

DIAZAPOLYCYCLIC COMPOUNDS XXII.
THE ACTION OF N-CHLOROSUCCINIMIDE OVER DIAZAQUINONE ADDUCTS
UNDER IONIC AND FREE RADICAL CONDITIONS

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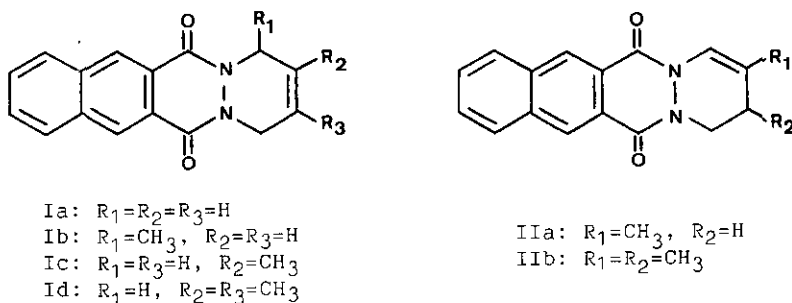
Abstract - The action of N-chlorosuccinimide over 4a,12a-diazatetracyclic systems obtained by cycloaddition of benzo(g)-phthalazine-1,4-dione with several dienes is reported. The reaction in acid aqueous medium leads to the formation of 1,2-chlorohydrins by ionic addition to the double bond at the terminal tetrahydropyridazine ring moiety. The stereochemical results of these additions are commented, and it can be deduced that the usual $A_{\text{D}}2$ mechanism is not followed. When the conditions favoring a free radical process are employed, the addition process is accompanied by substitution at the terminal aromatic ring.

The high reactivity of diazaquinones as dienophiles has been extensively used in recent years for the synthesis of new heterocyclic systems ¹. Among these, 4a,12a-diazatetracyclic compounds have been obtained by 4+2 cycloaddition reactions of benzo(g)phthalazine-1,4-dione with 1,3-butadiene derivatives ^{2, 3}. Further transformations have been performed over these structures in search of an improvement in the incipient biological activity as antibiotics shown by most of them. These transformations usually deal with the introduction of specific substituents at the terminal tetrahydropyridazine ring moiety ³⁻⁶ and, in many cases, the regio- and stereoselectivities of reactions performed led to interesting results ^{7, 8}, being specially noteworthy those in which the stereochemistry of the tetrahydropyridazine ring is involved, as happens with addition reactions of N-bromosuccinimide ⁸ or halogen azides ⁹.

Here we want to report the results obtained by treatment of these diazatetracyclic adducts with N-chlorosuccinimide (NCS) both under ionic and free radical conditions.

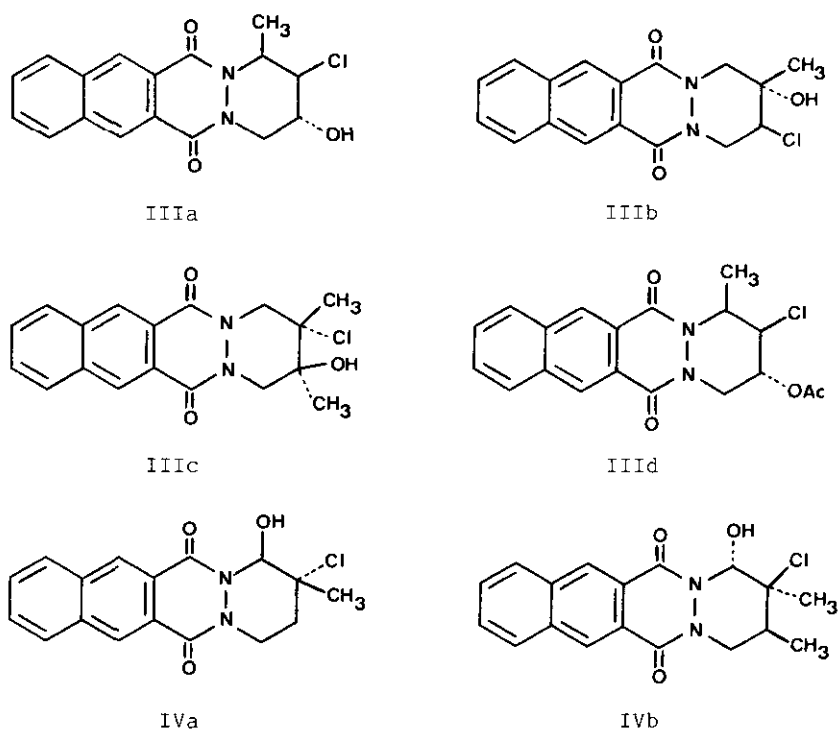
This reagent was selected for three reasons: the introduction of chlorine atoms

in the molecule should allow the comparison of the activities corresponding to chlorine and bromine (in fact, chlorine gives a higher antibacterial activity), replacement of NBS by NCS should be expected to favor free radical reactions on the aromatic rings and, finally, results obtained about the stereochemistry of NCS additions could confirm the hypothesis proposed for the NBS analogous reactions ⁸. In the first place, we checked the ionic addition of NCS to the double bond formed in the cycloaddition. In order to study the regioselectivity of the reaction, it was desirable to dispose of a variety of substrates in which the tetrahydropyridazine ring would be substituted in different positions. Therefore, the adducts Ia-d and rearrangement products IIa,b were selected as starting compounds. Ia-d were synthesized by the reaction of benzo(g)phthalazine-1,4-dione (formed "in situ" by oxidation of the corresponding hydrazide) with the respective diene. IIa,b were formed by rearrangement of the double bond in Ic and Id to the more conjugated 1,2-position in the presence of concentrated sulphuric acid ^{2, 3, 5}.



Scheme 1

Treatment of adducts Ib-d with NCS in aqueous suspension and in the presence of some drops of concentrated sulphuric acid (2 hr, 50°C) led to the formation of chlorohydrins IIIa (42% yield, mp 220-221°C, ν_{\max} (C₂Cl₄): 3270 (OH), 1660 (C=O), 1170, 1090 (secondary OH) cm⁻¹), IIIb (67% yield, mp 160-161°C, ν_{\max} (KBr): 3420 (OH), 1645 (C=O), 1280, 1130 (tertiary OH) cm⁻¹) and IIIc (89% yield, mp 200°C, ν_{\max} (C₂Cl₄): 3400 (OH), 1650 (C=O), 1210, 1120 (tertiary OH) cm⁻¹). In a similar way, chlorohydrins IVa (67% yield, mp 165-166°C, ν_{\max} (nujol): 3200 (OH), 1640 (C=O), 1280, 1080 (secondary OH) cm⁻¹) and IVb (81% yield, mp 190-191°C, ν_{\max} (C₂Cl₄): 3400 (OH), 1640 (C=O), 1250, 1080 (secondary OH) cm⁻¹) were obtained from adducts IIa,b. The most relevant data of the ¹H NMR spectra for these compounds are summarized in Table 1. In fact, the reactivity of the adducts towards electrophilic additions is greatly diminished by the electron-withdrawing effect of the amido groups. For example, no reaction is observed with iodine isocyanate, although it is an efficient reagent for electrophilic additions. Then,



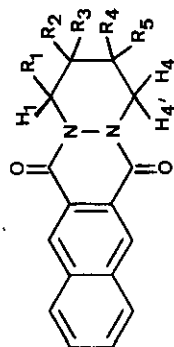
Scheme 2

the activating effect of the methyl groups is decisive and, as could be expected, the lowest yield corresponds to chlorohydrin IIIa, with the methyl group at the C₁ position, whereas IIIc is obtained in nearly quantitative yield. Contrary to what has been observed in the reactions with NBS⁸, the formation of the corresponding dichloro derivatives was not detected, but the starting hydrazide or 2,3-naphthalenedicarboxylic acid were usual by-products.

The reaction with NCS in aqueous acid medium has shown to be regio- and stereo-specific, being the only isomer isolated in every case the one represented in scheme 2. The relative position of the two new substituents at the piperazine ring was easily deduced from the chemical shifts of the adjacent methyl groups in the NMR spectra. The methyl substituents in a geminal disposition with respect to chlorine are more deshielded than those geminal to OH. This fact allowed the assignment in every case except in chlorohydrin IIIa, where the methyl group is less influenced by the nearest substituent. However, in the acetylated derivative IIIId, the introduction of an acetoxy group causes a strong deshielding of the geminal hydrogen (1.20 ppm) and a lower one of the adjacent equatorial methylenic proton (0.35 ppm) with respect to IIIa. It makes possible to use double resonance techniques which demonstrate that chlorohydrin IIIa has the proposed structure.

Table 1

^1H NMR spectroscopic data corresponding to the terminal piperidazine ring of the addition products with NCS in aqueous acid medium.



	R ₁	R ₂	R ₃	R ₄	R ₅
IIIa :	Me	Cl	H ₂	OH	H ₃
IIIb :	H ₁ '	Me	OH	Cl	H ₃
IIIc :	H ₁ '	Me	OH	Cl	Me
IIId :	Me	Cl	H ₂	OAc	H ₃
IVa :	OH	Me	Cl	H ₃	H ₃ '
IVb :	OH	Me	Cl	Me	H ₃

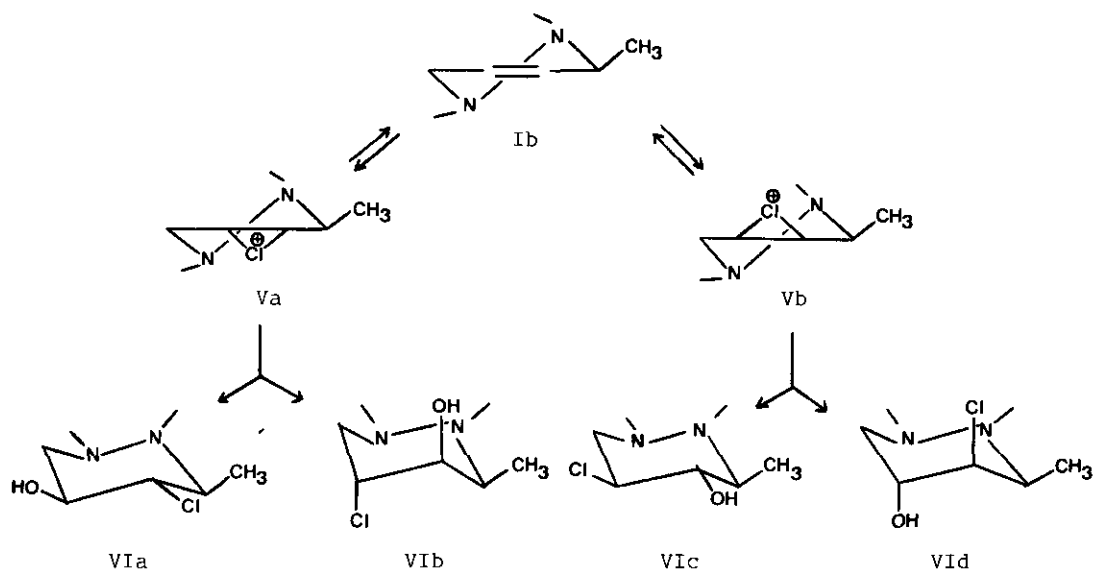
Compound	δ_{H_1}	δ_{H_3}	δ_{H_4}	$\delta_{\text{H}_4'}$	$\delta_{\text{Me-C}_2}$	J _{3,4}	J _{3,4'}	J _{4,4'}	Other significant data
IIIa	5.50(m)	4.05(m)	3.95(m)	4.65(m)	-	3.5	3.5	14.0	$\delta_{\text{H}_2}=4.45(\text{m})$, $\delta_{\text{Me-C}_1}=1.40(\text{d})$, $J_{\text{H}_3, \text{OH}}=4.0$, $J_{\text{Me}, \text{H}_1}=8.0$, $W_{1/2\text{H}_2}=8.0$
IIIb	3.95(d)	-	4.30-4.70	-	1.45(s)	-	-	-	$\delta_{\text{H}_1}=4.35(\text{d})$, $J_{1,1'}=14.0$
IIIc	3.95(d)	-	3.75(d)	4.65(d)	1.45(s)	-	-	14.5	$\delta_{\text{Me-C}_3}=1.75(\text{s})$, $\delta_{\text{H}_1}=4.85(\text{d})$, $J_{1,1'}=14.5$
IIId	5.40(m)	5.25(m)	3.95(dd)	5.00(dd)	-	3.0	3.0	15.0	$\delta_{\text{Me-C}_1}=1.40(\text{d})$, $\delta_{\text{H}_2}=4.25(\text{m})$, $J_{1,2}=4.0$, $J_{2,3}=2.0$
IVa	6.30(s)	2.30(m)	3.65(m)	5.00(m)	1.80(s)	-	-	$W_{1/2\text{H}_4}=21.0$ Hz	
IVb	6.25(m)	2.50-3.40	-	4.60(m)	1.70(m)	-	-	-	$\delta_{\text{Me-C}_3}=1.15(\text{m})$, $J_{\text{Me}, \text{H}_3}=3.0$

All spectra registered in DMSO-d₆. Chemical shifts measured in ppm (δ scale). Coupling constants measured in Hz.

On the other hand, spectroscopic data are consistent with the stereochemistry in which the terminal piperidazine ring appears in a slightly distorted chair form, and the new substituents are trans-diaxially oriented, whereas the methyl groups exhibit equatorial dispositions. Conformational features are supported by the chemical shift differences between axial and equatorial protons in the methylene groups, and also by the geminal coupling constant values, analogous to those obtained in other addition products studied in depth by X-ray diffraction techniques ^{10, 11}. The orientation of the ring substituents is also confirmed by the small values found for the couplings of both methylenic protons with the vicinal ones in the NMR spectra, which exclude the possibility of axial-axial relationships.

The regiospecificity of this reaction is worthy of a comment. The orientation of the substituents is not in accordance with the usual Ad_E2 mechanism. The activating effect of the methyl groups should favor attack of the nucleophile on the nearest carbon atom of the double bond, via the more stable carbonium ion, but this does not occur in compounds IIIa, IVa and IVb. Moreover, the strong deactivating effect of the amido groups does not affect either the orientation of the new substituents, as can be seen in IVa and IVb. The same features have been observed by us in some other electrophilic additions performed on other diazapolycyclic systems^{5, 8}. In a similar way, Berti and co-workers ^{12, 13} have reported that addition of N-haloamides to substituted cyclohexenes and dihydropyrans takes place in the anti-Markownikoff sense, and the same is noted by other authors in the iodoacetoxylation of cyclohexene derivatives ¹⁴. All these facts are usually explained on the basis of a mechanism in which the electrophilic step would be reversible, and the regio- and stereoselectivity of the reaction would be directed by a rate- and product-determining nucleophilic step ¹². The formation of an intermediate complex has been suggested in which the succinimido group is bonded to the epihalogenium ion. This species should be less reactive than the epihalogenium ion itself, and should favor a slow nucleophilic attack ¹².

The regiospecificity in the formation of chlorohydrins IIIa and IVb can be easily explained by this reasoning. In IIIa, the intermediate epichloronium ion must be the cis one, as shown in scheme 3, although the trans intermediate Va is more stable, this fact being in accordance with the hypothesis supposing that epichloronium ions are obtained in a reversible and fast step which does not control the steric course of the reaction. After that, attack of the nucleophile could take place over positions 2 or 3, and the specificity in the formation of VIId is due to the unfavorable conformational requirements leading to VIC (antiparallel attack at the 2 position would occur via a like-boat transition

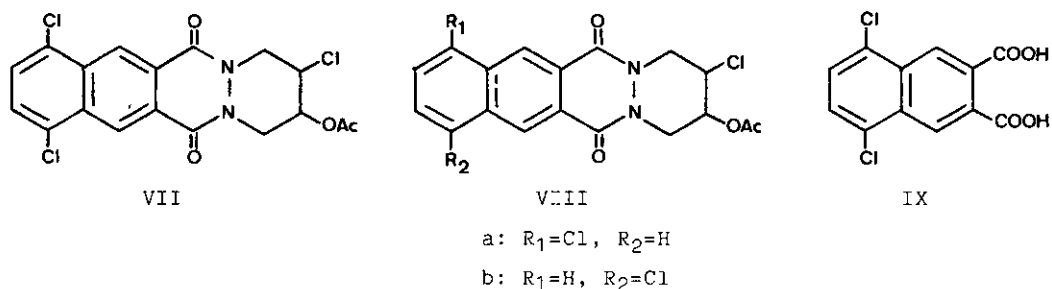


state ¹⁵). As can be seen, stereoelectronic factors in the nucleophilic step prevail over the inductive effects. The same arguments may be used for IVb. With respect to chlorohydrin IIIb, owing to the lack of steric requirements favoring cis or trans intermediates, only the activating effect of the methyl group may be considered, and the usual orientation rules are followed. It is not so in IVa, which is formed in spite of the combined effects of the amido and methyl groups directing the OH towards the C-2 position. This result is repeated in all kind of electrophilic additions performed on IIa ^{8, 9}, and has not been satisfactorily explained, although interaction between the nucleophile and the neighbouring amido group could be responsible.

It should be noted that stereochemical results obtained in the NCS additions to 4a,12a-diazatetracyclic compounds are strictly parallel to those reported with other electrophilic reagents, NBS included. On the contrary, it has been found that both N-haloamides gives place to different regioselectivities in additions to substituted cyclohexenes ¹².

Independently of the ionic additions commented above, adducts Ia, Ic and Id were treated with NCS/diethylamine in sulphuric acid/acetic acid solution, while irradiating for several hours at room temperature. These conditions usually lead to a free radical addition of chlorine and diethylamine to double bonds ¹⁶. Results obtained with these diazatetracyclic adducts were diverse and not easy to reproduce, involving addition to the double bond at the terminal tetrahydropyridazine ring and halogenation at the terminal aromatic ring. Opening to the corresponding hydrazide

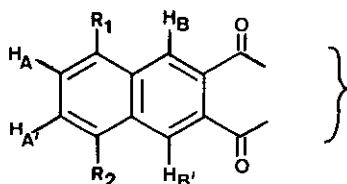
or dicarboxylic acid was also detected. Treatment of Ia under conditions described afforded a mixture of compounds VII (mp 118–120°C, ν_{\max} (nujol): 1750 (C=O acetate) 1625 (C=O amide), 1375, 1210 (C–O) cm^{-1} , m/e: 428(12, M^+), 426(14), 333(49), 331(74), 304(25), 196(31), 194(48), 136(100)) and VIII (mp 128–129°C, ν_{\max} (nujol): 1750 (C=O acetate), 1620 (C=O amide), 1380, 1220 (C–O) cm^{-1} , m/e: 393(15, M^+), 391(23), 333(8), 299(36), 297(100), 270(35), 188(25), 160(55)), which could be separated by preparative tlc in a ratio of 53/47. The position of the chlorine atoms in the aromatic ring of VII was determined on the basis of ^1H NMR data (Table 2). The for aromatic protons appear as two singlets at 9.20 and 7.65 ppm. The former clearly corresponds to the two hydrogens deshielded by the coplanar neighbouring carbonyl groups. The second singlet can be assigned by comparison with the chemical shifts of the aromatic hydrogens in the chlorohydrins (chlorine atoms have a negligible influence on the chemical shifts of protons in the same aromatic ring ¹⁷). In VIII, one of the hydrogens at the terminal aromatic ring has two ortho couplings (7.5 Hz and 12.0 Hz), whereas the other two protons have an



Scheme 4

Table 2

^1H NMR data of the aromatic rings in compounds obtained with NCS in sulphuric acid.



Compound	R_1	R_2	δ_{R_1}	δ_{R_2}	δ_{H_A}	$\delta_{\text{H}_A'}$	δ_{H_B}	$\delta_{\text{H}_B'}$
IIIc	H	H	8.30(m)	8.30(m)	7.95(m)	7.95(m)	8.85(s)	8.85(s)
VII	Cl	Cl	-	-	7.65(s)	7.65(s)	9.20(s)	9.20(s)
VIII	Cl	H	-	7.95(m)	7.70(m)	7.70(c)	9.25(s)	8.80(s)
IX	Cl	Cl	-	-	7.95(m)	7.95(m)	8.65(s)	8.65(s)

All spectra measured in CCl_3D , except IIIc (DMSO-d_6). Chemical shifts in ppm(δ).

ortho coupling each, indicating that the three hydrogens are consecutive. However, the relative position of the chlorine atoms with respect to the substituents at the piperidazine ring remains undetermined.

On the other hand, reaction of Id under the same conditions afforded chlorohydrin IIIc as the only product, whereas from Ic, 5,8-dichloro-2,3-naphthalenedicarboxylic acid, IX (mp 216–217°C, ν_{\max} (KBr): 3600–2300 (OH), 1700 (C=O), 1200 (C–O), 1060 cm^{-1}) was obtained by opening of a chlorinated product similar to VII and VIII. These free radical reactions could be an interesting procedure for introducing substituents in the aromatic rings, in order to approach the biological models, but lack of reproducibility and low yields obtained should be solved before using them for the synthesis of new diazatetracyclic derivatives.

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