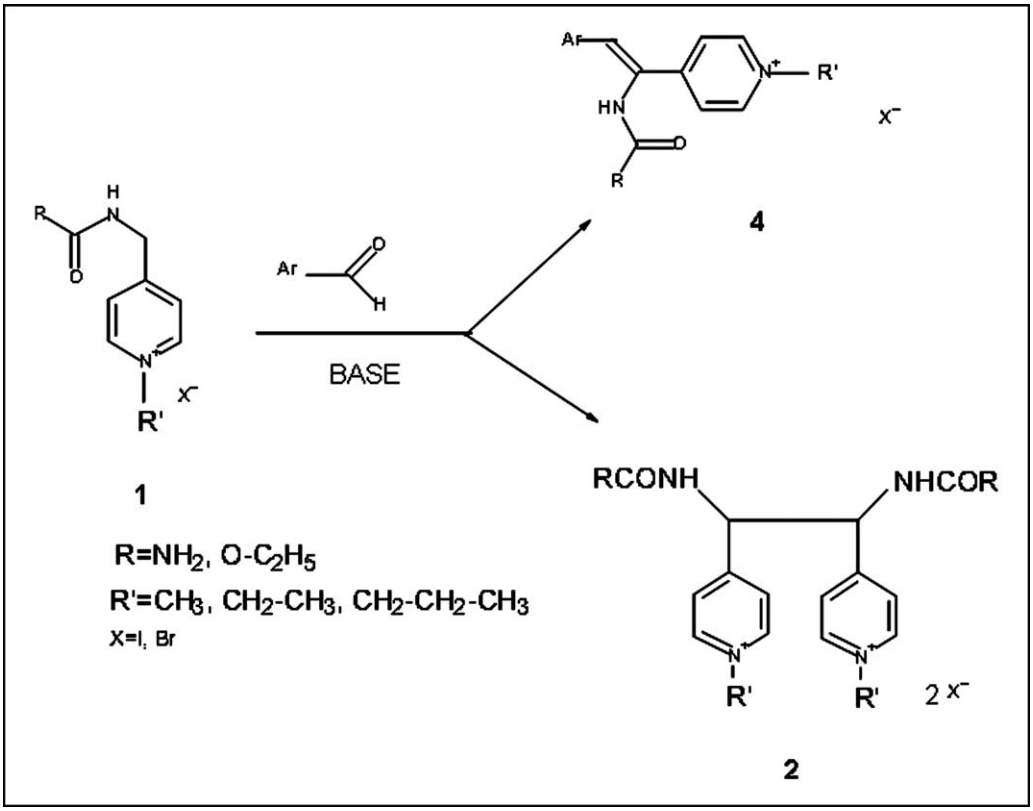
Paloma Posada,[a]* Miguel F. Braña,[b] Antonio L. Villarino,[a]
Vicente Domínguez,[c] Ismael Ortuño,[a] and Carmen Martínez[a]

[a]Departamento de Enfermería, Escuela Universitaria de Enfermería, Fisioterapia y Podología, Universidad Complutense de Madrid, 28040 Madrid, Spain
[b]Instituto Canario de Investigación del Cáncer (ICIC), Brasil 25, 28110 Algete, Spain
[c]Departamento de Medicina Preventiva y Salud Pública, Facultad de Medicina, Universidad Complutense de Madrid, 28040 Madrid, Spain
*E-mail: kekule34@hotmail.com
Received May 20, 2010
DOI 10.1002/jhet.616
Published online 22 February 2011 in Wiley Online Library (wileyonlinelibrary.com).



This article reports the reactions of salts of 4-ureylmethylpyridinium and 4-ethoxycarbonylaminomethylpyridinium with carbonylic compounds, performed with the aim of obtaining new vinylpyridinium salts. These reactions can lead to the formation of both condensation and dimerization products. The type of products formed is conditioned by the nature of the salts and carbonyl groups involved. The interest generated by the condensation products formed lies in their potential cholinergic activity.

J. Heterocyclic Chem., **48**, 549 (2011)

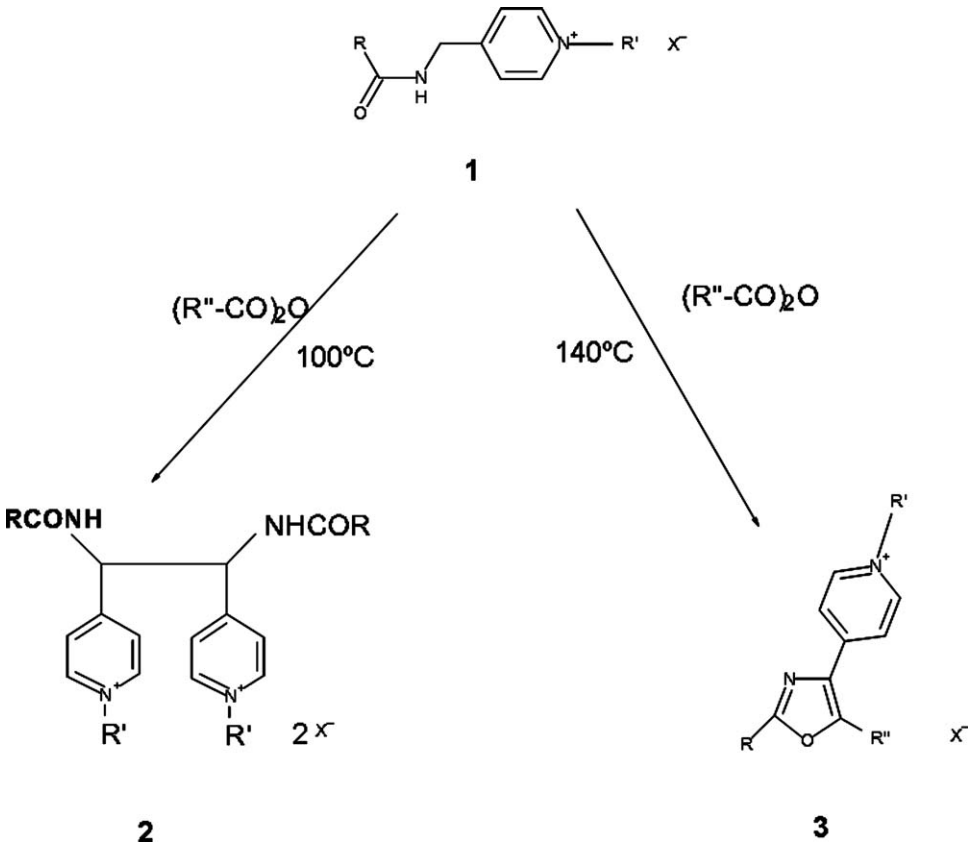
INTRODUCTION

Pyridinium salts (PSs) are a class of ammonium quaternary compounds with many applications in different areas of chemistry [1,2]. From the point of view of medicinal chemistry, PSs are very well known for their germicidal properties and their cholinergic activity as inhibitors of acetylcholinesterase (AChE) (EC 3.1.1.7) and/or cholineacetyltransferase (CAT) (EC 2.3.1.6). The dysfunction of these enzyme systems has been associated with several degenerative diseases [3–5].

4-Acylaminomethylpyridinium salts **1** show interesting behavior in their reaction with acid anhydrides. Small differences in temperature yield very different compounds [6]; at 100°C, dimeric compounds **2** are obtained, whereas at 140°C the main reaction products are oxazoles **3** (Scheme 1). The reaction in Scheme 1 describes a procedure for preparing oxazoles of structure **3**, some of which have shown interesting antitumoral activity [7].

This article reports reactions between 4-acylaminomethylpyridinium salts **1**, where the acyl group is an

Scheme 1



ethylcarbamate or urea with carbonylic compounds. Ethylcarbamate group has very well-known AChE-inhibiting properties [8]. When 4-acylaminomethylpyridinium salts **1** react with carbonylic compounds, products of general structure **4** are obtained (Fig. 1). The main interest in these lies in their structural similarity to those described by DeBernardis *et al*., and therefore their potential to inhibit CAT and AChE [9]. DeBernardis *et al*. established four structural moieties for the structure shown in Figure 2 as potentially responsible for strong inhibitory activity: (a) a mono or bicyclic aromatic system, [10]; (b) a double bond; (c) a pyridinium or quinolinium moiety; and (d) an alkylic chain. Other PSs, however, have shown low CAT inhibition activity [11].

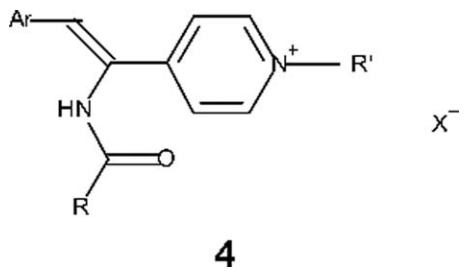


Figure 1. General structure of vinylpyridinium salts.

The salts produced in the reactions studied in this work show features similar to those of other synthesized cholinergic/anticholinergic agents that have been pharmacologically evaluated [12]. This work also reports initial investigations into the biological activity of one of the vinylpyridinium salt produced.

RESULTS AND DISCUSSION

The synthesis of 4-ethoxycarbonylaminomethylpyridinium and 4-ureylmethylpyridinium salts **1** was performed according to a previously published procedure

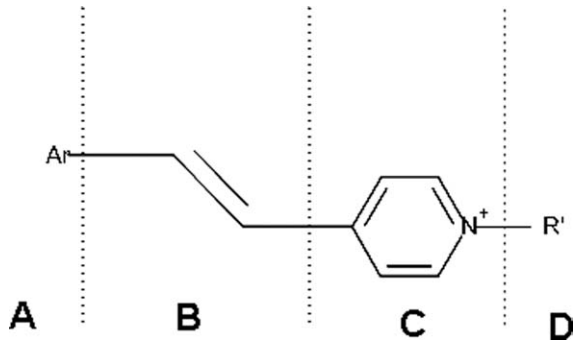
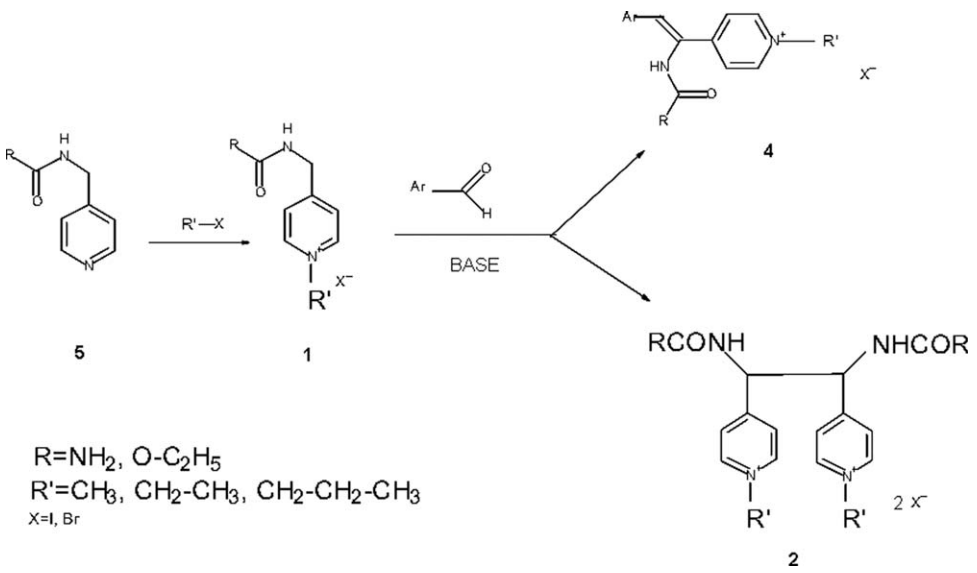


Figure 2. General structure of CAT inhibitors.

Scheme 2



[6]. The reaction of **1** with aromatic aldehydes selected from those available in our laboratory (2-methoxy, 4-methoxy, 4-hydroxy, 4-nitro, 3,4,5-trimethoxy, and 2-hydroxy-5-nitrobenzaldehyde) in the presence of piperidine or morpholine gave a mixture of the corresponding condensation **4** and dimerization **2** products (Scheme 2). These dimers are very insoluble and thus easily separated out by filtration. Thus, during the reaction, two competitive processes take place: the formation of condensation product **4** and the production of dimer **2**, both at low-medium yields (see Table 1).

The formation of condensation products is characteristic of aromatic aldehydes; when the reaction was performed with aliphatic aldehydes or ketones, only the dimerization product was obtained.

The production of **4** can be explained by the classical mechanism of addition–elimination *via* the formation of anhydrobase **6**. The latter is involved in a nucleophilic attack on the corresponding aldehyde, followed by water elimination from adduct **7** to yield compound **4** (Scheme 3).

The dimerization reaction may occur through a mechanism involving the initial formation of anhydrobase **6**, which would be in equilibrium with the corresponding acylimine **8**. The nucleophilic attack of **6** on **8** would give Michael type adduct **9**, which would lose a hydride ion that might be captured by the carbonyl compound in the medium (Scheme 4).

To show the formation of the hydride ion, PS **1** (R = NH_2; R′ = C_2H_5 and C_3H_7) was reacted with piperidine in the presence of an oxidant such as nitrobenzene [6], obtaining dimer **2** in improved yields (Scheme 5).

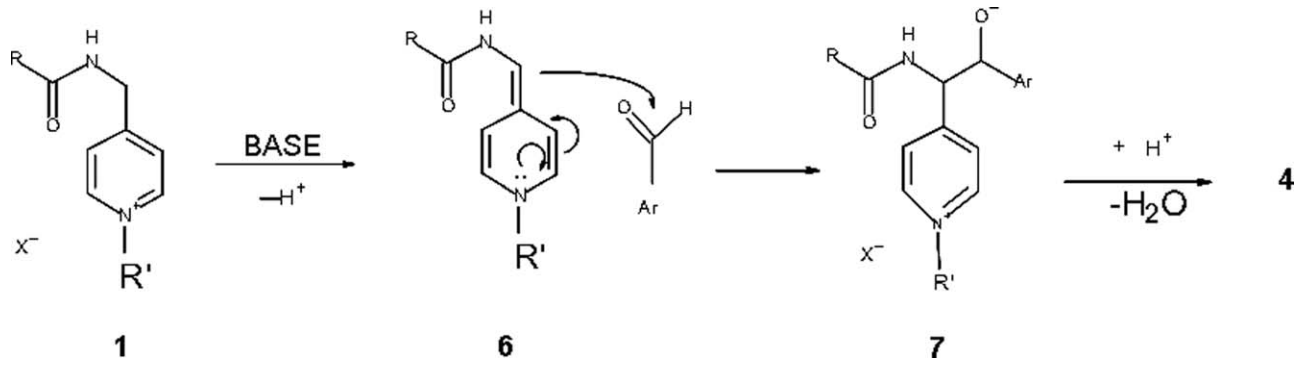
It is difficult to explain why, in two cases (**4e** and **4g**; Table 1), only the condensation product was obtained. The presence of the nitro group in 2-hydroxy-5-nitrobenzaldehyde would be expected to increase the dimer yield, but none was detected. More research is needed for any reliable conclusion to be drawn.

Table 1

Vinylpyridinium **4** and dimer **2** salts yields.

Entry	R	R′	Ar	X	Yield (%) **4**	Yield (%) **2**
a	NH_2	C_2H_5	2-Methoxyphenyl	Br	24	12
b	NH_2	C_2H_5	4-Methoxyphenyl	Br	16	23
c	NH_2	C_2H_5	4-Hydroxyphenyl	Br	33	17
d	NH_2	C_2H_5	4-Nitrophenyl	Br	18	57
e	NH_2	CH_3	3,4,5-Trimethoxyphenyl	I	64	0
f	NH_2	C_2H_5	3,4,5-Trimethoxyphenyl	Br	20	36
g	NH_2	C_2H_5	2-Hydroxy-5-nitrophenyl	Br	71	0
h	NH_2	*n*-C_3H_7	3,4,5-Trimethoxyphenyl	Br	46	21
i	O—C_2H_5	CH_3	3,4,5-Trimethoxyphenyl	I	21	52

Scheme 3



The stereochemistry of the double bond in **4f–i** was investigated by NOESY; these results will be published elsewhere [13].

Vinylpyridinium salt **4i** shows the optimum groups (carbamate and quaternary ammonium) affording cholinergic/anticholinergic properties. The behavior of this compound was compared to that of acetylcholine using the isolated organ technique [14].

Salt **4i** is remarkable as it behaves *per se* in the same way as acetylcholine (the product has a similar concentration-effect curve), with a corresponding pD_2 of 5.95.

In conclusion, this work opens up new avenues for the development of vinylpyridinium salts that may be useful as cholinergic agents.

EXPERIMENTAL

Melting points were determined using a Büchi 510 capillary melting point apparatus and are uncorrected. Infrared spectra were recorded using a Perkin-Elmer 297 spectrophotometer. ^{1}H-NMR spectra were obtained using a Varian T-60 (60 MHz) and T-90 (90 MHz) using deuterated dimethylsulfoxide or trifluoroacetic acid. NOESY experiments were performed using a Varian XL-300 operating at 300 MHz. Chemical shifts (δ) are reported in parts per million relative to an internal standard of tetramethylsilane. Coupling constants (*J*) are expressed in Hertz. Elemental analyses (C, H, N, X) of final compounds were performed by the Centro Nacional de Química Orgánica. Reaction progress was monitored by thin layer chromatography using silica gel plates (Merck 60 F_{254}) and ethyl acetate as an eluent.

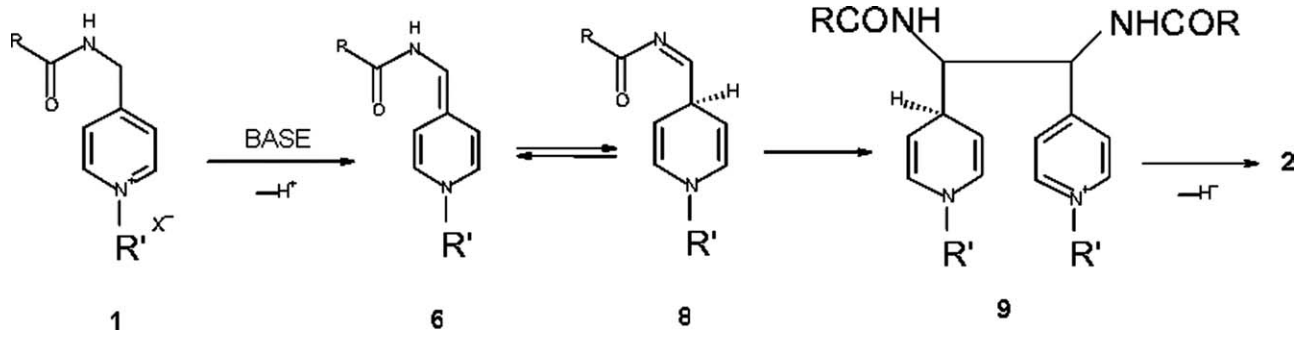
Double-bond configuration was investigated by NOESY using specific software: SYBYL [15], gopenMol [16,17], and Molekel [18].

General procedure (A) for the preparation of (Z)-1-alkyl-4-(2-aryl-1-acylvinyl)pyridinium halide 4. A solution containing 3 m*M* of PS, 3 m*M* of the corresponding aldehyde, 25 mL of absolute ethanol, and four drops of piperidine was refluxed for 4 h. The solid obtained was collected by suction filtration and purified by recrystallization (dimer **2**). The filtrate was collected, and the solvent was evaporated to dryness. The residual solid was purified by recrystallization (condensation product **4**).

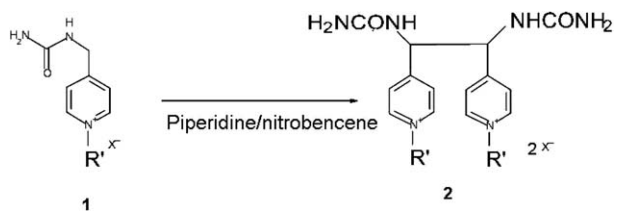
General procedure (B) for the preparation of *N*, *N*′-diaminocarbonyl-1,2-di(1-alkyl-4-pyridinium)ethylenediamine dihalides 2 [6]. A solution containing 3.4 m*M* of PS, 15 mL of absolute ethanol, four drops of piperidine, and four drops of nitrobenzene was refluxed for 4 h. After cooling, the solid was filtered and purified by recrystallization.

(Z)-1-Ethyl-4-[2-(2-methoxyphenyl)-1-ureylvinyl]pyridinium bromide 4a. This compound was obtained by general procedure A. Yield: 24%; mp 154–156°C (isopropanol); IR (potassium bromide) 3400 (NH), 3230, 3160 (NH_2), 1665 (C=O), 1640 (C=N), 1610 (C=C), 1255, 1025 ($ArOCH_3$) cm^{-1}; ^{1}H-NMR (dimethyl sulfoxide-d_6) δ 1.6 (t, 3H, CH_3—C—N^+, J = 7.0 Hz), 3.8 (s, 3H, CH_3—O), 4.6 (q, 2H, CH_2—N^+, J = 7.0 Hz), 6.1 (s, 2H, NH_2), 6.8–7.5 (m, 5H, CH=C and ArH), 7.8 (d, 2H, H-3, H-5 py, J = 7.0 Hz), 8.0 (s, 1H, NH), 8.7 (d, 2H, H-2, H-6 py, J = 7.0 Hz) ppm. Anal. Calcd. for $C_{17}H_{20}BrN_3O_2$: C, 53.97; H, 5.29; N, 11.11; Br, 21.13. Found: C, 53.69; H, 5.27; N, 10.90; Br, 20.98.

Scheme 4



Scheme 5



(Z)-1-Ethyl-4-[2-(4-methoxyphenyl)-1-ureylvinyl]pyridinium bromide 4b. This compound was obtained by general procedure A. Yield: 16%; mp 206–208°C (methanol-ethylic ether); IR (potassium bromide) 3380 (NH), 3240, 3180 (NH_2), 1660 (C=O), 1640 (C=N), 1600 (C=C), 1255, 1020 ($ArOCH_3$) cm^{-1}; ^{1}H-NMR (trifluoroacetic acid) δ 1.8 (t, 3H, CH_3—C—N^+, J = 7.0 Hz), 3.9 (s, 3H, CH_3—O), 4.5 (q, 2H, CH_2—N^+, J = 7.0 Hz), 7.1 (d, 2H, H-3, H-5 ArH, J = 8.0 Hz), 7.5–7.8 (m, 3H, CH=C and H-2, H-6 ArH), 8.0–8.3 (m, 3H, NH and H-3, H-5 py), 8.5 (d, 2H, H-2, H-6 py, J = 7.0 Hz) ppm. Anal. Calcd. for $C_{17}H_{20}BrN_3O_2$: C, 53.97; H, 5.29; N, 11.11; Br, 21.13. Found: C, 53.60; H, 5.34; N, 10.80; Br, 21.20.

(Z)-1-Ethyl-4-[2-(4-hydroxyphenyl)-1-ureylvinyl]pyridinium bromide 4c. This compound was obtained by general procedure A. Yield: 33%; mp 260–262°C (ethanol); IR (potassium bromide) 3410 (NH), 3300, 3140 (NH_2), 1660 (C=O), 1640 (C=N), 1595 (C=C), 1170 (ArOH) cm^{-1}; ^{1}H-NMR (dimethyl sulfoxide-d_6) δ 1.5 (t, 3H, CH_3—C—N^+, J = 7.0 Hz), 4.5 (q, 2H, CH_2—N^+, J = 7.0 Hz), 6.1 (s, 2H, NH_2), 6.8 (d, 2H, H-3, H-5 ArH, J = 8.0 Hz), 7.1 (s, 1H, CH=C), 7.3 (s, 1H, OH), 7,5 (d, 2H, H-2, H-6 ArH, J = 8.0 Hz), 7.9–8.2 (m, 3H, NH and H-3, H-5 py), 8.9 (d, 2H, H-2, H-6 py, J = 7.0 Hz) ppm. Anal. Calcd. for $C_{16}H_{18}BrN_3O_2$: C, 52.75; H, 4.94; N, 11.54; Br, 21.98. Found: C, 52.80; H, 5.02; N, 11.60; Br, 21.85.

(Z)-1-Ethyl-4-[2-(4-nitrophenyl)-1-ureylvinyl]pyridinium bromide 4d. This compound was obtained by general procedure A. Yield: 18%; mp 196–198°C (ethanol); IR (potassium bromide) 3380 (NH), 3220, 3170 (NH_2), 1660 (C=O), 1640 (C=N), 1610 (C=C), 1510, 1345 (NO_2) cm^{-1}; ^{1}H-NMR (dimethyl sulfoxide-d_6) δ 1.5 (t, 3H, CH_3—C—N^+, J = 7.0 Hz), 4.6 (q, 2H, CH_2—N^+, J = 7.0 Hz), 6.3 (s, 2H, NH_2), 7.1 (s, 1H, CH=C), 7.8–8.4 (m, 6H, 4 ArH and H-3, H-5 py), 8.8 (s, 1H, NH), 9.0 (d, 2H, H-2, H-6 py, J = 7.0 Hz) ppm. Anal. Calcd. for $C_{16}H_{17}BrN_4O_3$: C, 48.85; H, 4.32; N, 14.25; Br, 20.36. Found: C, 48.60; H, 4.35; N, 14.20; Br, 20.45.

(Z)-1-Methyl-4-[2-(3,4,5-trimethoxyphenyl)-1-ureylvinyl]-pyridinium iodide 4e. This compound was obtained by general procedure A. Yield: 64%; mp 231–233°C (ethanol); IR (potassium bromide) 3360 (NH), 3260, 3190 (NH_2), 1680 (C=O), 1640 (C=N), 1610 (C=C), 1250, 1045 ($ArOCH_3$) cm^{-1}; ^{1}H-NMR (trifluoroacetic acid) δ 3.7 (s, 3H, pCH_3—O), 3.8 (s, 6H, $2mCH_3$—O), 4.2 (s, 3H, CH_3—N^+), 6.9 (s, 2H, H-2, H-6 ArH), 7.2 (s, 1H, CH=C), 7.9 (d, 2H, H-3, H-5 py, J = 6.0 Hz), 8.4 (d, 2H, H-2, H-6 py, J = 6.0 Hz) ppm. Anal. Calcd. for $C_{18}H_{22}IN_3O_4$: C, 45.86; H, 4.67; N, 8.91; I, 26.94. Found: C, 45.73; H, 4.81; N, 8.62; I, 26.79.

(Z)-1-Ethyl-4-[2-(3,4,5-trimethoxyphenyl)-1-ureylvinyl]-pyridinium bromide 4f. This compound was obtained by general procedure A. Yield: 20%; mp 208–210°C (ethanol); IR (potassium bromide) 3380 (NH), 3290, 3160 (NH_2), 1680 (C=O), 1640 (C=N), 1600 (C=C), 1270, 1050 ($ArOCH_3$) cm^{-1}; ^{1}H-NMR (dimethyl sulfoxide-d_6) δ 1.5 (t, 3H, CH_3—C—N^+, J = 6.9 Hz), 3.6 (s, 3H, pCH_3—O), 3.7 (s, 6H, $2mCH_3$—O), 4.4–4.6 (m, 2H, CH_2—N^+), 6.1 (s, 2H, NH_2), 6.9 (s, 2H, H-2, H-6 ArH), 7.0 (s, 1H, CH=C), 7.8 (d, 2H, H-3, H-5 py, J = 6.0 Hz), 8.2 (s, 1H, NH), 8.7 (d, 2H, H-2, H-6 py, J = 6.0 Hz) ppm. Anal. Calcd. for $C_{19}H_{24}BrN_3O_4$: C, 52.05; H, 5.48; N, 9.59; Br, 18.26. Found: C, 52.20; H, 5.30; N, 9.50; Br, 18.10.

(Z)-1-Ethyl-4-[2-(2-hidroxy-5-nitrophenyl)-1-ureylvinyl]-pyridinium bromide 4g. This compound was obtained by general procedure A. Yield: 71%; mp 201–203°C (methanol); IR (potassium bromide) 3400 (NH), 3240, 3180 (NH_2), 1660 (C=O), 1640 (C=N), 1600 (C=C), 1510, 1310 (NO_2), 1180 (ArOH) cm^{-1}; ^{1}H-NMR (trifluoroacetic acid) δ 1.8 (t, 3H, CH_3—C—N^+, J = 7.0 Hz), 4.6 (q, 2H, CH_2—N^+, J = 7.0 Hz), 7.0 (d, 1H, H-3 ArH, J = 8.0 Hz), 7.3 (s, 1H, CH=C), 8.0–8.3 (m, 4H, NH, H-5 ArH and H-3, H-5 py), 8.3–8.5 (m, 1H, H-6 ArH), 8.6 (d, 2H, H-2, H-6 py, J = 7.0 Hz) ppm. Anal. Calcd. for $C_{16}H_{17}BrN_4O_4$: C, 46.98; H, 4.16; N, 13.69; Br, 19.53. Found: C, 46.80; H, 4.35; N, 13.48; Br, 19.40.

(Z)-1-Propyl-4-[2-(3,4,5-trimethoxyphenyl)-1-ureylvinyl]-pyridinium bromide 4h. This compound was obtained by general procedure A. Yield: 46%; mp 217–219°C (ethanol); IR (potassium bromide) 3360 (NH), 3280, 3170 (NH_2), 1690 (C=O), 1645 (C=N), 1610 (C=C), 1280, 1010 ($ArOCH_3$) cm^{-1}; ^{1}H-NMR (trifluoroacetic acid) δ 1.1 (t, 3H, CH_3—C—C—N^+, J = 7.0 Hz), 1.9–2.3 (m, 2H, CH_2—C—N^+), 4.0 (s, 3H, pCH_3—O), 4.1 (s, 6H, $2mCH_3$—O), 4.6 (t, 2H, CH_2—N^+, J = 7.0 Hz), 7.1 (s, 2H, H-2, H-6 ArH), 7.5 (s, 1H, CH=C), 8,2 (d, 2H, H-3, H-5 py, J = 7.0 Hz), 8.4 (s, 1H, NH), 8.6 (d, 2H, H-2, H-6 py, J = 7.0 Hz) ppm. Anal. Calcd. for $C_{20}H_{26}BrN_3O_4$: C, 53.09; H, 5.75; N, 9.29; Br, 17.70. Found: C, 53.22; H, 5.85; N, 9.04; Br, 17.33.

(Z)-4-[1-Ethoxycarbonylamine-2-(3,4,5-trimethoxyphenyl)-vinyl]-1-methylpyridinium iodide 4i. This compound was obtained by general procedure A. Yield: 21%; mp 210–212°C (ethanol); IR (potassium bromide) 3180 (NH), 1715 (C=O), 1645 (C=N), 1610 (C=C), 1270, 1050 ($ArOCH_3$) cm^{-1}; ^{1}H-NMR (trifluoroacetic acid) δ 1.3 (t, 3H, CH_3O, J = 7.0 Hz), 3.9 (s, 3H, pCH_3—O), 4.0 (s, 6H, $2mCH_3$—O),4.2 (q, 2H, CH_2, J = 7.0 Hz), 4.3 (s, 3H, CH_3—N^+), 6.8 (s, 2H, H-2, H-6 ArH), 7.1 (s, 1H, CH=C), 7.5 (s, 1H, NH), 7.9 (d, 2H, H-3, H-5 py, J = 7.0 Hz), 8.3 (d, 2H, H-2, H-6 py, J = 7.0 Hz) ppm. Anal. Calcd. for $C_{20}H_{25}IN_2O_5$: C, 48.00; H, 5.00; N, 5.60; I, 25.40. Found: C, 47.65; H, 5.27; N, 5.84; I, 25.23.

N,N′-Diaminocarbonyl-1,2-di-(1-ethyl-4-pyridinium)ethylenediamine dibromide 2a. This compound was obtained by general procedure B. Yield: 69%; mp 245–247°C (methanol); IR (potassium bromide) 3430 (NH), 3300, 3120 (NH_2), 1680 (C=O), 1650 (C=N), 1580, 1510 (Ar) cm^{-1}; ^{1}H-NMR (trifluoroacetic acid) δ 1.8 (t, 6H, $2CH_3$, J = 7.5 Hz), 4.6 (q, 4H, $2CH_2$, J = 7.5 Hz), 6.0–6.2 (m, 2H, 2CH), 7.6–7.8 (m, 2H, 2NH), 8.2 (d, 4H, 2H-3, 2H-5 py, J = 6.0 Hz), 8.5 (d, 4H, 2H-2, 2H-6 py, J = 6.0 Hz) ppm. Anal. Calcd. for $C_{18}H_{26}Br_2N_6O_2$: C, 41.74; H, 5.02; N, 16.22; Br, 30.85. Found: C, 41.50; H, 4.95; N, 15.97; Br, 30.84.

N,N′-Diaminocarbonyl-1,2-di-(1-propyl-4-pyridinium)ethylenediamine dibromide 2b. This compound was obtained by general procedure B. Yield: 58%; mp 244–246°C (methanol); IR (potassium bromide) 3390 (NH), 3300, 3210 (NH_2), 1680 (C=O), 1645 (C=N), 1580, 1525 (Ar) cm^{-1}; ^{1}H-NMR

(trifluoroacetic acid) δ 1.0 (t, 6H, $2CH_3$, $J = 6.9$ Hz), 1.7–2.4 (m, 4H, $2CH_2$—C—N^+), 4.5 (t, 4H, $2CH_2$—N^+, $J = 6.9$ Hz), 5.8–6.0 (m, 2H, 2CH), 7.5–7.8 (m, 2H, 2NH), 8.4 (d, 4H, 2H-3, 2H-5 py, $J = 6.0$ Hz), 8.7 (d, 4H, 2H-2, 2H-6 py, $J = 6.0$ Hz) ppm. Anal. Calcd. for $C_{20}H_{30}Br_2N_6O_2$: C, 43.99; H, 5.49; N, 15.38; Br, 29.27. Found: C, 43.77; H, 5.42; N, 15.23; Br, 29.17.

N,N′-Diethoxycarbonyl-1,2-di-(1-methyl-4-pyridinium)ethylenediamine diiodide 2c. This compound has been described previously [6].

Acknowledgment. The authors thank Dr. Antonio Chana for performing the NOESY study.

REFERENCES AND NOTES

[1] Madaan, P.; Tyagi, V. K. J. Oleo Sci 2008, 57, 197.

[2] Pernak, J.; Rogoza, J. Arkivoc 2000, 6, 889.

[3] Henderson, T. R.; Gray, A. P.; Platz, R. D.; Kellar, K. J.; Dretchen, K. L. Toxicol Appl Pharmacol 1991, 107, 336.

[4] Roldan-Tapia, L.; Parron, T.; Sánchez-Santed, F. Neurotoxicol Teratol 2005, 27, 259.

[5] Gandia, L.; Álvarez, R. M.; Hernández-Guijo, J. M.; González-Rubio, J. M.; Pascual, R.; Rojo, J., Tapia, L. Rev Neurol 2006, 42, 471.

[6] Braña, M. F.; Castellano, J. M.; De Miguel, P.; Posada, P.; Sanz, C. R.; Migallón, A. S. Tetrahedron 1994, 50, 10061.

[7] Martín-Cantalejo, Y.; Sáez, B.; Soto, J.; Villa, M. J.; Braña, M. F. Synthesis 2003, 14, 2211.

[8] Darvesh, S.; Darvesh, K. V.; McDonald, R. S.; Mataija, D.; Walsh, R.; Mothana, S.; Lockridge, O.; Martin, E. J Med Chem 2008, 51, 4200.

[9] DeBernardis, J. F.; Gifford, P.; Rizk, M.; Ertel, R.; Abraham, D. J.; Siuda, J. F. J Med Chem 1988, 31, 117.

[10] Kontoyianni, M.; McGaughey, G. B.; Stewart, E. L.; Cavallito, C. J.; Bowen, J. P. J Med Chem 1994, 37, 3128.

[11] Alcalde, E.; Barat, A.; Goya, P.; Martínez, A.; Ramírez, G.; Roca, T.; Rozas, I. Biorg Med Chem 1997, 5, 949.

[12] Cannon, J. G. In Burger's Medicinal Chemistry and Drug Discovery, 6th ed.; Abraham, D. J., Ed.; Wiley: New York, 2003; Vol. 6, p 39.

[13] Chana, A. Personal communication.

[14] Ozaka, I.; Arioglu, E.; Guner, S.; Altan, U. M.; Ozcelikay, A. T. Pharmacology 2007, 80, 227.

[15] Tripos Inc. Sybyl/Unit, Version 6.9; Tripos Inc: St. Louis, 2002.

[16] Laaksonen, L. A. J Mol Graph 1992, 10, 33.

[16] Bergman, D. L.; Laaksonen, L.; Laaksonen, A. J Mol Graph 1997, 15, 301.

[18] Portmann, S.; Lüthi, H. P. Chimia 2000, 54, 766.