Unusual Nitration of Substituted 7-Amino-1,8-naphthyridine in the Synthesis of Compounds with Antiplatelet Activity

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Several 1,8-naphthyridine derivatives have been diazotizated to obtain the corresponding hydroxy derivatives or mixture of hydroxy and hydroxy nitro derivatives. The respective amounts of hydroxy and hydroxy nitro derivatives depends on the nature of the substituents, on their position on the naphthyridine nucleus, on the amount of sodium nitrite and on the reaction temperature. A study of the electronic density of some molecules suggests a possible explanation of the effects induced by the nature of the substituents and of their position. Some of the compounds were tested for their ability to inhibit human platelet aggregation *in vitro* induced by arachidonic acid. Only compound **26** showed interesting antiplatelet activity.

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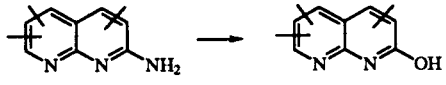
Diazotization of a considerable number of amino-1,8-naphthyridines **1** [1-19] in concentrated sulfuric acid with sodium nitrite has been carried out under different temperature conditions, generally from 0° to -15°, to give the corresponding hydroxy derivatives **2**.



1 **2**

In the course of our investigations on new molecules with antiplatelet activity we required the preparation of the known 2,7-dichloro-3-phenyl-1,8-naphthyridine **3** [12]. Thus, the 7-amino-2-hydroxy-3-phenyl-1,8-naphthyridine **4** [20] was diazotizated at 0°, as reported by Carboni *et al.* [12], to obtain a crude solid (Scheme 1, Table 1), that we found very difficult to purify either by crystallization or by flash chromatography because of its very low solubility. The crude solid was therefore refluxed with phosphoryl chloride to give, surprisingly and in contrast to our expectations, a mixture of dichloro derivative **3** [12] and dichloro nitro derivative **5**, in a ratio of about 1:1, that were separated by flash chromatography (Scheme 1, Table 2,3). Consequently the crude solid obtained by diazotization of compound **4** was a mixture of dihydroxy derivative **6** [12] and dihydroxy nitro derivative **7** likely in the ratio 1:1. The structures of **3** and **5** were confirmed by elemental analyses, mass spectroscopy and ^{1}H nmr data. The ^{1}H nmr spectrum of **3** shows a singlet at δ 8.60 due to H_4 and two doublets at δ 8.55 and δ 7.75 due to H_5 and H_6 respectively, whereas the ^{1}H nmr spectrum of **5** shows two singlets at δ 8.72 and δ 9.37 due to H_4 and H_5 respectively (Table 4).

The structure of **5** was then unequivocally demonstrated by chemical evidence.

Compounds **3** and **5** were then treated with sodium methoxide to give the corresponding dimethoxy derivatives **8** and **9** respectively (Scheme 1, Table 3). The compound **9** was transformed by catalytic reduction to 6-amino-2,7-dimethoxy-3-phenyl-1,8-naphthyridine **10** (Scheme 1, Table 3) confirming the presence of the nitro group on the 1,8-naphthyridine nucleus.

Moreover, compound **4** was treated with concentated nitric acid, in the mole ratio 1:1.1, in acetic anhydride, to obtain the 7-amino-2-hydroxy-6-nitro-3-phenyl-1,8-naphthyridine **11** (Scheme 2, Table 3), because in these conditions the nitration occurs only on the naphthyridine nucleus, as reported for 7-amino-2-hydroxy-4-phenyl-1,8-naphthyridine **12** [16].

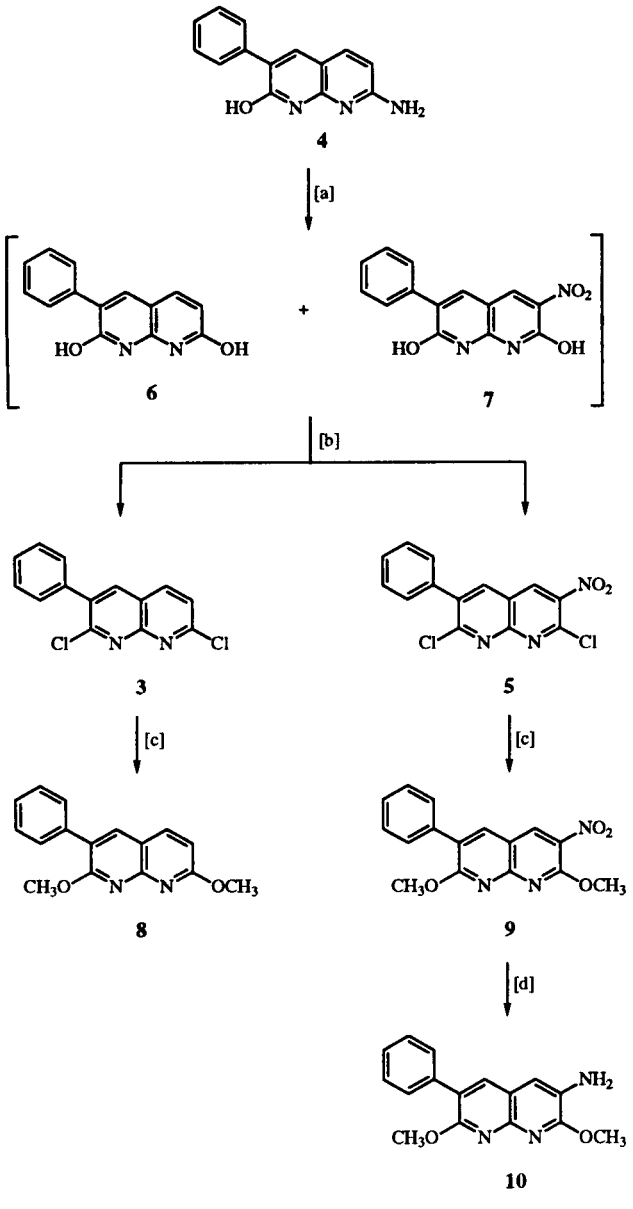
The structure of **11** was established by mass spectroscopy, elemental analysis and ^{1}H nmr data. The ^{1}H nmr spectrum of **11** (Table 4) shows two singlets at δ 8.02 and δ 8.82 due to H_4 and H_5 respectively.

Diazotization of **11** carried out at 0° gave a very low soluble mixture of **7** and **13** (Table 1), that was treated with refluxing phosphoryl chloride (Scheme 2) to obtain the 2,7-dichloro-6-nitro-3-phenyl-1,8-naphthyridine **5** and the 2,7-dichloro-6-nitro-3-(*p*-nitrophenyl)-1,8-naphthyridine **14** (Tables 2 and 3) which were separated by flash chromatography. In this way the structure of nitro derivative **7** obtained by diazotization of **4** was unequivocally proved.

An analogous behaviour has been verified by Nishigaky *et al.* during the diazotization of variously substituted pyrimidines [21].

In the light of these results we have carefully reinvestigated the diazotization of **4** [12], because, in that paper it was reported by mistake that the diazotization was carried out at 0° instead at -20°. When this reaction was repeated at -20° crude solid was obtained which was treated with refluxing phosphoryl chloride to give a mixture of dichloro

Scheme 1

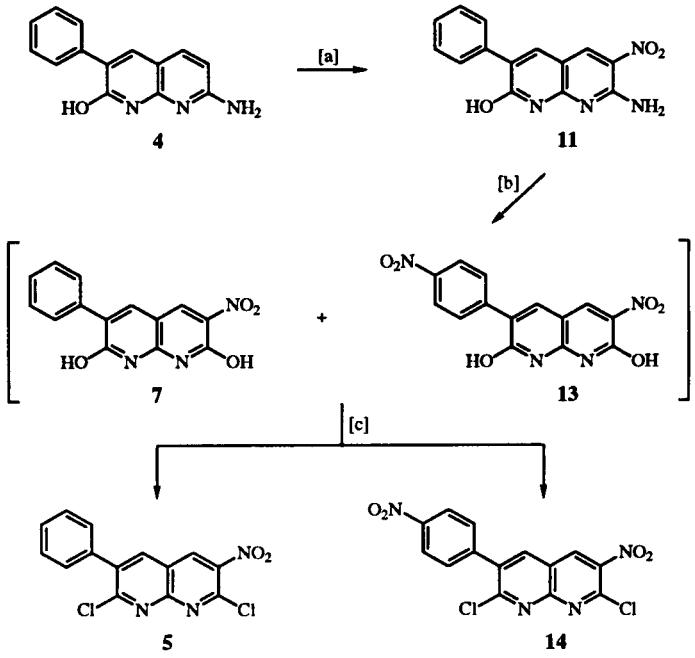


[a] = $NaNO_2/H_2SO_4$, [b] = $POCl_3$, [c] = CH_3ONa, [d] = H_2, Pd/C

derivatives **3** and **5**, in a molar ratio of 7:1 that were separated by flash chromatography (Scheme 1, Tables 1 and 2).

Treating the 2-chloro derivatives **15** [12], **19** [22] and **23**, prepared by reaction of **24** [23] with refluxing phosphoryl chloride (Scheme 5), with a suitable amine, the corresponding amino derivatives **16**, **20** and **25** were obtained (Schemes 3, 4, and 5, Table 3). The diazotization of these compounds, carried out at 0° in concentrated sulfuric acid, gave a mixture of the hydroxy derivatives **17**, **21** and **26** and the corresponding hydroxy nitro derivatives **18**, **22** and **27**, separated by flash chromatography (Schemes 3, 4, and 5, Table 3). The structure of **27** with the nitro group in the 3 position of the 1,8-naphthyridine

Scheme 2

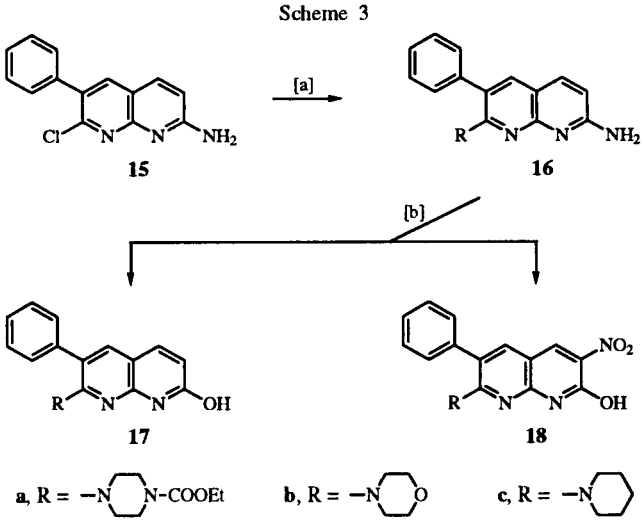


[a] = HNO_3/Ac_2O, [b] = $NaNO_2/H_2SO_4$, [c] = $POCl_3$.

nucleus was confirmed by ^1H nmr spectrum; in fact, the ^1H nmr spectrum of **27** (Table 4) shows two doublets at δ 7.86 and δ 6.43 due to H_5 and H_6 respectively.

Attempts to prepare the same derivative **27** by reaction of **26** with potassium nitrate in concentrated sulfuric acid gave isomer **28** (Scheme 5, Table 3), with the nitro group in the 6-position. Nitration of **25**, carried out under the same conditions, gave the 6-nitro derivative **29** (Scheme 5, Table 3). The structures of **28** and **29** were confirmed by the presence of two singlets due to H_3 and H_5 in their ^1H nmr spectra (Table 4).

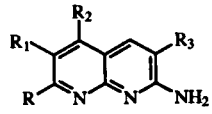
Scheme 3

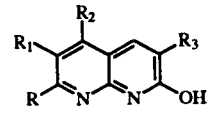


[a] = *N*-Carbethoxypiperazine, Piperidine, Morpholine, [b] = $NaNO_2/H_2SO_4$

Table 1

Diazotization of Substituted 7-Amino-1,8-naphthyridine Derivatives





Starting amino derivatives					mole ratio Compound/ $NaNO_2$	Temperature °C	Hydroxy derivative products without nitration		with nitration			
No.	R	R_1	R_2	R_3			No.	yield %	No.	R_1	R_3	yield %
4	OH	C_6H_5	H	H	1/4	0	**6**	[a]	**7**	C_6H_5	NO_2	[a]
4	OH	C_6H_5	H	H	1/4	-20	**6**	[a]	**7**	C_6H_5	NO_2	[a]
11	OH	C_6H_5	H	NO_2	1/4	0	**7**	[a]	**13**	p-$NO_2C_6H_4$	NO_2	[a]
12	OH	H	C_6H_5	H	1/4	0	**36**	95	–	–	–	–
15	Cl	C_6H_5	H	H	1/4	0	**33**	90	–	–	–	–
16a	A	C_6H_5	H	H	1/5	r.t	**17a**	18	**18a**	C_6H_5	NO_2	60 [b]
16a	A	C_6H_5	H	H	1/5	0	**17a**	28	**18a**	C_6H_5	NO_2	55 [b]
16a	A	C_6H_5	H	H	1/5	-5	**17a**	32	**18a**	C_6H_5	NO_2	38 [b]
16a	A	C_6H_5	H	H	1/5	-10	**17a**	40	**18a**	C_6H_5	NO_2	25 [b]
16a	A	C_6H_5	H	H	1/5	-15	**17a**	43	**18a**	C_6H_5	NO_2	12 [b]
16a	A	C_6H_5	H	H	1/5	-20	**17a**	52	**18a**	C_6H_5	NO_2	5 [b]
16a	A	C_6H_5	H	H	1/1	0	**17a**	62	**18a**	C_6H_5	NO_2	7 [b]
16a	A	C_6H_5	H	H	1/2	0	**17a**	43	**18a**	C_6H_5	NO_2	15 [b]
16a	A	C_6H_5	H	H	1/3	0	**17a**	35	**18a**	C_6H_5	NO_2	28 [b]
16a	A	C_6H_5	H	H	1/4	0	**17a**	26	**18a**	C_6H_5	NO_2	52 [b]
16a [c]	A	C_6H_5	H	H	1/5	0	**17a** [d]	44	**18a**	C_6H_5	NO_2	8 [b]
16b	B	C_6H_5	H	H	1/5	0	**17b**	38	**18b**	C_6H_5	NO_2	44 [b]
16c	C	C_6H_5	H	H	1/5	0	**17c**	35	**18c**	C_6H_5	NO_2	42 [b]
20	A	H	C_6H_5	H	1/5	0	**21**	63	**22**	H	NO_2	23 [b]
25	B	H	Cl	H	1/4	0	**26**	29	**27**	NO_2	H	31 [b]
31	OCH_3	C_6H_5	H	H	1/4	0	**34**	92	–	–	–	–
32	OCH_3	H	C_6H_5	H	1/4	0	**35**	93	–	–	–	–

[a] Mixture not separated. [b] Separated by flash chromatography with ethyl acetate as eluent. [c] The reaction was carried out in concentrated hydrochloric acid. [d] Compound **30** was also obtained in this reaction in 38% yield. A = *N*-Carbethoxypiperazinyl; B = Morpholinyl; C = Piperidinyl.

These last results confirm that the nitration effected with sodium nitrite proceeds *via* nitrosation according to a mechanism, in which the NO^+ group attacks the more nucleophilic 3 position, whereas the NO_2^+ more large group, for the steric hindrance, attaks preferentially the less hindered 6 position of the 1,8-naphthyridine nucleus.

Table 2

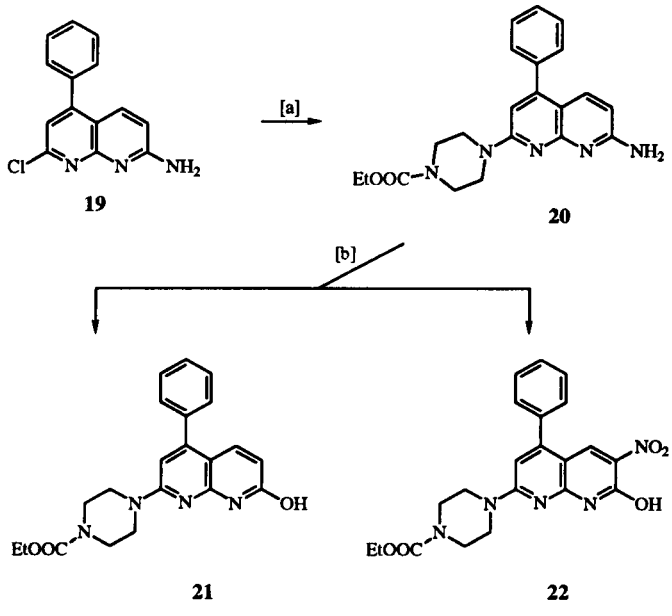
Starting mixture No.	Chloroderivatives obtained No.	yield %	Flash chromat. eluent
6 [a]	**3**	27	[b]
7	**5**	28	
6 [c]	**3**	56	[b]
7	**5**	8	
7 [a]	**5**	25	[b]
13	**14**	14	

[a] Mixture obtained at 0°. [b] Ethyl acetate/petroleum ether 40-70°, 1:4. [c] Mixture obtained at -20°.

Moreover it was of interest to examine the correlation between the mole ratio nitro hydroxy derivative/hydroxy derivative obtained and the amount of sodium nitrite and the temperature used in the diazotization of these compounds, carried out in concentrated sulfuric acid. We have therefore examinated the diazotization of the compound **16a** using different amounts of sodium nitrite at 0° or the same amount of sodium nitrite at a different temperature. We have then established that the mole ratio **18a/17a** decreased with a decreasing amount of sodium nitrite and with a decreasing temperature as reported in Table 1.

Moreover, when we attempted to prepare the hydroxy derivative **17a** by diazotization of **16a** in concentrated hydrochloric acid at -20°, a mixture of 7-hydroxy derivative **17a**, 7-hydroxy-6-nitro derivative **18a** and 7-chloro derivative **30** was obtained (Scheme 6, Table 3). The formation of the chloro derivative **30**, by diazotization was in accord with the behaviour observed with 2-acetamido-

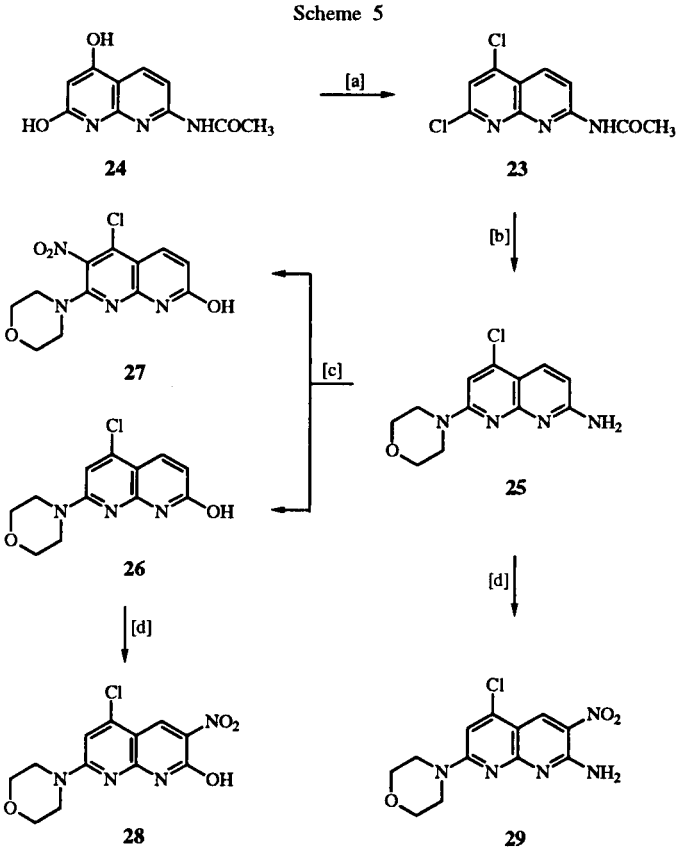
Scheme 4



[a] = *N*-Carbethoxypiperazine, [b] = $NaNO_2/H_2SO_4$

6-aminopyridine, which under these conditions gave the corresponding 2-acetamido-6-chloropyridine, as reported in a previous paper [24].

Scheme 5



[a] = $POCl_3$, [b] = Morpholine, [c] = $NaNO_2/H_2SO_4$, [d] = KNO_3/H_2SO_4

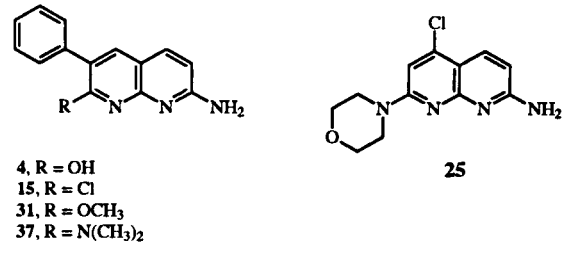
Compounds **15** and **19** were allowed to react with sodium methoxide to give the corresponding 2-methoxy derivatives **31** and **32** respectively (Schemes 7 and 8, Table 3).

All the 7-amino derivatives **15**, **31**, **32** and **12** were diazotized in concentrated sulfuric acid at 0° to give the corresponding hydroxy derivatives **33**, **34**, **35** and **36** [3] (Schemes 7, 8, and 9, Tables 1 and 3).

The structure of all the compounds were confirmed by elemental analysis, ir, ^1H nmr data and mass spectroscopy (Table 4).

Theoretical Calculations.

In order to understand the behavior of the compounds considered with respect to the diazotization reaction, theoretical calculations were carried on four compounds: **4**, **15**, **31** and **37**. Derivative **37** is a model compound of **16a-c** and can be considered as a molecule that undergoes nitration during the diazotization reaction; **4** is a compound possessing the same behavior; **15** and **31** are compounds which are not nitrated during the diazotization reaction (Figure 1).



4, R = OH
15, R = Cl
31, R = OCH_3
37, R = $N(CH_3)_2$

Figure 1. Molecules used for the theoretical calculations.

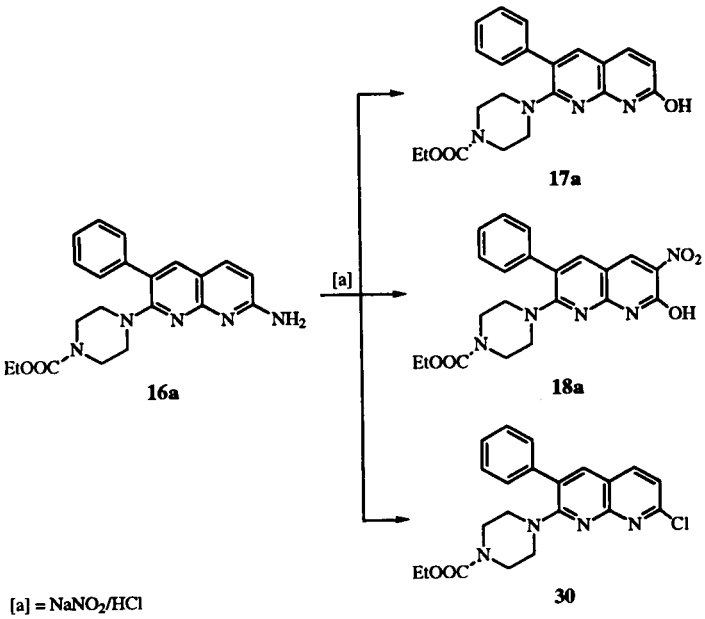
It seemed to us that the reactivity difference among **4**, **37** and **15**, **31** could not be explained through conformational, steric or solvation effects because the molecules are too rigid and the structural differences (different substituents are only in position 2 of the nucleus) are too far from the position 6 where (but only for **4** and **37**) there can be nitration. It could be more reasonable to try to rationalize such difference in electronic terms because the high conjugation present in the molecules could allow the substituent in position 2 to influence the reactivity in position 6 of the 1,8-naphthyridine nucleus. Therefore the eletronic density of **4**, **15**, **31** and **37** was calculated and analyzed.

The geometries of **4**, **15**, **31** and **37** were fully optimized through the program MOPAC [25], using the PM3 hamiltonian; all compounds were considered in their totally protonated form (charge +4 on **37** and +3 on **4**, **15** and **31**) which should be present in the extremely acid reaction environment.

Figure 2 reports the three-dimensional maps of the electronic density of the molecules in their preferred conformation, obtained from the PM3 wave function.

It can be pointed out that compounds **4** and **37**, which undergo the nitration reaction, possess in position 6 a

Scheme 6



higher electronic density than in **15** and **31**, which, in contrast, are not nitrated.

This fact is an agreement with the mechanism of electrophilic substitution of the nitration in position 6. The diazonium salts of **4**, **15**, **31** and **37** were also considered; their totally protonated form was optimized and the electronic density was calculated in the same manner as described above. However, in this case no correlation was found between the nitration reaction and the electronic density; this fact could suggest that the nitration takes place before the formation of the diazonium salts.

In order to understand the behavior of **25** (Figure 1) which undergoes the nitration reaction during diazotation in position 3, instead of in position 6, analogous calculations were carried on the totally protonated form of this compound.

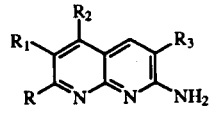
The electronic density map reported in Figure 3 shows a higher density on position 3, in agreement with the experimental data.

With regard to the behavior of **19**, which undergoes nitration in position 6 of the 1,8-naphthyridine nucleus, it can be pointed out that position 3 is very hindered due to the presence of bulky rings in both positions 2 and 4, and therefore the attack of the electrophilic agent in this position should be quite unfavoured.

Conclusions.

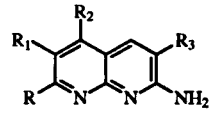
The experimental results obtained in the diazotization of substituted 7-amino-1,8-naphthyridines, effected with

Table 3



Compound No.	R	R_1	R_2	R_3	R_4	Yield %	mp°C [a]	Empirical Formula	Elemental Analyses Calcd./Found		
5	Cl	C_6H_5	H	NO_2	Cl	[b]	210-212 [c]	$C_{14}H_7N_3O_2Cl_2$	52.53 52.71	2.20 2.15	13.13 12.96
8	OCH_3	C_6H_5	H	H	OCH_3	85	113-115 [c]	$C_{16}H_{14}N_2O_2$	72.15 71.96	5.30 5.11	10.52 10.76
9	OCH_3	C_6H_5	H	NO_2	OCH_3	96	210-212 [d]	$C_{16}H_{13}N_3O_4$	61.72 61.63	4.21 4.01	13.50 13.67
10	OCH_3	C_6H_5	H	NH_2	OCH_3	83	226-228 [e]	$C_{16}H_{15}N_3O_2$	68.30 68.15	5.38 5.53	14.94 14.81
11	OH	C_6H_5	H	NO_2	NH_2	77	>320 [f]	$C_{14}H_{10}N_4O_3$	59.56 59.30	3.57 3.42	19.86 19.63
14	Cl	p-$NO_2C_6H_4$	H	NO_2	Cl	[b]	200-202 [c]	$C_{14}H_6N_4O_4Cl_2$	46.16 46.29	1.66 1.61	15.39 15.27
16a	A	C_6H_5	H	H	NH_2	98	236-238 [e]	$C_{21}H_{23}N_5O_2$	66.81 66.67	6.15 6.29	18.56 18.33
16b	B	C_6H_5	H	H	NH_2	97	174-176 [e]	$C_{18}H_{18}N_4O$	70.55 70.63	5.93 5.85	18.30 18.46
16c	C	C_6H_5	H	H	NH_2	93	234-236 [e]	$C_{19}H_{20}N_4$	74.96 74.72	6.63 6.51	18.41 18.59
17a	A	C_6H_5	H	H	OH	[g]	234-236 [h]	$C_{21}H_{22}N_4O_3$	66.64 66.36	5.86 5.95	14.81 14.71
17b	B	C_6H_5	H	H	OH	[g]	220-222 [g]	$C_{18}H_{17}N_3O_2$	70.33 70.36	5.58 5.60	13.68 13.39
17c	C	C_6H_5	H	H	OH	[g]	176-178 [e]	$C_{19}H_{19}N_3O$	74.72 74.44	6.28 6.42	13.77 13.85
18a	A	C_6H_5	H	NO_2	OH	[g]	304-306 [h]	$C_{21}H_{21}N_5O_5$	59.55 59.33	5.00 4.79	16.55 16.73

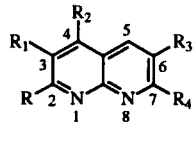
Table 3 (continued)



Compound No.	R	R_1	R_2	R_3	R_4	Yield %	mp°C [a]	Empirical Formula	Elemental Analyses Calcd./Found		
18b	B	C_6H_5	H	NO_2	OH	[g]	288-290 [i]	$C_{18}H_{16}N_4O_4$	61.34 61.58	4.58 4.39	15.91 15.85
18c	C	C_6H_5	H	NO_2	OH	[g]	275-277 [i]	$C_{19}H_{18}N_4O_3$	65.12 65.22	5.18 5.30	16.00 16.11
20	A	H	C_6H_5	H	NH_2	81	242-244 [e]	$C_{21}H_{23}N_5O_2$	66.81 66.59	6.15 6.00	18.56 18.38
21	A	H	C_6H_5	H	OH	[g]	202-204 [j]	$C_{21}H_{22}N_4O_3$	66.64 66.52	5.86 6.01	14.81 14.63
22	A	H	C_6H_5	NO_2	OH	[g]	>320 [i]	$C_{21}H_{21}N_5O_5$	59.55 59.26	5.00 5.17	16.55 16.33
23	Cl	H	Cl	H	$NHCOCH_3$	77	218-220 [k]	$C_{10}H_7N_3OCl_2$	47.06 46.92	2.77 2.83	16.47 16.40
25	B	H	Cl	H	NH_2	75	208-210 [e]	$C_{12}H_{13}N_4OCl$	54.53 54.33	4.96 5.09	21.21 21.10
26	B	H	Cl	H	OH	29	265-267 [e]	$C_{12}H_{12}N_3O_2Cl$	54.33 54.28	4.56 4.42	15.85 15.68
27	B	NO_2	Cl	H	OH	31	285-287 [h]	$C_{12}H_{11}N_4O_4Cl$	46.44 46.18	3.58 3.54	18.07 18.29
28	B	H	Cl	NO_2	OH	39	>320 [l]	$C_{12}H_{11}N_4O_4Cl$	46.44 46.28	3.58 3.39	18.07 18.00
29	B	H	Cl	NO_2	NH_2	46	>320 [h]	$C_{12}H_{12}N_5O_3Cl$	46.59 46.42	3.91 3.96	22.65 22.48
30	A	C_6H_5	H	H	Cl	38	154-156 [m]	$C_{21}H_{21}N_4O_2Cl$	63.61 63.72	5.34 5.42	14.14 14.02
31	OCH_3	C_6H_5	H	H	NH_2	92	187-189 [e]	$C_{15}H_{13}N_3O$	71.68 71.61	5.22 5.33	16.73 16.60
32	OCH_3	H	C_6H_5	H	NH_2	72	203-205 [c]	$C_{15}H_{13}N_3O$	71.68 71.52	5.22 5.41	16.73 16.58
33	Cl	C_6H_5	H	H	OH	90	248-250 [e]	$C_{14}H_9N_2OCl$	65.61 65.75	3.54 3.62	10.94 10.82
34	OCH_3	C_6H_5	H	H	OH	92	294-296 [e]	$C_{15}H_{12}N_2O_2$	71.40 71.31	4.80 4.92	11.11 11.00
35	OCH_3	H	C_6H_5	H	OH	93	220-222 [n]	$C_{15}H_{12}N_2O_2$	71.40 71.28	4.80 4.68	11.11 11.22

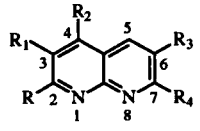
[a] Recrystallization solvent. [b] See table 2. [c] 2-Propanol. [d] Methanol. [e] Toluene. [f] DMF. [g] See Table 1. [h] Ethyl acetate. [i] Dioxane. [j] Cycloexane. [k] Acetone. [l] CH_3CN. [m] Petroleum benzin 100/140°. [n] Acetic acid/water. [A] *N*-Carbethoxypiperazinyl. [B] Morpholinyl. [C] Piperazinyl.

Table 4



Compound No.	^1H NMR Spectral data (δ) H_3	H_4	H_5	H_6	C_6H_5	N⌒X	Others	MS m/z M^+
5	–	8.72 s	9.37 s	–	7.55 m	–	–	319
8	–	7.75 s	7.85 d	6.82 d	7.39 m	–	4.15 (2,7-OCH_3) s	–
9	–	7.95 s	8.65 s	–	7.47 m	–	4.17 (OCH_3) s, 4.25 (OCH_3) s,	311
10	–	7.93 s	7.09 s	–	7.50 m	–	3.45 (NH_2) br, 4.15 (OCH_3) s, 4.25 (OCH_3) s	281
11	–	8.02 s	8.82 s	–	7.52 m	–	3.25 (NH_2) br, 12.00 (OH) br	282

Table 4 (continued)



Compound No.	H_3	H_4	H_5	H_6	C_6H_5	N⌒X	Others	MS m/z M+
					¹H NMR Spectral data (δ)			
14	–	8.84 *s*	9.44 *s*	–	7.89 d, 8.39 d	–	–	364
16a	–	7.61 s	7.69 d	6.53 d	7.33 m	3.32 m [a]	1.23 (CH_3) t, 4.91 (CH_2) q, 5.00 (NH_2) br	–
16b	–	7.75 *s*	7.81 d	6.65 d	7.50 m	3.12 m [b], 3.55 m [b]	6.60 (NH_2) br	
16c	–	7.65 *s*	7.75 d	6.55 d	7.45 m	1.48 m [c], 3.11 m [c]	6.51 (NH_2) br	304
17a	–	7.52 *s*	7.56 d	6.44 d	7.39 m	3.88 m [a]	1.22 (CH_3) t, 4.09 (CH_2) q, 9.55 (OH) br	378
17b	–	7.55 s	7.65 d	6.50 d	7.39 m	3.32 m [b], 3.61 m [b]	11.50 (OH) br	307
17c	–	7.69 *s*	7.73 d	6.25 d	7.50 m	1.50 m [c], 3.18 m [c]	11.55 (OH) br	305
18a	–	7.79 *s*	8.85 *s*	–	7.48 m	3.34 m [a]	1.51 (CH_3) t, 4.05 (CH_2) q, 10.15 (OH) br	423
18b	–	7.92 *s*	8.80 *s*	–	7.45 m	3.32 m [b], 3.51 m [b]	11.25 (OH) br	352
18c	–	7.83 s	8.77 s	–	7.39 m	1.50 m [c], 3.30 m [c]	11.95 (OH) br	350
20	6.70 *s*	–	7.76 d	6.53 d	7.63 m	3.80 m [a]	1.33 (CH_3) t, 4.30 (CH_2) q, 5.00 (NH_2) br	–
21	6.47 *s*	–	7.73 d	6.27 d	7.50 m	3.70 m [a]	1.27 (CH_3) t, 4.30 (CH_2), 12.56 (OH) br	–
22	6.96 *s*	–	8.46 *s*	–	7.66 m	3.55 m [a]	1.22 (CH_3) t, 4.13 (CH_2) q	423
23	7.44 *s*	–	8.70 d	8.48 d	–	–	2.34 (CH_3) *s*, 9.41 (NH) br	–
25	6.93 *s*	–	7.83 d	6.58 d	–	3.39 m [b], 3.63 m [b]	6.64 (NH_2) br	264
26	6.86 *s*	–	6.76 d	6.21 d	–	3.28 m [b], 3.64 m [b]	11.70 (OH) br	265
27	–	–	7.86 d	6.43 d	–	3.46 m [b], 3.66 m [b]	12.15 (OH) br	310
28	7.15 *s*	–	8.60 *s*	–	–	3.42 m [b], 3.65 m [b]	11.60 (OH) br	310
29	7.29 *s*	–	8.72 *s*	–	–	3.26 m [b], 3.54 m [b]	7.85 (NH_2) br	–
30	–	8.22 *s*	8.32 d	7.35 d	7.50 m	3.25 m [a]	1.31 (CH_3) t, 4.00 (CH_2) q	–
31	–	7.73 s	7.79 d	6.53 d	7.40 m	–	4.10 (OCH_3) *s*, 5.11 (NH_2) br,	–
32	6.78 *s*	–	7.80 d	6.57 d	7.52 m	–	3.38 (NH_2) br, 4.00 (OCH_3) *s*	–
33	–	8.21 *s*	7.91 d	6.63 d	7.50 m	–	11.45 (OH) br	256
34	–	8.10 *s*	7.90 d	6.44 d	7.50 m	–	4.01 (OCH_3) *s*, 10.17 (OH) br	–
35	6.67 *s*	–	7.78 d	6.45 d	7.66 m	–	4.10 (OCH_3) *s*	–

[a] Piperazinyl. [b] Morpholinyl. [c] Piperidinyl; s singlet, d doublet, m multiplet, t triplet, q quartet, br broad.

sodium nitrite in concentrated sulfuric acid, show that the respective amounts of hydroxy and hydroxy nitro derivatives is dependent on (1) the nature of the substituents and their position on the 1,8-naphthyridine nucleus, (2) the amount of sodium nitrite used in the reaction, (3) the reaction temperature. The significance of the nature of the substituents and of their position on the 1,8-naphthyridine nucleus, in these reactions, could be explained by theoretical calculations in terms of differences of electronic density on the position on which the nitration can take place.

Biological Results.

Some of these compounds, **16a-c**, **17a-c**, **18a,c**, **25**, **26**, **27** and **28**, were tested *in vitro* by the method previously reported [26], for their inhibitory activity on 0.7 m*M* arachidonate induced aggregation in human platelets in rich plasma, because of their analogy to the compounds

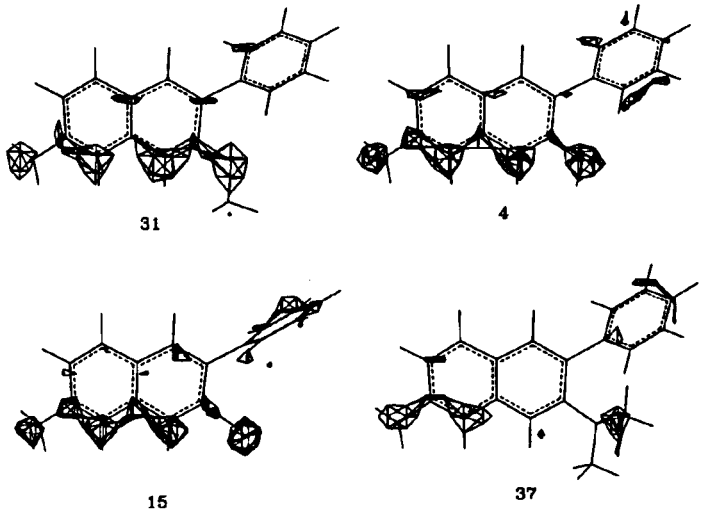
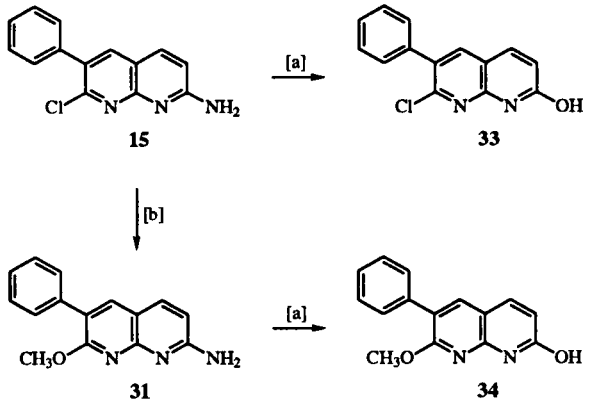


Figure 2. Three-dimensional maps of the electronic density of the considered molecules in their preferred conformation.

Scheme 7



[a] = $NaNO_2/H_2SO_4$, [b] = CH_3ONa

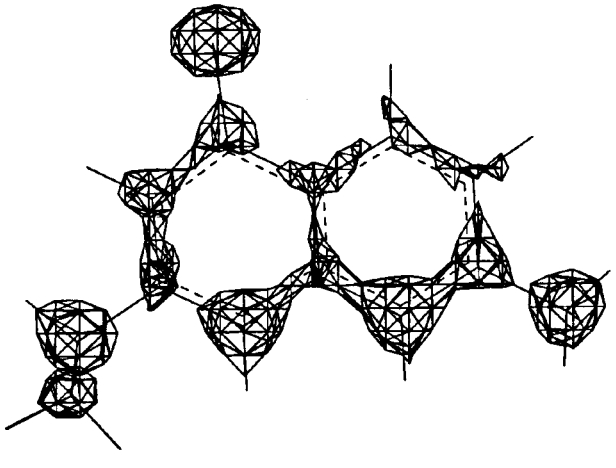
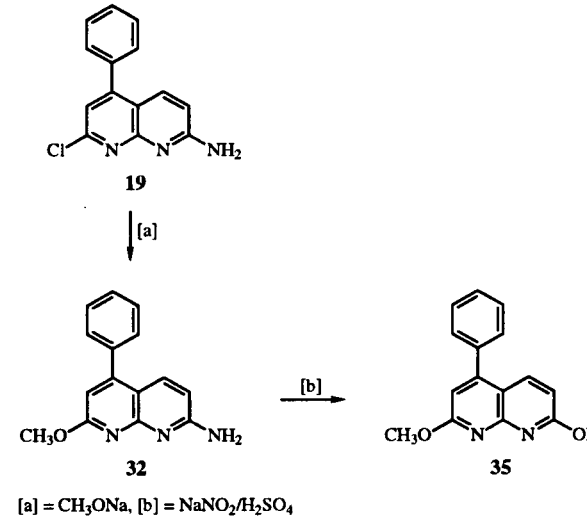


Figure 3. Three-dimensional map of the electonic density of compound **25** in its preferred conformation.

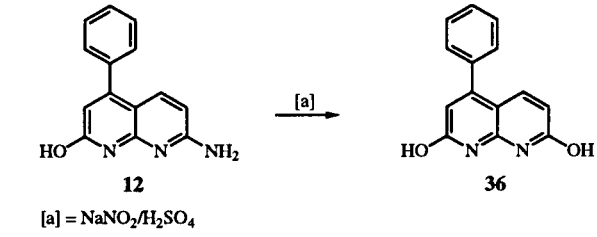
synthesized and tested [26]. The results of the biological evaluation indicate that compounds **16a** and **28** were found to be inactive, whereas most of the tested compounds, **16b,c**, **17a-c**, **18a,c**, **25** and **27** exhibited a feeble and generally insignificant activity (5-27% of inhibition to the concentration of 10 μ*M*). Only compound **26** showed remarkable antiplatelet activity (99% of inhibition at a concentration of 10 μ*M*). For this last compound, the IC_{50} values (μ*M*) calculated as the half reducing concentration both maximal aggregation (2.0 ± 1.0) and aggregation rate (0.3 ± 0.2).

Scheme 8



[a] = CH_3ONa, [b] = $NaNO_2/H_2SO_4$

Scheme 9



[a] = $NaNO_2/H_2SO_4$

EXPERIMENTAL

Chemistry.

All compounds were routinely checked for their structure by ir and ^1H nmr spectroscopy. Melting points were determined in a Köfler hot-stage and are uncorrected. The ir spectra were measured on a Perkin-Elmer Infracord Model 1310 as Nujol mulls. The ^1H nmr spectra were determined in DMSO-d_6 or deuteriochloroform with tetramethylsilane as the internal standard, on a Fourier transform spectrometer Varian Model CFT 20. Mass spectra were obtained by Hewlett-Packard 5988A spectrometer, 70 eV. Analytical tlc was carried out on Merck 0.2 mm precoated silica-gel glass plates (60 F-254) and spot location was detected

by illumination with a uv lamp. Flash chromatography was carried out on silica gel (60 size 0.04-0.063 mm) at low pressure. Elemental analyses were determined in our laboratories.

General Procedure of Diazotization of 7-Amino-1,8-naphthyridines **4**, **11**, **12**, **15**, **16**, **20**, **25**, **31** and **32**. Preparation of 7-Hydroxy-1,8-naphthyridine or 7-Hydroxy and 7-Hydroxy-nitro-1,8-naphthyridines **6** and **7**, **7** and **13**, **36**, **33**, **17** and **18**, **21** and **22**, **26** and **27**, **34**, **35**.

To a solution of 2.0 mmoles of a 7-amino derivative in 6 ml of concentrated sulfuric acid sodium nitrite was added portionwise under the conditions reported in Table 1. After standing at room temperature for 60 minutes crushed ice was added and then concentrated ammonium hydroxide until *p*H 4-5. The solid was collected by filtration and purified to give **6** and **7**, **7** and **13** (mixtures not separated), **36** [3], **33**, **17** and **18**, **21** and **22**, **26** and **27**, **34**, **35** (Tables 1, 3, and 4).

When the diazotization of 2.0 mmoles of **16a** was carried out in 12 ml of concentrated hydrochloric acid, **17a**, **18a** and the chloro derivative **30** was obtained (Tables 1, 3, and 4).

General Procedure for the Preparation of Chloro Derivatives **23**, **3** and **5** or **5** and **14**

A suspension of 1.0 g of **24** or a mixture of **6** and **7** or a mixture of **7** and **13** in 10 ml of phosphoryl chloride was refluxed (5 hours for **24** and 45 minutes for the mixture of **6** and **7** or **7** and **13**) and, after cooling, crushed ice was added. The solution was then made basic with concentrated ammonium hydroxide and the solid collected by filtration, washed with water and purified to give **23**, **3** [12] and **5** or **5** and **14** (Tables 2, 3, and 4).

General Procedure for the Preparation of Cycloamino-1,8-naphthyridine Derivatives **16** and **20**.

A mixture of 1.5 mmoles of the appropriate chloronaphthyridine **15** or **19** and 4.5 mmoles of the suitable ammine was kept in a sealed tube at 140° for 16 hours. The crude residue was treated with water and the solid collected by filtration, washed with water and purified by crystallization to obtain **16** or **20** respectively (Tables 3 and 4).

7-Amino-4-chloro-2-morpholino-1,8-naphthyridine **25**.

A solution of 2.5 mmoles of **23** and 7.5 mmoles of morpholine in 25 ml of toluene was refluxed for 6 hours and the solvent was evaporated to dryness *in vacuo*. The crude residue was treated with 50 ml of 10% aqueous sulfuric acid and the mixture was refluxed for 2 hours. After cooling, the mixture reaction was made basic with concentrated ammonium hydroxide. Derivative **25** was collected by filtration, washed with water and purified by crystallization (Tables 3 and 4).

General Procedure for the Preparation of 2,7-Dimethoxy- and 2-Methoxy-1,8-naphthyridine Derivatives **8**, **9**, **31** and **32**.

A solution of 10 mmoles of freshly prepared sodium methoxide and 1.0 mmole of the chloro derivative **3**, **5**, **15** or **19** in 10 ml of anhydrous methanol was refluxed for 2.5 hours. The reaction mixture was evaporated to dryness *in vacuo* and the crude residue was treated with water, neutralized with 10% hydrochloric acid and the solid precipitate collected by filtration and purified by crystallization to obtain **8**, **9**, **31** or **32** (Tables 3 and 4).

7-Amino-2-hydroxy-6-nitro-3-phenyl-1,8-naphthyridine **11**.

To a suspension of 4.2 mmoles of **4** in 10 ml of acetic anhydride, 16.7 mmoles of urea and 1.12 ml (6.0 mmoles) of concentrated nitric acid (d = 1.5) were added and the mixture stirred at room temperature for 24 hours. Compound **11** was collected by filtration, washed with ethanol and then with water and purified by crystallization (Tables 3 and 4).

6-Amino-2,7-dimethoxy-3-phenyl-1,8-naphthyridine **10**.

A solution of 1.1 mmoles of 6-nitro derivative **9** in glacial acetic acid was hydrogenated in the presence of 0.03 g of 10% palladium on charcoal at room temperature and at atmospheric pressure for 3 hours. The catalyst was filtered and the solvent evaporated to dryness *in vacuo* to give compound **10**, which was purified by crystallization (Tables 3 and 4).

General Procedure for the Preparation of Nitro Derivative **28** and **29**.

To an ice cooled solution of 0.5 mmole of **26** or **25** in 1.5 ml of concentreted sulfuric acid was added portionwise 0.55 mmole of potassium nitrate. The reaction mixture was stirred at room temperature for 30 minutes and treated with crushed ice and concentrated ammonium hydroxide to *p*H 5. The solid precipitate was collected by filtration, washed with water and purified by flash chromatography with ethyl acetate as the eluent to give **28** or **29** respectively (Tables 3 and 4).

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