	8.27
	δ(Me)	2.63	2.62	2.58
	$J_{8,Me}$, Hz	1.0	0.9	0.9
2b	δ(H-6)	8.72	8.73	8.75
	δ(H-8)	8.03	8.23	8.20
	δ(H-9)	8.54	8.58	8.57
	δ(Me)	2.79	2.76	2.77
	$J_{6,8}$, Hz	2.3	2.3	2.2
	$J_{8,9}$, Hz	8.7	8.7	8.6
2c	δ(H-6)		7.96	7.9-8.0
	δ(H-8)		7.93	7.9-8.0
	δ(H-9)		7.80	7.9-8.0
	δ(Me)	2.68	2.70	2.67
	$J_{8,9}$, Hz		9.0	

[a] a/b/c ratio: 80/16/4 in $CDCl_3$, 25/55/20 in acetone-d_6, 10/63/27 in Me_2SO-d_6.

propriate *o*-nitroanilines with cyanamide gave 3-aminobenzo-*as*-triazine N^1-oxides that were reduced with sodium dithionite to 3-aminobenzo-*as*-triazines; diazotization of these amines in concentrated hydrobromic acid yielded 3-bromobenzo-*as*-triazines **5–7**, from which **2–4**, respectively, were obtained by substituting the azide for the bromide anion.[8] As an alternative way of reaching **5–7**, 3-aminobenzo-*as*-triazine 1-oxides were diazotized in hydrobromic acid to give 3-bromobenzo-*as*-triazine 1-oxides **8–10**, which were then reduced with sodium dithionite, but the overall yields did not increase. Treatment of **8–10** with sodium azide afforded 3-azidobenzo-*as*-triazine 1-oxides **11a–13a**, also studied in this work.



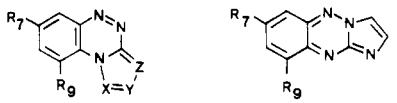
	R_5	R_7
5	H	Me
6	H	OMe
7	Me	Me

8, X = Br **11a**, X = $\bar{N}\overset{+}{N}N$
9, X = Br **12a**, X = $\bar{N}\overset{+}{N}N$
10, X = Br **13a**, X = $\bar{N}\overset{+}{N}N$

Influence of a Methyl Group at Position 7 on the Equilibrium. On TLC, **2** gave three spots, the separation of which by preparative TLC was achieved with a benzene–methanol mixture as the eluent, but the three products recovered from the plate were spectroscopically identical, and each of them gave again the three originally observed spots.[9]

In the IR spectrum of **2** in KBr a very weak band at 2140 cm^{-1} was observed, whereas bands at 1100, 1085, 995, and 980 cm^{-1}, which can be attributed to the tetrazole form,[5] were among the strongest ones. In Me_2SO solution, a small band at 2130 cm^{-1} was also present. By contrast, as is quite common in azide–tetrazole equibria,[5] the azide band was the strongest one of the spectrum in $CHCl_3$ solution.

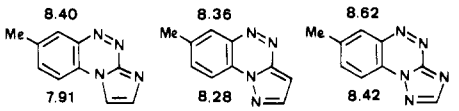
An overview of ^{1}H NMR spectra of **2** confirmed that we were dealing with the expected ternary equilibrium,[4] since, even though only two tautomers were clearly apparent in $CDCl_3$, three different methyl signals could be observed in acetone-d_6 and in Me_2SO-d_6. The assignment of each peak or group of peaks to the corresponding tautomer (see Table I) was not easy, owing to an extensive overlap of signals, but was accomplished by keeping in mind the following: (i) the qualitative results afforded by the IR spectra regarding the intensity of the azide band; (ii) the proton chemical shifts observed for bromo compounds **5–7**, which should be almost identical with those of their respective azides **2a–4a** in view of the similar electron-withdrawing character of the bromo and azido substituents;[5d] (iii) the recently reported[1] NMR spectra of angular imidazo[2,1-*c*]benzo-*as*-triazines **14** (or of their analogous pyrazolo[5,1-*c*]benzo-*as*-triazines **15** and *s*-triazolo[5,1-*c*]-benzo-*as*-triazines **16**) and of linear imidazo[1,2-*b*]benzo-*as*-triazines **17**, which are suitable model compounds for tetrazole forms **2b–4b** and **2c–4c**, respectively.



14, X=Y=CH; Z=N
15, X=N; Y=Z=CH
16, X=Z=N; Y=CH

17

Thus, in the ^{1}H NMR spectrum **2** in $CDCl_3$, the signals of the most abundant tautomer—a methyl band at δ 2.63 that occurs as a doublet, indicating a benzylic coupling with one of the aromatic protons, a two-proton signal at δ 7.80 appearing as a doublet, and a broad one-proton peak at 8.20—can confidently be assigned to the azide tautomer **2a**, because in the IR spectrum in $CHCl_3$ the azide band is very strong and, what is more, because the corresponding bromo derivative (**5**) exhibits the same NMR features, i.e., the chemical shifts of H-5 and H-6 are by chance identical while H-8 is coupled to the methyl, as could easily be confirmed by double-resonance experiments (see also below). This behavior is also present with the other solvents used in this work. The minor tautomer present in $CDCl_3$ has its methyl group signal shifted downfield with regard to that of **2a**, and its aromatic protons appear as a very deshielded "quasi-AMX" system. If the H-6 and H-9 chemical shifts of this minor tautomer are compared with those of **14–16** (R_7 = Me and R_9 = H; see structures below)



in the same solvent,[1] there seems to be no doubt regarding its angular tetrazole structure **2b**. Finally, it should be noted that the NMR spectrum of **2** in $CDCl_3$ shows a small intermediate methyl signal (ca. 4% of the total amount of product) at δ 2.68, probably due to tautomer **2c**, but its aromatic protons can hardly be seen.

By contrast, in acetone-d_6 and in Me_2SO-d_6 the proportion of **2c** increases to 20% and 27%, respectively, as can be deduced from the intensities of the three observed methyl peaks. Moreover, it is noteworthy that the signals corresponding to the H-6, H-8, and H-9 protons of this tautomer are very close and lie at higher field than those of the aromatic protons of **2b** (and even, at least in part, than those of **2a**). However, this is not surprising since the benzo protons of linear, quinone-like imidazobenzo-*as*-triazine **17** also lie at higher field than those of its angular counterpart (**14**).[10]

(7) (a) J. Jiu and G. P. Mueller, *J. Org. Chem.*, **24**, 813 (1959); (b) H. E. Baumgarten, W. F. Murdock, and J. E. Dirks, *ibid.*, **26**, 803 (1961); (c) J. C. Masson and G. Tennant, *J. Chem. Soc. B*, 911 (1970).

(8) Attempts to prepare these azides from the amines by diazotization followed by addition (or in the presence) of the azide ion or by diazo group transfer [see, for example, W. Fischer and J. P. Anselme, *J. Am. Chem. Soc.*, **89**, 5284 (1967)] were unsuccessful.

(9) We observed similar facts in most compounds reported in this paper.

(10) Proton H-6 is the most influenced by the structural change, since the chemical shift difference between H-6 of **14** and H-6 of **17** is 0.74 ppm in $CDCl_3$ (0.65 ppm in Me_2SO-d_6).

Table II. ^{1}H NMR Spectral Data of 3

compd[a]	parameter	solvent: $CDCl_3$	acetone-d_6	Me_2SO-d_6
3a	δ(H-5)	7.72	7.72	7.76
	δ(H-6)	7.72	7.72	7.76
	δ(H-8)	7.62	7.65	7.70
	δ(OMe)	4.03	4.04	4.02
3b	δ(H-6)		8.28	8.45
	δ(H-8)		7.95	8.00
	δ(H-9)		8.56	8.65
	δ(OMe)		4.13	4.10
	$J_{6,8}$, Hz		2.7	2.7
	$J_{8,9}$, Hz		9.3	9.3
3c	δ(H-6)	7.17	7.32	7.40
	δ(H-8)	7.70	7.72	7.82
	δ(H-9)	7.97	8.00	8.10
	δ(OMe)	4.12	4.13	4.10
	$J_{6,8}$, Hz	2.7	2.9	2.7
	$J_{8,9}$, Hz	9.3	9.7	9.7

[a] a/b/c ratio: 60/0/40 in $CDCl_3$, 21/12/67 in acetone-d_6, 10/18/72 in Me_2SO-d_6.

With regard to the effect of solvents on this ternary equilibrium, it can be observed that the azide proportion diminishes as the polarity of the solvent increases, as expected,[5] but it is remarkable that the proportion of both tetrazole tautomers grows in a similar way. On the other hand, the comparison of our results in Me_2SO-d_6 with those of Messmer et al.[4] for 1 (25/65/10) indicates that a methyl group at position 7 decreases the relative azide content while slightly favoring the linear tetrazole tautomer.

Influence of a Methoxy Group at Position 7. Although overlaps of NMR peaks take place here more often than in the methyl derivative, arguments similar to those adduced above allow the assignments shown in Table II to be made. For instance: (i) In the three solvents employed, only two methyl peaks appear,[11] that a higher field being the taller one in $CDCl_3$, the smaller one in acetone-d_6, and the much smaller one in Me_2SO-d_6. Since a parallel change does occur in the IR azide band intensity on changing the solvent from $CHCl_3$ to Me_2SO, that methyl signal was assigned to the azide **3a**. This was confirmed by comparing the NMR spectra under discussion with those of bromo derivative **6**.

(ii) No signals of aromatic protons with δ values higher than 8 ppm are observed in $CDCl_3$, despite the fact that the H-9 protons of angular-structure compounds **15** and **16** (R_7 = OMe and R_9 = H in both the cases) lie at δ 8.29 and 8.37, respectively.[1] Therefore, the presence of **3b** must be ruled out in that solvent; i.e., the minor tautomer which accompanies **3a** must be **3c**. In acetone-d_6, however, **3b** can be detected, and in Me_2SO-d_6 its relative amount is even greater. (There is no evidence for this form in the aliphatic region of the spectrum, as mentioned above, but it is due to the fact that the methoxy groups of both tetrazole tautomers show practically identical δ(Me) values.)[11]

Concerning the **3a**/**3b**/**3c** ratios, the predominance of the linear (**3c**) over the angular (**3b**) tetrazole tautomer in the three solvents should be noted. This striking inversion with respect to compounds **1** and **2**, in which the angular tetrazole form is always preferred, indicates how much the equilibrium depends on minor structural changes, e.g., the replacement of a methyl group by a methoxy group. It seems the more electron-donating the group is, the more the quinone-like linear structure is stabilized.

Dimethyl Derivative 4. The ^{1}H NMR spectrum of **4** in $CDCl_3$ at 60 MHz shows two broad aromatic singlets of different area and three partially overlapped methyl singlets of different height.[12] At 90 MHz the spectrum is, however, better resolved (see Table III): four methyl peaks are clearly seen, the two more intense ones being attributed to the azide **4a** and the smaller ones to the linear tetrazole form **4c** by simply comparing their chemical shifts with those of **7** and **17** (R_7 = R_9 = Me). These assignments can be readily confirmed by the chemical shifts of the aromatic protons. It is remarkable that the two highfield methyl groups, Me-7 of **4a** and Me-7 of **4c**, are only coupled to the H-8 and H-6 protons, respectively, whereas the remaining methyl groups (i.e., those near the triazine ring) appear as rather broad signals due to a small para benzylic coupling in addition to the normal ortho benzylic coupling, as demonstrated by double-resonance experiments. With regard to the third tautomer, only minute amounts are detected.[12]

Table III. ^{1}H NMR Spectral Data of 4

compd[a]	parameter	solvent: $CDCl_3$	acetone-d_6	Me_2SO-d_6
4a	δ(H-6)	7.70	7.80	7.90
	δ(H-8)	8.12	8.10	8.10
	δ(Me-5)	2.68	2.67	2.65
	δ(Me-7)	2.60	2.60	2.57
	$J_{8,Me\text{-}7}$, Hz	1.0	1.0	1.0
4b	δ(H-6)	8.54	8.55	8.52
	δ(H-8)	7.90	7.90	7.90
	δ(Me-7)			2.75 (or 2.65)
	δ(Me-9)	3.12	3.12	3.09
4c	δ(H-6)	7.75	7.80	7.90
	δ(H-8)	7.70	7.80	7.90
	δ(Me-7)	2.63	2.67	2.65
	δ(Me-9)	2.83	2.77	2.75
	$J_{6,Me\text{-}7}$, Hz	1.0	1.0	1.0

[a] a/b/c ratio: 64/3/33 in $CDCl_3$, 45/10/45 in acetone-d_6, 20/13/67 in Me_2SO-d_6.

In acetone-d_6 at 90 MHz the overlap of signals is greater than above, but nevertheless the spectrum can be readily interpreted (Table III). The three tautomers are clearly distinguished, although **4b** continues to be the minor component.

The ^{1}H NMR spectrum **4** in Me_2SO-d_6 shows four methyl signals of different intensities (the two stronger peaks being assigned to **4c** on the basis of their chemical shifts) and signals of aromatic protons plainly attributable to tetrazole forms **4c** (major) and **4b** (minor). Thus, at first sight, **4c** and **4b** seem to be the only tautomers present. Nevertheless, a small azide band can be seen in the IR spectrum in Me_2SO. The ^{13}C NMR spectrum in Me_2SO-d_6 solves the problem, since six methyl peaks are observed at δ 15.1, 16.4, 20.2, 20.6, 21.1, and 21.9.[13] The second and the sixth signals, the strongest ones, are assigned to **4c**, whereas the smallest signals, at δ 20.2 and 21.1, may be atrributed to **4b**, because the chemical shifts for the corresponding methyl carbons of reference compounds are very similar (e.g., the methyl groups of **15**, R_7 = R_9 = Me, appear at δ 20.5 and 21.7 in the same solvent). Therefore, the signals at δ 15.1 and 20.6 should correspond to **4a**. Although the aromatic region of the ^{13}C NMR spectrum has not been fully analyzed yet,[13] the available data account for the corresponding ^{1}H NMR spectrum. In fact,

(11) In Me_2SO-d_6, however, it seems that two partially overlapping singlets are present in the downfield methyl signal.

(12) By enhancing the sensitivity to the maximum, one can see another peak at δ 3.12 and the signals of two aromatic protons at δ 8.54 and 7.90. These very deshielded protons agree with those of **14**–**16** (R_7 = R_9 = Me), so that this minor tautomer should be the angular one (**4b**).

(13) A detailed ^{13}C NMR study of such systems will be reported later on.

Table IV. ^{1}H NMR Spectral Data of 11

compd[a]	parameter	solvent		
		$CDCl_3$	acetone-d_6	Me_2SO-d_6
11a	δ(H-5)	7.75	7.88	7.89
	δ(H-6)	7.75	7.76	7.81
	δ(H-8)	8.15	8.09	8.14
	δ(Me)	2.60	2.60	2.55
	$J_{8,Me}$, Hz	1.0	1.0	1.0
11b	δ(H-6)		8.41	8.41
	δ(H-8)		8.17	8.12
	δ(H-9)		8.50	8.52
	δ(Me)	2.70	2.71	2.65
	$J_{6,8}$, Hz		2.0	2.0
	$J_{8,9}$, Hz		8.7	8.7

[a] a/b/c ratio: 97/3/0 in $CDCl_3$, 60/40/0 in acetone-d_6, 33/67/0 in Me_2SO-d_6.

the confusion was mainly due to an unusual overlap of the methyl proton signals, since Me-7 of **4b** lies under Me-9 (or Me-7) of **4c** and Me-5 and **4a** under Me-7 of **4c**.

In short, the three tautomers are apparent in all the solvents employed, as in **2**, and the linear tetrazole tautomer becomes predominant in more polar solvents, as in **3**.[14] This last fact may be explained by the additive effect of two moderate electron-donating groups. However, it is also possible that the steric hindrance between Me-9 and the angular-arranged tetrazole ring plays an important role,[15] as is indirectly reflected in the large δ values of the Me-9 of the angular tricyclic compounds with regard to the remaining methyl groups considered in this paper.

Effect of the N^1-Oxido Group. To the best of our knowledge, all the 3-azido-*as*-triazine 1-oxides previously known have been reported to be true azides, both in the solid state and in solution.[2,5,16] The IR spectra of **11–13** in KBr seem to confirm this general observation because of the appearance of strong azide bands at 2140, 2130, and 2140 cm^{-1}, respectively. Nevertheless, a careful examination of their ^{1}H NMR spectra in Me_2SO-d_6 indicates that, beside the azide, a second tautomer is always present. Taking into account the observed chemical shifts, we attribute angular structures **11b–13b** to these tetrazole tautomers, the proportions of which in the respective equilibria amount to 67%, 30%, and 20%. On comparison of **11–13** with **2–4**, the N^1-oxido groups appears to behave as a moderate electron-withdrawing substituent (viz., the azide form is generally favored)[5] that preferentially "deactivates" its ortho position (i.e., the cyclization on N-4 instead of on N-2 is preferred).

The striking case of **11**, in which the angular tetrazole form predominates in Me_2SO, encouraged us to study it in more depth. In its ^{1}H NMR spectrum run at 90 MHz in $CDCl_3$ (see Table IV) only one compound can clearly be seen, which must be **11a**, since the NMR spectrum of bromo derivative **8** is almost identical and the IR spectrum in $CHCl_3$ shows a strong azide band. However, a very small methyl peak (≤3% of the mixture), which we tentatively assigned to **11b**, can be detected too. The aromatic protons of the major species appear as an AXX′ system, with $|J_{AX} + J_{AX'}| = 2.5$ Hz, when the methyl group at δ 2.60 is irradiated. Moreover, the methyl doublet collapses to a singlet by decoupling the proton at δ 8.15 (H-8, part A of the above-mentioned AXX′ system). Thus, the assignments for the NMR spectrum of **11a** in $CDCl_3$ shown in Table IV, which agree with those of **2a** (Table I), are conclusively established.

In acetone-d_6 two tautomers in almost equal proportions are observed. The δ values for one of them correlate with those observed in $CDCl_3$, and, therefore, they can be assigned to **11a**. The aromatic signals of the second tautomer are only compatible with **11b**.

As stated before, the relative amount of **11b** increases in Me_2SO-d_6. In fact, the NMR spectra in acetone-d_6 and in Me_2SO-d_6 are practically identical except for a small difference in the relative intensities of the aromatic and methyl peaks of tautomers **11a** and **11b**.

Experimental Section

Melting points were obtained on a Büchi apparatus and are uncorrected. IR spectra were determined on Perkin-Elmer 283 or Pye Unicam instruments. The 60-MHz ^{1}H NMR spectra were obtained on Perkin-Elmer R-12B and R-24 spectrometers, 90-MHz ^{1}H NMR spectra on a Varian EM-390 (IQOG, Madrid), and ^{13}C NMR spectra on a Varian XL-200 (Facultad de Quimica, Barcelona); chemical shifts are reported in parts per million with respect to internal Me_4Si in all the cases, and J values are given in hertz. Mass spectra were recorded on a Hewlett-Packard 5930A spectrometer. Elemental analyses were performed by Ms. M. Guerra, Instituto de Quimica Bio-orgânica, Barcelona.

3-Bromobenzo-*as*-triazine 1-Oxides 8-10. Solutions of 9.0 mmol of sodium nitrite in a minimum amount of water were added dropwise to stirred solutions of 1.6 mmol of the 7-methyl, 7-methoxy, and 5,7-dimethyl derivatives of 3-aminobenzo-*as*-triazine 1-oxide[7] in 5 N hydrobromic acid cooled to 5 °C. The solutions were stirred overnight and then extracted with methylene chloride. The organic extracts were dried over anhydrous potassium carbonate and filtered, and the solvent was evaporated to give crude solids, which were purified by column chromatography over silica gel with benzene as the eluent (in a hood) to afford **8–10** in yields of 30–35%.

7-Methyl derivative (**8**): mp 206–207 °C; IR (KBr) 3090, 3060, 1615, 1565, 1505, 1480, 1445, 1375, 1328, 1265, 1180, 1075, 960, 838 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.89 (br s, H-5 and H-6), 8.22 (br s, H-8), 2.60 (d, J = 1.0, Me); mass spectrum, m/e 241 and 239 (M^+).

7-Methoxy derivative (**9**): mp 195–196 °C; IR (KBr) 3105, 3040, 1620, 1570, 1505, 1480, 1375, 1230, 955 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.75 (br s, H-5 and H-6), 7.93 (br s, H-8), 4.03 (s, OMe); mass spectrum, m/e 257 and 255 (M^+).

5,7-Dimethyl derivative (**10**): mp 202–204 °C; IR (KBr) 3090, 3045, 1615, 1570, 1500, 1487, 1460, 1420, 1378, 1320, 1250, 1188, 1170, 980, 865 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.62 (br s, H-6), 7.98 (br s, H-8), 2.53 (br s, Me-7), 2.68 (br s); mass spectrum, m/e 255 and 253 (M^+).

3-Bromobenzo-*as*-triazines 5–7 from 3-Aminobenzo-*as*-triazines. The procedure was identical with that described above for the *N*-oxido derivatives, with similar yields. For **6**, a second column chromatography, over alumina with chloroform as the eluent, was necessary (to separate the desired compound from a dibrominated product).

Reduction of 8–10 to 5–7. To solutions of 3 mmol of **8–10** in 300 mL of ethanol was added 4 mmol of sodium dithionite in 30 mL of water, and the mixtures were heated at reflux for 2 h. The resulting solutions were evaporated to dryness, the solid residues dissolved in methylene chloride, and the inorganic products filtered off. Evaporation of the solvent gave solids which were purified by column chromatography over alumina, with chloroform as the eluent, to give **5–7** in 70–75% yields.

7-Methyl derivative (**5**): mp 160–161 °C; IR (KBr) 3070, 3050, 1622, 1555, 1540, 1492, 1395, 1275, 1172, 1035, 1005, 830 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.90 (br s, H-5 and H-6), 8.28 (br s, H-8), 2.60 (d, J = 1.0, Me); mass spectrum, m/e 225 and 223 (M^+).

7-Methoxy derivative (**6**): mp 190–191 °C; IR (KBr) 3090, 3040, 1615, 1500, 1420, 1215, 1185, 1145, 1045, 1005, 845 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.76 (br s, H-5 and H-6) 7.89 (br s, H-8), 4.07 (s, OMe);

(14) The **4a**/**4b**/**4c** ratios given are those measured after the equilibrium position was reached in the NMR sample tube, usually after 1 h. In fact, the barriers for isomerization seem to be greater in this case than in the other compounds. Work is in progress to establish the effect of the temperature on this ternary equilibrium.

(15) For a study of the influence of steric effects on an azide–tetrazole equilibrium, see: M. Rull and J. Vilarrasa, *Tetrahedron Lett.*, 4175 (1976).

(16) T. Sasaki and M. Murata, *Chem. Ber.*, **102**, 3818 (1969).

mass spectrum, m/e 241 and 239 (M^+).

5,7-Dimethyl derivative (**7**): mp 170–171 °C; IR (KBr) 3050, 2970, 1620, 1565, 1482, 1435, 1410, 1380, 1255, 1157, 1147, 1050, 1008, 860 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.74 (br s, H-6), 8.12 (br s, H-8), 2.68 (br s, Me-7), 2.71 (br s, Me-5); mass spectrum, m/e 239 and 237 (M^+).

3-Azidobenzo-*as*-triazine N^1-Oxides 11–13. To solutions of 2 mmol of **8–10** in 50 mL of acetone was added 2.2 mmol of sodium azide dissolved in a minimum volume of water, and the resulting solutions were heated at reflux for 3 h. The reaction mixtures were then diluted with water and extracted with methylene chloride. The organic extracts were dried over magnesium sulfate and, after being filtered, concentrated to 5–7 mL. On addition of hexane, products **11–13**, in 55%, 70%, and 68% yields, respectively, were obtained.

7-Methyl derivative (**11**): mp 118–119 °C; mass spectrum, m/e 202 (M^+). Anal. Calcd for $C_8H_6N_6O$: C, 47.53; H, 2.99; N, 41.57. Found: C, 47.31; H, 3.22; N, 41.30.

7-Methoxy derivative (**12**): mp 139–141 °C; mass spectrum, m/e 218 (M^+). Anal. Calcd for $C_8H_6N_6O_2$: C, 44.04; H, 2.77; N, 38.52. Found: C, 44.00; H, 2.57; N, 38.31.

5,7-Dimethyl derivative (**13**): mp 157–158 °C; mass spectrum, m/e 216 (M^+). Anal. Calcd for $C_9H_8N_6O$: C, 50.00; H, 3.73; N, 38.87. Found: C, 50.28; H, 3.98; N, 38.60.

3-Azidobenzo-*as*-triazines 2–4. The general procedure was identical with that described for the corresponding N^1-oxido derivatives but started from **5–7**. Compounds **2–4** were obtained in 43%, 89%, and 47% yields, respectively.

7-Methyl derivative (**2**): mp 90–92 °C; mass spectrum, m/e 186 (M^+). Anal. Calcd for $C_8H_6N_6$: C, 51.61; H, 3.26; N, 45.14. Found: C, 51.84; H, 3.01; N, 44.88.

7-Methoxy derivative (**3**): mp 146–148 °C; mass spectrum, m/e 202 (M^+). Anal. Calcd for $C_8H_6N_6O$: C, 47.52; H, 3.00; N, 41.56. Found: C, 47.20; H, 3.24; N, 41.29.

5,7-Dimethyl derivative (**4**): mp 111–113 °C; mass spectrum, m/e 200 (M^+). Anal. Calcd for $C_9H_8N_6$: C, 53.99; H, 4.03; N, 41.98. Found: C, 53.78; H, 4.31; N, 41.85.

Registry No. 2a, 82581-98-4; **2b**, 82581-99-5; **2c**, 82582-00-1; **3a**, 82582-01-2; **3b**, 82582-02-3; **3c**, 82582-03-4; **4a**, 82582-04-5; **4b**, 82582-05-6; **4c**, 82582-06-7; **5**, 54448-63-4; **6**, 82582-07-8; **7**, 82582-08-9; **8**, 82582-09-0; **9**, 82582-10-3; **10**, 82582-11-4; **11a**, 82582-12-5; **11b**, 82582-13-6; **12a**, 82582-14-7; **12b**, 82582-15-8; **13a**, 82582-16-9; **13b**, 82582-17-0; 7-methyl-3-aminobenzo-*as*-triazine 1-oxide, 27281-74-9; 7-methoxy-3-aminobenzo-*as*-triazine 1-oxide, 27238-35-3; 5,7-dimethyl-3-aminobenzo-*as*-triazine 1-oxide, 82582-18-1.

Heterocyclic Deformations from Molecular Enlargement

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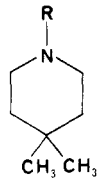
The ease of distortion of saturated nitrogen heterocycles has been examined by progressively increasing the bulk of the substituent at nitrogen. The heterocycles included the pharmacophoric piperidine and morpholine six-membered rings, as well as the five-membered oxazolidine ring. Response to increased bulk of substitution was intended to be a crude model for distortions within the drug–receptor complex. Substitution at nitrogen included methyl, (1-adamantyl)methyl, and 6-substituted β-cyclodextrin within a tetrahedral series, and acetyl and (1-adamantyl)carbonyl within a trigonal series. With methyl and acetyl serving as standards for the undistorted rings, we have found that the NCH_2CH_2X dihedral angle within all three heterocycles is decreased only by about 1° on introduction of the adamantyl groups. In agreement with this flattening distortion, the barrier to ring reversal of the piperidine is decreased by 1.4 kcal/mol on replacement of *N*-methyl by *N*-adamantylmethyl. The β-cyclodextrin ring imposes a much more severe distortion, as this same dihedral angle in the piperidine and morpholine rings decreases 5–6°. The barrier to rotation about the amide bond decreases 5–6 kcal/mol in all three heterocycles on going from acetyl to adamantylcarbonyl. These studies show that the response of these heterocycles to increased steric bulk of N substitution is a flatter and hence more flexible ring.

When a drug or hormone complexes with its biochemical receptor, it adopts an appropriate conformation. This conformation may be the same as that of the ground state, a distorted variety of the ground state, or a new, stable conformation. For many cyclic molecules, full rotations about single bonds are not possible, so that the conformational alternatives comprise either rearrangement of substituent positions or distortions of the ground-state conformation. These distortions may consist of partial rotations about single bonds (torsional modifications) or alterations of bond angles (valence-angle deformations).

In order to examine the ability of ring compounds to distort on complexation with a larger molecular entity, we have prepared a series of N-substituted heterocycles, which would be termed partially flexible in the Williams classification.[2] Piperidine and morpholine rings are particularly common in drugs, so we have selected **1** and **2** as



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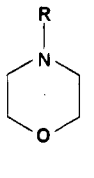

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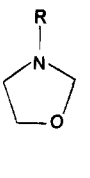

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subjects for this study. Whereas the six-membered ring is relatively rigid and subject only to the high-energy process of ring reversal (aside from the deformations mentioned above), the five-membered ring is quite flexible and subject to the low-energy process of pseudorotation. Thus the oxazolidine **3** may respond in a different fashion from the piperidine and the morpholine compounds. The *gem*-dimethyl group was placed in the piperidine ring in order to simplify the ^1H spectrum.

Our objective was to examine rings **1–3** in order to assess their sensitivities to distortion on progressive enlargement of the group R attached at nitrogen. The results would give some insight into the events that occur on formation

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(2) Williams, R. J. P. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 766–777.

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