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The Steric Course of Some Electrophilic Additions to the Tetrahydropyridazine Ring Moiety of Benzo[g]phthalazino[1,2-b]pyridazine-6,13-dione Derivatives. I.

M. Carmen Cano, Fernando Gómez-Contreras*, Ana M. Sanz, and María J. R. Yunta

Departamento de Química Orgánica I, Facultad de Ciencias Químicas, Universidad Complutense
28040 Madrid (Spain)

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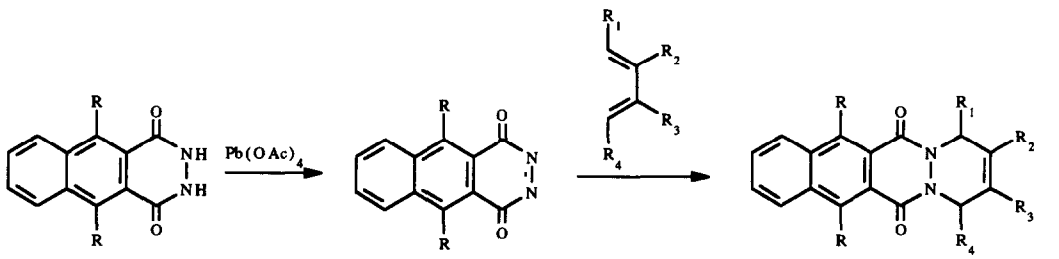
Abstract: *The functionalization of ring A in diazatetracyclic analogues of anthracyclinones via electrophilic addition of positive halogen sources has been investigated. Bromine azide, iodine azide, NBS/H_2O/DMSO and NBS/EtOH were the reactants of choice. Dehydrohalogenation and further regiospecific addition products to the C-1/C-2 double bond have been found in most cases besides the expected addition compounds. Conformational homogeneity and trans-axial orientations are shown by all the isolated compounds. The influence of the attacking species over the nucleophilic step and that of the carbonyl neighbouring groups over the conformational features have been evaluated.*

Much effort has been devoted in recent years to the synthesis of the antitumor anthracyclines and anthracenediones.[1] However, considerable room for improvement exists, due to the limitations imposed by the high dose-dependent cardiotoxicity shown by most of the known synthetic anthracyclines.[2] The undesirable effects of anthracyclines seem to be related to the redox potential of the quinone moiety of the anthracyclinone aglycon.[3] This fact has led to the preparation of a wide variety of anthracyclinone and anthracenedione mimetics with different redox properties including analogous polycyclic structures containing heteroatoms in the backbone rings.[4]

Benzo[g]phthalazino[1,2-b]pyridazino-6,13-dione derivatives 1 can be considered as nitrogenated analogues of anthracyclinones and, therefore, they are valuable as potential anticancer agents. Compounds 1 contain the three main features that seem to be responsible for the intercalating properties of anthracyclinones: an adequate planarity area in the aromatic rings moiety, a quinone-like system and a conformationally flexible terminal ring with substituents capable of binding to the DNA bases.[5]

The synthesis of the diazatetracyclic backbone has been achieved via the [4+2] cycloaddition of benzo[g]phthalazine-1,4-dione derivatives with the appropriate dienes[6] (Scheme 1). The dienophiles are quite unstable and must be formed *in situ* by oxidation of the corresponding cyclic hydrazides.[7] Care should always be taken to use dienes unable to react with the oxidant (or to be oxidized by the diazaquinone itself) under the reaction conditions employed. This means that functionalization of the tetrahydropyridazine terminal ring moiety has to be performed after the formation of the diazatetracyclic adduct.



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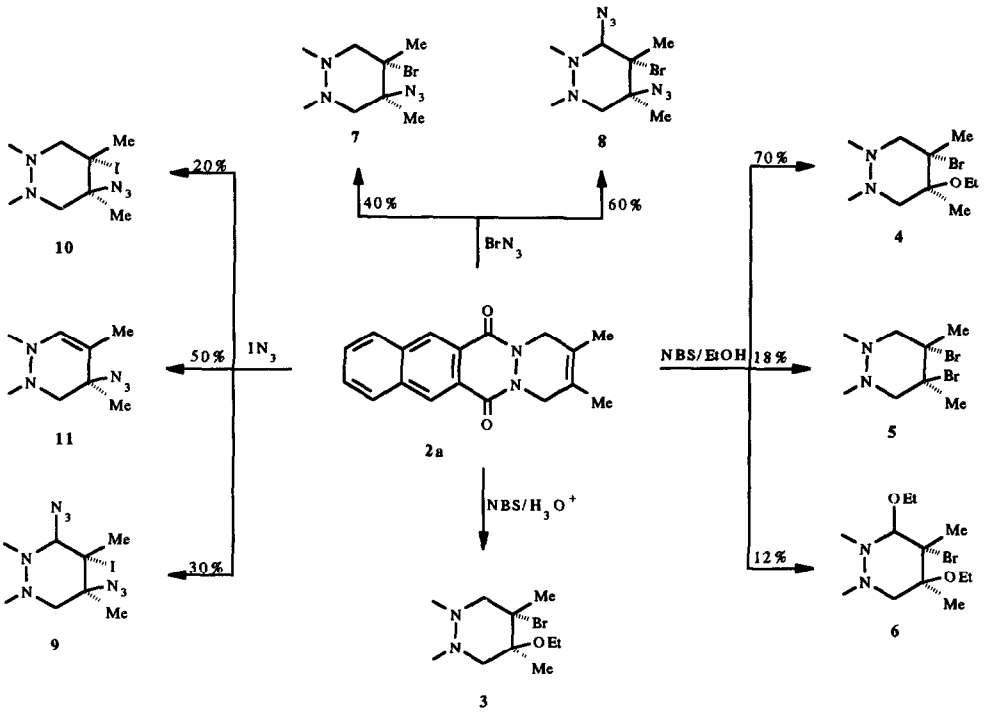
Scheme 1

Electrophilic additions to the C-2/C-3 double bond seem to be useful for the introduction of substituents providing the desired DNA intercalating properties. As has been repeatedly shown,[5] the position and stereochemistry of the ring A substituents and the conformation adopted by the ring itself are decisive factors for achieving the required level of intercalation. In this respect, it should be noted that the presence of the carbonyl groups in the ring B of compounds **1** greatly affects the geometry of ring A.[8] Substitution at C-1 leads to derivatives with the substituent axially oriented, whereas C-1/C-4 disubstitution gives like-boat conformations, in order to minimize interactions with the C=O groups at the ring B moiety.

All these facts prompted us to analyze the course of electrophilic additions to the C-2/C-3 double bond in derivatives alkylsubstituted at different positions of the tetrahydropyridazine ring. In order to test the reactivity of ring A and the influence of the electronic effect due to the substituent, the stereochemically "not conflictive" 2,3-dimethyl and 2-methyl substituted adducts **2a** and **2b** were chosen for the first attempts. Bromine azide, iodine azide, N-bromosuccinimide/H_2O and N-bromosuccinimide/EtOH were the reactants selected, as all of them were able to introduce hydroxy, alkoxy or amino-precursor groups into the ring A moiety.

Scheme 2 displays the results obtained by treatment of 2,3-dimethyl-1,4,6,13-tetrahydrobenzo[g]-pyridazino[1,2-b]phthalazine-6,13-dione **2a** with the reactants of choice. In all cases, considerable amounts of unchanged **2a** were recovered, due to the lack of reactivity caused by the electron-withdrawing effect of the amido groups. However, ring-opening took place easily under harder reaction conditions to give mainly high amounts of benzo[g]phthalic anhydride. A range of experiments was performed with every

reactant employed. Conditions described in the experimental part were those ones combining the highest yield in the addition products with the least extent of ring-opening. In fact, the formation of ring-opening products was not detected under conditions reported below.



Scheme 2

In spite of the symmetry shown by the substrate, a range of products were obtained in every case but the NBS/H_2O reaction. This last, as previously described,[9] afforded exclusively bromohydrin **3**. Treatment of **2** with NBS/H_2SO_4/EtOH at 50°C led to the isolation of the r-2-bromo-t-3-ethoxy (**4**), r-2-t-3-dibromo (**5**), and t-2-bromo-r-1,c-3-diethoxy (**6**) derivatives in relative percentages of 70:18:12. Bromine azide in dichloromethane/nitromethane at room temp. originated the r-1,c-3-diazido-t-2-bromo (**7**) and t-3-azido- -r-2-bromo (**8**) derivatives in a 60:40 relation, and iodine azide in chloroform/acetonitrile yielded the r-1,c-3-diazido-t-2-iodo (**9**) and the t-3-azido-r-2-iodo (**10**) derivatives, together with allylazide **11** in 30:20:50 relative percentages. The products were isolated in a grade of purity enough for identification after laborious preparative t.l.c. work, and previous 300 MHz ^{1}H NMR spectroscopic analyses were made in order to confirm that no structural changes had occurred during the purification procedure. The distribution of the addition derivatives in the reaction mixtures was calculated from the integration of the signals displayed by the methyl groups in the ^{1}H NMR spectra. Table 1 shows some properties of products of addition to the substrate **2a**.

Table 1. Some Analytical and Spectroscopic Data of the Addition Products from 2a and 2b

Compd.	Yield[a] (%)	Rf[b]	MS m/e (%)			IR KBr, cm^{-1}		
3	56	0.67	388(10,M^+)	308(22)	293(8)	3440(O-H)	1645(C=O)	1065(C-O)
4	30	0.35	416(34,M^+)	371(2)	291(62)	1655(C=O)	1240(C-O)	670(C-Br)
5	8	0.4	452(8,M^+)	292(11)	212(16)	3050(C=C)	1665(C=O)	1630(C=C)
6	6	0.43	460(10,M^+)	416(3)	335(7)	1655(C=O)	1150(C-O)	670(C-Br)
7	36	0.61	454(4,M^+)	412(10)	292(30)	2095(N_3)	1650(C=O)	675(C-Br)
8	28	0.53	412(9,M^+)	371(10)	292(29)	2100(N_3)	1660(C=O)	1625(C=C)
9	6	0.43	503(10,M^+)	461(41)	292(30)	2100(N_3)	1655(C=O)	1625(C=C)
10	8	0.36	461(15,M^+)	333(2)	291(22)	2105(N_3)	1655(C=O)	1625(C=C)
11	28	0.30	333(2,M^+)	292(30)	277(15)	2100(N_3)	1655(C=O)	1620(C=C)
13	46	0.09	374(8,M^+)	294(30)	276(10)	3410(O-H)	1645(C=O)	620(C-Br)
14	6	0.09	374(8,M^+)	294(30)	276(10)	3410(O-H)	1645(C=O)	620(C-Br)
15	28	0.20	438(21,M^+)	357(13)	278(25)	3010(C=C)	1670(C=O)	1635(C=C)
16	24	0.09	402(56,M^+)	321(17)	277(67)	1640(C=O)	1155(C-O)	665(C-Br)
17	4	0.15	402(10,M^+)	321(16)	277(67)	1660(C=O)	1110(C-O)	665(C-Br)
18	8	0.26	482(10,M^+)	342(4)	262(36)	1645(C=O)	1095(C-O)	665(C-Br)
19	10	0.37	440(10,M^+)	398(4)	277(7)	2105(N_3)	1665(C=O)	660(C-Br)
20	16	0.37	440(10,M^+)	398(4)	277(7)	2105(N_3)	1665(C=O)	660(C-Br)
23	6	0.30	447(12,M^+)	319(4)	277(22)	2100(N_3)	1655(C=O)	1615(C=C)
24	14	0.42	319(3,M^+)	277(23)	254(21)	2095(N_3)	1655(C=O)	1615(C=C)

a) Whole yields taking into account the percentage of unreacted adduct recovered.

b) Measured under conditions described in the experimental part

The methyl groups chemical shifts are strongly affected by the nature of the substituents attached to the same carbon,[10] as can be seen in the NMR data shown in Table 2 ($\delta_{Me\text{-}C\text{-}I} > \delta_{Me\text{-}C\text{-}Br} > \delta_{Me\text{-}C\text{-}N3} = \delta_{Me\text{-}C\text{-}OH} > > \delta_{Me\text{-}C\text{-}OEt}$). This fact allows the use of δ_{Me} values for assignment purposes in the C-1-substituted compounds. Also J_{gem} in the methylene groups appear to be dependant on the substituent at the neighbouring carbon[11]

($J_I > J_{Br} > J_{N3} > J_{OEt} > J_{OH}$). On the other hand, the two protons corresponding to the same methylene group display $\Delta\delta$ (1.0-1.5 ppm) and J_{gem} (13-15 Hz) values that are indicative of conformational homogeneity for all the addition products, with the pseudoequatorial hydrogen falling under the deshielding effect of the carbonyl group. This behaviour contrasts with that one shown by substrates **2a** and **2b**, which exhibit conformational equilibrium via nitrogen inversion[6]. The presence of 1,3-*syn*-diaxial interactions between the axial hydrogens at C-1/C-4 and the substituents at C-2/C-3 (for example, in the azidoiodo derivative **10**, $\delta_{H\text{-}1a}$= 3.58 ppm and $\delta_{H\text{-}4a}$=3.95 ppm, figure 1) confirms that addition to the double bond occurs in a transdiaxial manner, as has been shown for related reactions performed on these substrates.[12]

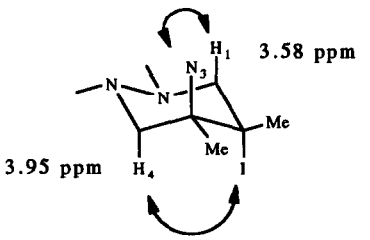


Fig. 1

Table 2. ^{1}H NMR Chemical Shifts (ppm, δ scale) and Coupling Constants (Hz) at the Terminal Tetrahydropyridazine Ring of the Addition Products of 2a, measured in $CDCl_3$.[a)]

Compd.	δ_{H1a}	δ_{H1a}	δ_{H4a}	δ_{H4e}	$\delta_{Me\text{-}C2}$	$\delta_{Me\text{-}C3}$	$J_{H1a\text{-}H1e}$	$J_{H4a\text{-}H4e}$
3[b)]	4.00(d)	5.02(d)	4.00(d)	4.80(d)	2.06(s)	1.73(s)	14.5	13.3
4	3.88(dd)	5.23(d)	4.10(d)	5.10(d)	2.01(s)	1.57(s)	14.8	14.0
5	3.98(d)	5.12(d)	3.98(d)	5.12(d)	2.13(s)	2.13(s)	14.6	14.6
6	-	6.36(s)	3.95(d)	4.92(d)	2.05(s)	1.56(s)	-	14.2
7	-	6.90(s)	4.03(d)	5.14(d)	2.17(s)	1.75(s)	-	14.2
8	3.97(d)	5.25(d)	4.06(d)	5.13(d)	2.20(s)	1.76(s)	15.0	14.4
9	-	6.86(s)	3.95(d)	5.00(d)	2.33(s)	1.78(s)	-	14.0
10	3.58(d)	5.03(d)	3.95(d)	4.95(d)	2.18(s)	1.78(s)	14.7	14.1
11	-	7.69(s)	4.00(d)	4.83(d)	1.95(s)	1.48(s)	-	13.6

a) TMS as internal standard; b) Measured in DMSO-d_6

In compounds **6**, **7**, and **9**, the high values obtained for H-1 (6.36-6.90 ppm) support an equatorial allocation coplanar with the neighbouring carbonyl. It has been previously established that the presence of alkyl substituents at C-1 freezes the conformational equilibrium with the C-1 substituents in a sterically favored pseudoaxial orientation.[8]

As can be seen, the expected addition products were not the only compounds obtained. All the reactions led to the isolation of products containing a second nucleophile at C-1, except when NBS/H_2O was the reactant. Although radical substitution at C-1 could be favored by stabilization of the radical intermediate by the amido group[9], we think that these compounds are formed via dehydrohalogenation of the initial electrophilic addition product and further regiospecific addition to the C-1/C-2 double bond on the basis of the following reasonings:

a) Conditions employed are in all cases typical for an ionic mechanism.[13] Control experiments performed in the dark and under a stream of molecular oxygen did not give significative changes in the products distribution.

b) Dehydrohalogenation is favored by the arising conjugation of the C-2/C-3 double bond with the amido group. This fact explains the easy isomerization of the C-1/C-2 double bond when compounds of the type **2** are treated with strong acids.[14]

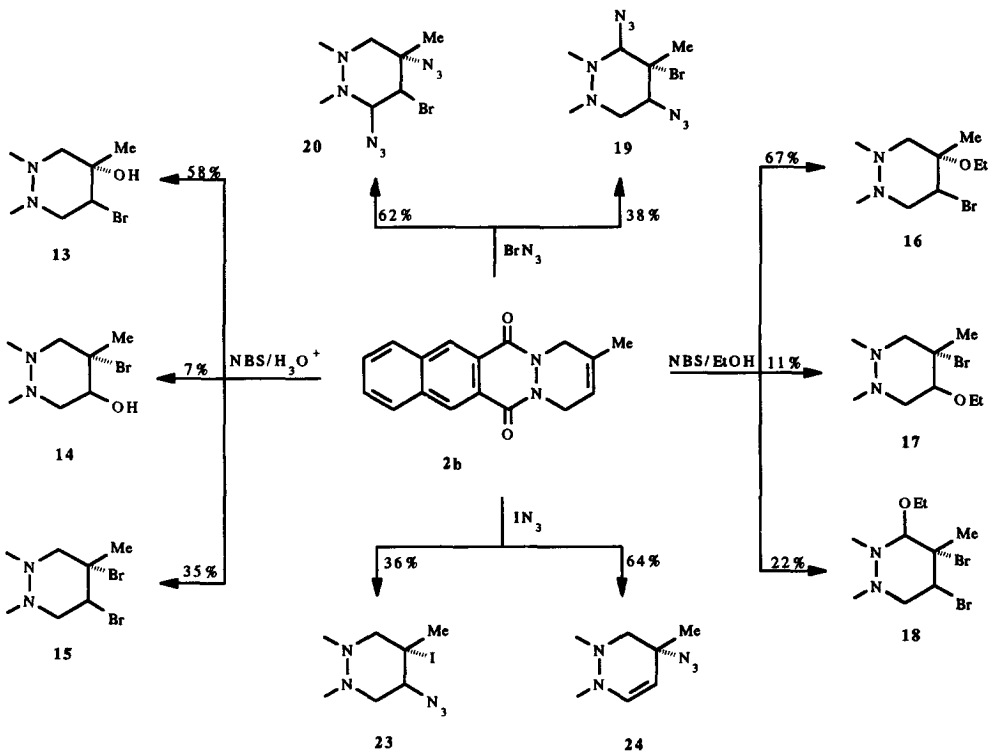
c) Allylic dehydrohalogenation of haloazides has been shown to be much favored in cyclic compounds.[15] Treatment of the so formed allylazides with a further amount of reactant led to halodiazido derivatives related to **6**, **7**, or **9**.[16] In our case, the intermediate allylazide **11** has been isolated together with the trisubstituted derivative **9**.

d) Regiospecificity found in additions to the C-1/C-2 double bond is analogous to that one described for electrophilic additions to compounds **12a** and **12b**, the acidic isomerization products of substrates **2a** and **2b**.[17]

Analogous treatment of 2-methyl-1,4,6,13-tetrahydrobenzo[g]pyridazino[1,2-b]phthalazine-6,13--dione, **2b** , led to results displayed in Scheme 3. The reaction of **2b** with NBS/H_2O/H^+ afforded the two isomeric bromohydrins **13** and **14**, and the dibromo derivative **15** in 58:7:35 percentage. With NBS/EtOH, the corresponding regioisomeric bromoethoxy derivatives **16** and **17** were found, together with an appreciable amount of the t-2,c-3-dibromo-r-1-ethoxy compound **18** (67:11:22). This last probably arises from the dehydrohalogenation of **15** and further addition of bromine and ethoxyl to the C-1/C-2 double bond. Dibromoderivatives related to **15** have been shown to dehydrohalogenate easily even under mild conditions.[18] The r-1,c-3-diazido-t-2-bromo derivatives **19** and **20** (38:62) are isolated by treatment of **2b** with bromine azide. Both of them must originate in the dehydrohalogenation and consecutive addition of the initially formed regioisomeric bromoazides **21** and **22**. Last, treatment of **2b** with iodine azide led to the t-3-azido-r-2-iodo compound **23** and the allylazide **24** (36:64). The last one is the dehydrohalogenation product from the major regioisomer **25**.

As commented previously for the 2,3-dimethylsubstituted substrate, the nature of the C-2 substituent is deduced from the methyl group chemical shifts ($\delta_{Me\text{-}C\text{-}Hal}$=1.8-2.2 ppm, $\delta_{Me\text{-}C\text{-}OEt}$, $\delta_{Me\text{-}C\text{-}N3}$=1.5-1.7 ppm, Table 3). An axial orientation can be assumed for the substituents at C-1 and C-3

respectively on the basis of the chemical shifts found for H-1 and the coupling constants values $J_{H\text{-}3,H\text{-}4e}$ and $J_{H\text{-}3,H\text{-}4a}$ (not higher than 4 Hz). It can be seen that $J_{H\text{-}3,H\text{-}4a} < J_{H\text{-}3,H\text{-}4e}$ in all cases. This fact is due to the transcoplanarity between H-4a and the electronegative substituent at C-3, that reduces $J_{H\text{-}3,H\text{-}4e}$,[19] as has been shown for related diazatetracycles.[12] Furthermore, long-range W couplings between H-1 and H-3 (0.8-1.4 ppm) appearing both in the C-1 substituted and unsubstituted products confirm the axial orientation of the C-1 and C-3 substituents.



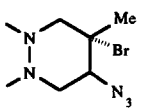
Scheme 3

The chemical shift differences between the two methylenic protons at C-1 in compounds **13- 17** and **23** are substantially higher than those found for the methylene at C-4. This fact has also been observed in related derivatives of **2b**,[12] and it has been suggested that the lower steric requirements in the C-3/C-4/N-5 moiety causes a prevalence of the distorting effect due to the amido group, giving place to an enhanced planarity. Therefore, the axial methylenic hydrogens approach the plane of the carbonyl groups whereas the equatorial ones move away. We have calculated the torsion angles between the C-3 and C-4 protons by means of the Altona relationship[20] from the experimental coupling constants. Results obtained (Table 4) are indicative of a distortion from the "pure" chair form around the C-3/C-4/N-5 moiety. As could be expected, compound **20** exhibits the highest $\phi_{H\text{-}3,H\text{-}4e}$ value (67.9°), because the tetrahydropyridazine ring is puckered in order to minimize the C-4 substituent/carbonyl group interaction.

Table 3. ^{1}H NMR Chemical Shifts (δ scale) and Coupling Constants (Hz) at the Terminal Tetrahydropyridazine Ring of the Addition Products from 2b, measured in $CDCl_3$.[a)]

Compd	δ_{H1a}	δ_{H1e}	δ_{H3}	δ_{H4a}	δ_{H4e}	$\delta_{Me\text{-}C2}$	$J_{H1a\text{-}H1e}$	$J_{H1\text{-}H3}$	$J_{H3\text{-}H4a}$	$J_{H3\text{-}H4e}$	$J_{H4a\text{-}H4e}$
13	3.97(d)	4.30(d)	4.25(m)	4.46(dd)	4.58(dd)	1.50(s)	13.2	-	3.3	5.4	14.8
14	3.95(d)	4.82(d)	4.72(m)	4.44(dd)	4.90(dd)	1.90(s)	14.4	-	3.5	3.9	14.7
15	4.01(d)	4.92(dd)	4.70(m)	4.56(dd)	4.95(dd)	2.01(s)	14.3	1.4	3.0	3.6	13.8
16	3.82(d)	4.77(dd)	4.32(m)	4.38(d)	4.90(d)	1.50(s)	14.1	1.4	2.9	3.9	13.8
17	3.94(d)	4.92(d)	4.49(d)	4.46(dd)	4.81(dd)	2.11(s)	14.4	-	2.8	2.5	13.4
18	-	6.30(s)	4.79(m)	4.63(dd)	4.95(dd)	2.17(s)	-	1.0	6.4	4.3	13.6
19	-	6.74(d)	4.11(dt)	4.46(dd)	4.98(dd)	2.19(s)	-	0.8	3.6	3.9	14.1
20	3.73(d)	4.81(dd)	4.36(t)	-	6.93(d)	1.70(s)	13.7	1.8	-	2.1	-
23	3.98(d)	4.64(dd)	4.54(m)	3.75(dd)	4.60(m)	2.20(s)	14.3	0.8	3.5	3.6	13.5
24	3.70(d)	4.96(dd)	5.40(dd)	-	7.81(d)	1.50(s)	13.5	1.3	-	8.2	-

a) TMS as internal standard.



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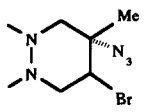

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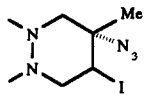

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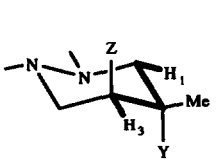
From all this evidence it can be concluded that the addition products are conformationally homogeneous and that compounds **13**, **14**, **15**, **16**, **17** and **23** assume a r-2-Y,t-3-Z disposition (**26**), with the electronegative substituents axially oriented and ring A appearing as a flattened chair form in the neighborhood of C-4, whereas **18**, **19**, and **20** have an all axial r-1-Y,t-3-Z,c-2-Y disposition (**27**, **28**), in which the chair form is distorted to a greater extent owing to the C-1 substituent/carbonyl interaction. In fact, the presence of the carbonyl groups at ring B forces a conformation with two bulky substituents in a 1,3-*syn*-diaxial orientation.



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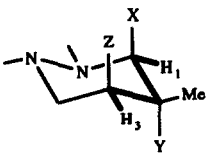

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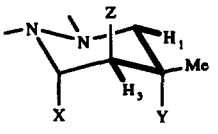

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The influence of the attacking species over the nucleophilic step can be inferred from additions performed on the 2-methylsubstituted substrate, since in this case the product distribution does not depend on the electrophilic step owing to the absence of steric requirements.[21] Therefore, the high percentage of C-2 attack is really indicative of the great influence exerted by the electronic effect of the methyl group. A higher selectivity in the nucleophilic attack is found for the NBS reactions with respect to those ones performed with halogen azides (Table 5). It is well known that azide ions have a notorious preference for attacking the less substituted carbon atoms in unsymmetrical epoxides, in conformity with the dominance of primary steric effects over polar effects in S_N2 displacement reactions.[15] From a stereoelectronic point of view, the energetically more favored transdiaxial addition products are exclusively obtained in all reactions performed. Antiperiplanar attack of the nucleophile is favored both over C-2 and C-3, owing to the coexistence of two epihalogenonium ions in conformational equilibrium which are interconverted at a rate that is much higher than that of the nucleophilic attack.[21]

Table 4. Torsion Angles (°C) Calculated for the Tetrahydropyridazine Terminal Ring of the Addition Products to 2b.

Compd.	$\phi_{H3\text{-}H4e}$	$\phi_{H3\text{-}H4a}$
15	54.6	305.4
16	52.1	304.6
17	59.2	311.3
18	49.4	329.4
19	55.4	313.4
20	67.9	-
23	55.4	311.2

Table 5. Regioselectivity in the Nucleophilic Attack for Electrophilic Additions to 2b.

Reactant	Distribution (C-2:C-3 attack)
NBS/H_2O	89:11
NBS/EtOH	86:14
BrN_3	62:38
IN_3	64:36
HBr (epoxide)	60:40

EXPERIMENTAL

M.p.s are uncorrected, and were determined in open capillary tubes with a Gallenkamp apparatus. IR spectra were recorded in KBr pellets on a Perkin-Elmer 257 spectrophotometer. NMR spectra were obtained with a Varian XL-300 spectrophotometer for solutions in $CDCl_3$ or d_6-DMSO with Me_4Si as internal reference. Assignments were made by appropriate decoupling experiments and comparison of the spectra of related structures. Direct inlet mass spectra were measured on a Hitachi Perkin-Elmer RMV-GM6 spectrometer. Chromatographic separations were carried out by using 20x20 cm preparative TLC plates coated with a 2 mm layer of silica gel $60PF_{254}$ Merck. Dichloromethane was refluxed over P_2O_5 and rectified. Chloroform was purified by washing with 2N NaOH, concentrated H_2SO_4 and water, drying with K_2CO_3 and distillation, and was inmediately used. "Dry" ethanol was obtained via the formation of the magnesium ethanolate and distillation. Nitromethane was purified by standing for a day with H_2SO_4, washing with water, drying over $MgSO_4$ and distillation. Acetonitrile was shaken with molecular sieve and, subsequently, with CaH_2 until no further hydrogen was evolved, and fractionally distilled over CaH_2. $MgSO_4$ was always used as the drying agent in the addition reactions work-up.

Benzo[g]phthalic hydrazide was obtained from $\alpha,\alpha,\alpha',\alpha'$-tetrabromo-o-xylene and maleic anhydride according to Cava et al.[22] Substrates **2a** and **2b** were prepared by oxidation of the hydrazide in the presence of the appropriate diene, following a procedure previously described.[23] The haloazide solutions were prepared as follows:

Bromine azide.

To a suspension of 0.05 mole of sodium azide in 30 mL of dichloromethane, 7 mL 0f 37% HCl were added. The heterogeneous mixture was stirred for 10 minutes at 0°C and 0.05 mole of molecular bromine was addded. After 30 minutes stirring, the organic layer was collected and used without further purification.

Iodine azide.

0.006 Mole of commercial chlorine iodide were added over a solution of 0.01 mole of sodium azide in 30 mL of dry acetonitrile cooled to 0°C. The mixture was stirred for 10 minutes and used without further purification.

The reaction mixtures of the electrophilic additions consisted of an appreciable amount of unreacted alkene (see yields in Table 1) and the addition products above described, and the percentages were calculated from the integration of the signals displayed by the methyl groups in the 300 MHz ^1H NMR spectra. Several runs were carried out for every condition and results reported are average values. The reaction mixtures were chromatographed, and IR, NMR and mass spectra were obtained for each one of the recovered fractions in order to confirm the identity and solve the stereochemistry of compounds involved. The stereoisomeric mixtures **13/14**, **16/17**, **19/20** and **21/22** could not be separated, as they gave only one spot in analytical t.l.c., but could be easily assigned on the basis of the NMR spectra.

Addition reactions conditions

a) *With NBS/H_2O.*- Equimolecular amounts of **2a-b** and N-bromosuccinimide were suspended in water

containing one drop of concentrated sulfuric acid. The suspension was stirred for 24 hours at 50°C and filtered after cooling. The white precipitate was repeatedly washed with water, dried, and submitted to preparative t.l.c. over silica gel by using toluene/ethanol (94/6) as the eluent.

b) *With NBS/EtOH*.- Equimolecular amounts of **2a-b** and N-bromosuccinimide were suspended in "dry" ethanol and stirred for 5 hours at 50°C. After addition of water, the solvent was removed to half of the initial volumen and the remaining solution was filtered. Work-up of the precipitate as in a) afforded a solid which was chromatographed over silica gel by using toluene/ethanol (98:2) as the eluent.

c) *With* BrN_3.- 0.03 Mole of **2a-b** in 30 mL of nitromethane were added to 35 mL of a solution of bromine azide in dichloromethane prepared as described above. After 30 min. stirring at room temperature the solvent was evaporated at reduced pressure to give a yellow residue which was submitted to preparative t.l.c. over silica gel by using toluene/ethanol (98/2) as the eluent.

d) *With* IN_3.- 0.03 Mole of **2a-b** in 30 mL of chloroform were added to 35 mL of a solution of iodine azide in acetonitrile prepared as described above. After 24 hours stirring at room temperature the reaction mixture was poured over 100 mL of cold water, extracted three times with 50 mL of chloroform, and the organic layer was sucessively washed with NaOH 0.1N, HCl 0.1N and aqueous sodium bicarbonate. After drying and evaporation of the solvent under reduced pressure, the residue was submitted to preparative t.l.c. over silica gel by using toluene/ethanol (98/2) as the eluent.

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