Heterocyclic Betaines. 13.[1] Synthesis and Electronic and Molecular Structures of Methylenepyridinium and Methyleneimidazolium Azolate Inner Salts

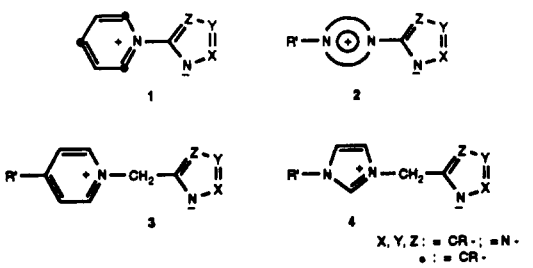
Ermitas Alcalde,*,† Lluïsa Pérez-García,† Carlos Miravitlles,‡ Jordi Rius,‡ and Eduard Valentí§

Laboratorio de Química Orgánica, Facultad de Farmacia, Universidad de Barcelona, E-08028-Barcelona, Spain, Instituto de Ciencias de Materiales, C.S.I.C., E-08193-Bellaterra, Spain, and Departamento de Química Médica, Laboratorios Dr. Esteve, E-08026-Barcelona, Spain

Received December 2, 1991

A convenient synthesis of several examples of betaines 3 and 4 is reported. The electronic and molecular structure of the title betaines 3 and 4 is investigated in terms of a single-crystal diffraction X-ray analysis of compound 7, spectroscopic methods, and experimental dipole moment values (12.34–15.34 D). Semiempirical molecular orbital calculations (MNDO and AM1 methods) provide a useful complementary information to the experimental results.

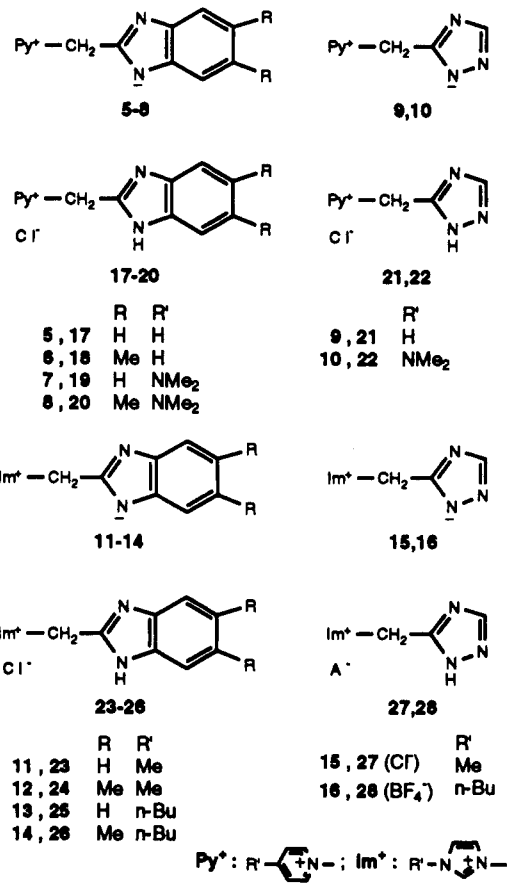
Heterocyclic betaines have been the subject of extensive investigation, mainly because their dipolar character has a dominant influence upon their chemistry. In the context of a current search for organic substrates with high dipole moments, and our interest in the chemistry of the azinium azolate 1 and azolium azolate inner salts 2,[1-3] we have now investigated a new type of heterocyclic betaine homologues of the *N*-ylides 1 and 2, the methylenepyridinium and methyleneimidazolium azolate inner salts 3 and 4. Owing to their structure, they can be incorporated as subunit(s) in host molecules and could confer unusual properties to the cavities—either cavitates or clathrates.



Results and Discussion

Synthesis. A facile entry into the unknown inner salts of methylenepyridinium benzimidazolate 5–8, triazolate 9 and 10 and methyleneimidazolium benzimidazolate 11–14, triazolate 15 and 16 is described,[4] as well as their precursors, the (azolylmethyl)pyridinium and -imidazolium salts 17–28 according to a general procedure shown in Scheme I. In this connection, other 1-(1*H*-benzimidazol-2-ylmethyl)pyridinium salts have been so far reported by Dorofeenko et al.[5a,b] and by Alvarez-Builla et al.[5c]

Firstly, 2-(chloromethyl)benzimidazole (29), 2-(chloromethyl)-5,6-dimethylbenzimidazole (30), and 3(5)-(chloromethyl)-1,2,4-triazole (31) were prepared by standard methods.[6] Then, the (azolylmethyl)pyridinium salts 17–22 and the (azolylmethyl)imidazolium salts 23–28 were obtained by reaction of a pyridine or an 1-alkylimidazole and the accessible 2-(chloromethyl)azoles 29–31, following a general method for preparation of quaternary heteroaromatic compounds (Menschutkin reaction). Transformation of compounds 17–28 into the title betaines 5–16 was achieved using an anion-exchange Amberlite IRA-401 resin (OH^- form)[7] (Scheme I). The physical data of all new



compounds described in this work (5–28) are listed in Tables I and II.

† Universidad de Barcelona.
‡ Instituto de Ciencias de Materiales, C.S.I.C., Campus de la U. A.B., Bellaterra.
§ Laboratorios Dr. Esteve Barcelona.

(1) (a) Part XII: Alcalde, E.; Pérez-García, Ll.; Dinarès I.; Frigola, J.; Coombs, G. H. *Eur. J. Med. Chem.* **1992**, *27*, 171. (b) Abstracted from the Ph.D. Thesis of Lluïsa Pérez-García, Facultad de Farmacia, Universidad de Barcelona, 1991 (microfilm no. 000, Universidad de Barcelona).

(2) (a) Alcalde, E.; Dinarès, I.; Elguero, J.; Fayet, J.-P.; Vertut, M.-C.; Miravitlles, C.; Molins, E. *J. Org. Chem.* **1987**, *52*, 5009. (b) Alcalde, E.; Dinarès, I.; Elguero, J.; Frigola, J.; Osuna A.; Castanys, S. *Eur. J. Med. Chem.* **1990**, *25*, 309.

(3) (a) Alcalde, E.; Dinarès, I.; Frigola, J.; Jaime, C.; Fayet, J.-P.; Vertut, M.-C.; Rius, J.; Miravitlles, C. *J. Org. Chem.* **1991**, *56*, 4223, and references quoted therein. (b) Alcalde, E.; Dinarès, I. *J. Org. Chem.* **1991**, *56*, 4233.

(4) For an earlier report see: Alcalde, E.; Pérez, L.; Fayet, J.-P.; Vertut, M.-C. *Chem. Lett.* **1991**, 845.

(5) (a) Dorofeenko, G. N.; Narkevich, A. N.; Zhdanov, Yu. A.; Soroka, T. G. *Khim. Geterosilk. Soedin.* **1970**, 315. (b) Dorofeenko, G. N.; Zvezdina, E. A.; Zhdanova, M. P.; Barchan, I. A. *Khim. Geterosikl. Soedin.* **1973**, 1682. (c) Cuadro, A. M.; Novella, J. L.; Molina, A.; Alvarez-Builla, J.; Vaquero, J. J. *Tetrahedron* **1990**, *46*, 6033 and references quoted therein.

0022-3263/92/1957-4829$03.00/0

Table I. Physical Data of Methylenepyridinium Azolate Inner Salts 5–10 and Their Corresponding *N*-(Azolylmethyl)pyridinium Salts 17–22

compd[a]	azolyl or azolate	R′	method[b] (yield, %)	reaction time, h	mp, °C (solvent)[c]
17	1*H*-benzimidazol-2-yl	H	A (83)	0.25	221–2 (A)
18	5,6-dimethyl-1*H*-benzimidazol-2-yl	H	A (61)	1	224–5 (B)
19	1*H*-benzimidazol-2-yl	NMe_2	B (80)	1	263–4 (C)
20	5,6-dimethyl-1*H*-benzimidazol-2-yl	NMe_2	B (92)	0.80	215–6 (D)
21	1*H*-1,2,4-triazol-3(5)-yl	H	C (79)	0.75	162–3 (D)
22	1*H*-1,2,4-triazol-3(5)-yl	NMe_2	B (46)	0.25	253–5[d]
5	2-benzimidazolate	H	D (76)		78–80[e] (A)
6	5,6-dimethyl-2-benzimidazolate	H	D (86)		208–10[e] (D)
7	2-benzimidazolate	NMe_2	D (95)		199 (C)
8	5,6-dimethyl-2-benzimidazolate	NMe_2	D (94)		182 (C)
9	3(5)-1,2,4-triazolate	H	D (33)		160–1 (A)
10	3(5)-1,2,4-triazolate	NMe_2	D (98)		202 (E)

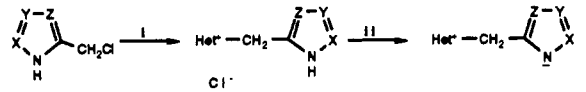
[a] Satisfactory analytical data (±0.4% for C, H, N) were obtained for all new compounds. [b] Yields were not optimized. [c] A, acetonitrile; B ethyl acetate; C, ethanol; D, 2-propanol; E, 85% ethanol. [d] See Experimental Section. [e] Not analytically pure.

Table II. Physical Data of Methyleneimidazolium Azolate Inner Salts 11–16 and Their Corresponding *N*-(Azolylmethyl)imidazolium Salts 23–28

compd[a]	azolyl or azolate	R′	method[b] (yield, %)	reaction time, h	mp, °C (solvent)[c]
23	1*H*-benzimidazol-2-yl	Me	C (76)	0.50	254 (A)
24	5,6-dimethyl-1*H*-benzimidazol-2-yl	Me	C (78)	2	238–9 (B)
25	1*H*-benzimidazol-2-yl	Bu	C (70)	1.5	173 (C)
26	5,6-dimethyl-1*H*-benzimidazol-2-yl	Bu	C (80)	1.50	183–4 (C)
27	1*H*-1,2,4-triazol-3(5)-yl	Me	C (77)	1	163 (D)
28	1*H*-1,2,4-triazol-3(5)-yl	Bu	E (48)	0.50	130–2[d]
11	2-benzimidazolate	Me	D (89)		164 dec
12	5,6-dimethyl-2-benzimidazolate	Me	D (97)		190 (A)
13	2-benzimidazolate	Bu	D (97)		140 dec
14	5,6-dimethyl-2-benzimidazolate	Bu	D (98)		214 dec
15	3(5)-1,2,4-triazolate	Me	D (81)		*e*
16	3(5)-1,2,4-triazolate	Bu	C (95)		*e*

[a] Satisfactory analytical data (±0.4% for C, H, N) were obtained for all new compounds. [b] Yields were not optimized. [c] A, ethanol; B, acetonitrile; C, acetone; D, 2-propanol. [d] See Experimental SEction. [e] Hydroscopic oily compound.

Scheme I[a]



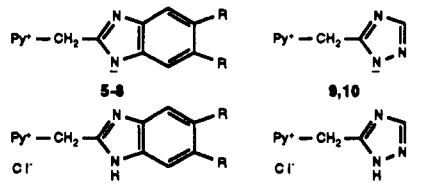
[a] Reagents and conditions: (i), pyridine or *N*-alkylimidazole as reagent and solvent, or 4-(dimethylamino)pyridine in dimethylformamide, at 130 °C under an atmosphere of nitrogen; (ii) anion-exchange resin IRA-401 (OH^- form). Overall yields: **5–8** and **11–14** > 61%; **9, 10, 15, 16** > 25%.

Spectroscopic Methods. The IR spectra of the compounds **17–28** showed absorptions in the range of 3400–3200 cm^{-1} (ν_{NH}) and 2775–2500 cm^{-1} (hydrochlorides) (compounds **17–27**) or 1200–1000 cm^{-1} (tetrafluoroborates) (compound **28**), while these bands were absent for the methylenepyridinium and methyleneimidazolium azolate inner salts **5–10** and **11–16**.

^1H and ^{13}C NMR data for betaines **5–16** proved very important for structural proof of their highly dipolar structure, as they were for the previously reported *N*-ylides **1** and **2**. Selected ^1H and ^{13}C NMR chemical shifts of betaines **5–16** and their precursors **17–28** are shown in Table III and IV (see Tables V–VIII in the supplementary material).

The chemical shifts of the CH protons in the azolate moiety move upfield with respect to their precursors **17–28**,

Table III. Selected ^1H and ^{13}C NMR Spectra Data of Methylenepyridinium Azolate Inner Salts 5–10 and Their Corresponding *N*-(Azolylmethyl)pyridinium Salts 17–22[a]



compd	H-2′,6′	CH_2	H-4,7	CH_2	C-2
5[b]	9.18	5.89	7.31		
17	9.29	6.26	7.55	57.3	146.3
Δδ	−0.11	−0.37	−0.24		
6[b]	9.16	5.84	7.08		
18	9.26	6.19	7.31	59.0	146.7
Δδ	−0.10	−0.35	−0.23		
7	8.38	5.41	7.26	58.2	155.2
19	8.45	5.75	7.53	53.6	148.8
Δδ	−0.07	−0.34	−0.27	+4.6	+6.4
8	8.36	5.50	7.16	55.9	152.0
20	8.46	5.71	7.28	53.8	148.3
Δδ	−0.10	−0.21	−0.12	+2.1	+3.7

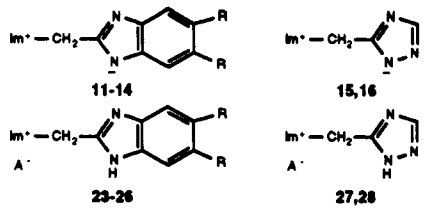
compd	H-2′,6′	CH_2	H-4,7	CH_2	C-5(3) [CH]
9[b]	9.11	5.77	7.61		
21	9.29	6.14	8.59	57.1	146.1
Δδ	−0.18	−0.37	−0.98		
10	8.29	5.28	7.58	55.3	151.5
22	8.36	5.55	8.51	53.4	145.7
Δδ	−0.07	−0.27	−0.93	+1.9	+5.8

[a] In DMSO-d_6. [b] The instability of betaines **5**, **6**, and **9** in solution precludes recording their ^{13}C NMR spectra. Δδ: Observed chemical shift difference between the methylenepyridinium azolate inner salts **5–10** and their corresponding (azolylmethyl)pyridinium salts **17–22**.

(6) (a) Lettré, H.; Fritsch, W.; Porath, J. *Chem. Ber.* **1951**, 719. (b) Mamalis, P.; Petrow, V.; Sturgeon, B. *J. Chem. Soc.* **1950**, 1600. (c) Jones, R. G.; Ainsworth, C. *J. Am. Chem. Soc.* **1955**, *77*, 1538.

(7) The use of an anion-exchange Amberlite IRA-401 resin (OH^- form) had been conveniently applied to other betaines[1-3b] or compounds with a betaine character.[3a]

Table IV. Selected ^1H and ^{13}C NMR Spectra Data of Methyleneimidazolium Azolate Inner Salts 11–16 and Their Corresponding *N*-(Azolylmethyl)imidazolium Salts 23–28 in DMSO-d_6



compd	H-2′	CH_2	H-4,7	CH_2	C-2
11	9.22	5.41	7.29	50.5	156.3
23	9.38	5.78	7.55	46.4	148.0
$\Delta\delta^a$	−0.16	−0.37	−0.26	+4.1	+8.3
12	9.18	5.34	7.05	49.7	153.6
24	9.36	5.71	7.31	46.5	147.4
$\Delta\delta^a$	−0.18	−0.37	−0.26	+3.3	+6.2
13	9.31	5.40	7.27	50.8	156.6
25	9.48	5.78	7.55	46.4	148.8
$\Delta\delta^a$	−0.17	−0.38	−0.28	+4.5	+8.6
14	9.25	5.34	7.05	51.1	156.2
26	9.62	5.76	7.30	46.5	147.3
$\Delta\delta^a$	−0.37	−0.42	−0.25	+4.6	+8.9

compd	H-2′	CH_2	H-4,7	CH_2	C-5(3) [CH]
15	9.13	5.27	7.57	47.6	151.5
27	9.29	5.55	8.62	45.9	145.5
$\Delta\delta^a$	−0.16	−0.28	−1.05	+1.7	+6.0
16	9.23	5.28	7.58	47.8	151.6
28	9.29	5.55	8.63	46.2	145.6
$\Delta\delta^a$	−0.06	−0.27	−1.05	+1.7	+6.0

[a] $\Delta\delta$: Observed chemical shift difference between the methyleneimidazolium azolate inner salts 11–16 and their corresponding (azolylmethyl)imidazolium salts 23–28.

indicating the high electron density on the azolate ring, and they are consistent with the ^1H chemical shifts for anionic species in the azole series,[2,3a] (see Figure 1, supplementary material). Moreover, the δC values of the carbon atoms were in excellent agreement with data reported for a variety of benzimidazolate ions and the not less frequently reported 1,2,4-triazolate species.[2,3a] With regard to the quaternary pyridinium or imidazolium rings, both the ^1H and ^{13}C NMR chemical shifts accord perfectly with the data previously reported for betaines of pyridinium azolate **1** and imidazolium azolate **2**, respectively.[2,3] From these spectral data, the fact that the methylene interannular linkage values are the most affected ones is noteworthy (see Figure 2, supplementary material).

X-ray Data. The molecular structure of 2-[[4-(dimethylamino)-1-pyridinio]methyl]benzimidazolate inner salt **7** was determined by a single X-ray diffraction analysis. In this connection, the aromatic parent compound is diphenylmethane (DPM). Mislow et al.[8] reported its accurate crystalline and molecular structure, which is of a helical type with approximate C_2 symmetry (ϕ_A = 63.9°, ϕ_B = 71.1°); the central C–C–C interannular bond value is of 112.5°. Moreover, Claramunt et al.[9] have investigated a variety of poly(azolylmethane) ligands, and several X-ray diffraction analysis have been carried out.

Figure 3 shows the perspective diagram of betaine **7** with the corresponding atom numbering.[10] Selected bond

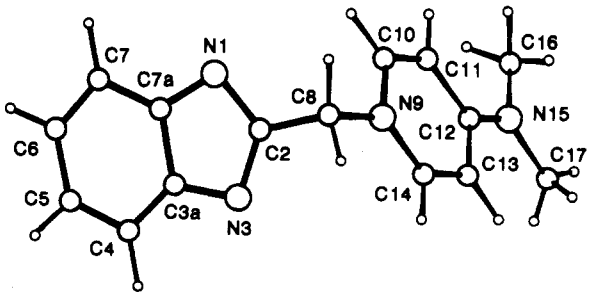


Figure 3.

Table IX. Bond Length (Å) with esd's in Parentheses for Compound 7

C2–N1	1.342 (3)	N9–C8	1.489 (3)
C7a–N1	1.383 (3)	C10–N9	1.357 (3)
N3–C2	1.344 (3)	C14–N9	1.344 (3)
C8–C2	1.498 (3)	C11–C10	1.358 (3)
C3a–N3	1.382 (3)	C12–C11	1.408 (3)
C4–C3a	1.406 (3)	C13–C12	1.421 (3)
C7a–C3a	1.398 (3)	N15–C12	1.331 (3)
C5–C4	1.373 (4)	C14–C13	1.356 (3)
C6–C5	1.395 (5)	C16–N15	1.462 (4)
C7–C6	1.363 (4)	C17–N15	1.448 (4)
C7a–C7	1.406 (4)		

lengths are given in Table IX, and further details are provided in the supplementary material. The structure of **7** has twist angles of 105° (ϕ_A) and 103.1° (ϕ_B). The central C_2–C_8–N_9 interannular bond angle of 111.0° resembles that found for DPM.

The unit cell packing diagram is shown in Figure 4. The shortest intermolecular contacts are N(1)···C(14)* = 3.37 (1) Å; C(13)···N(1)* = 3.46 (1) Å; C(13)···C(2)* = 3.37 (1) Å; C(16)···C(3a)* = 3.47 (1) Å; C(16)···C(7a) = 3.33 (1) Å; C(16)···C(7)* = 3.47 (1) Å. The X-ray analysis confirmed that compound **7** forms a dihydrate, and the water molecules are placed forming rows along [100]. The shortest contacts and H-bonds involving water molecules are O(1)···N(3)* = 2.90 (1) Å; O(1)···O(1)* = 2.90 (1) Å; O(1)···O(2) = 2.78 (1) Å; O(1)···C(17) = 3.41 (1) Å; O(1)···C(17)* = 3.39 (1) Å; O(2)···N(1) = 2.83 (1) Å; O(2)···O(2)* = 2.81 (1) Å.

Dipole Moments. In our previous investigation[3a] of heterocyclic mesomeric betaines of azolium azolate type **2**, it was pointed out that the perturbing effect of self-association leading to formation of nonpolar dimers was not completely eliminated, with consequent decrease of the measured values. A similar situation holds for the present study, and different dipole moment measurements were determined in the manner already described[3a] for four examples of the title betaines: compounds **7**, **10**, **13**, and **16**. Large experimental dipole moments were observed with the anhydrous methylenepyridinium benzimidazolate and methyleneimidazolium benzimidazolate inner salts **7** (12.34 D) and **13** (12.56 D), and were even higher for the triazolate analogues **10** (14.82 D) and **16** (15.34 D).[11] These values were extrapolated to extreme dilution (ω < 0.000 15, in anhydrous dioxane, 298 K) to reduce as far as possible the perturbing dominance of self-association for reliable interpretation of the experimental dipole moment data previously reported[4] (see later, Theoretical Study).

Theoretical Study. The geometries of the eight selected betaines of methylenepyridinium azolate, **5**, **7**, **9**, **10**, **32**, and methyleneimidazolium azolate, **13**, **16**, **33**, were

(8) Barnes, J. C.; Paton, J. D.; Damewood, J. R., Jr.; Mislow, K. *J. Org. Chem.* **1981**, *46*, 4975 and references quoted therein.

(9) Foces-Foces, C.; Hernández Cano, F.; Martinez-Ripoll, M.; Faure, R.; Roussel, Ch.; Claramunt, R. M.; Lõpez, C.; Sanz, D.; Elguero, J. *Tetrahedron Asymm.* **1990**, *1*, 65 and references quoted therein.

(10) The dipole moments and polarization data in dioxane at 298 K are summarized in an earlier report.[4]

(11) The atom numbering system is not the same as the IUPAC numbering system.

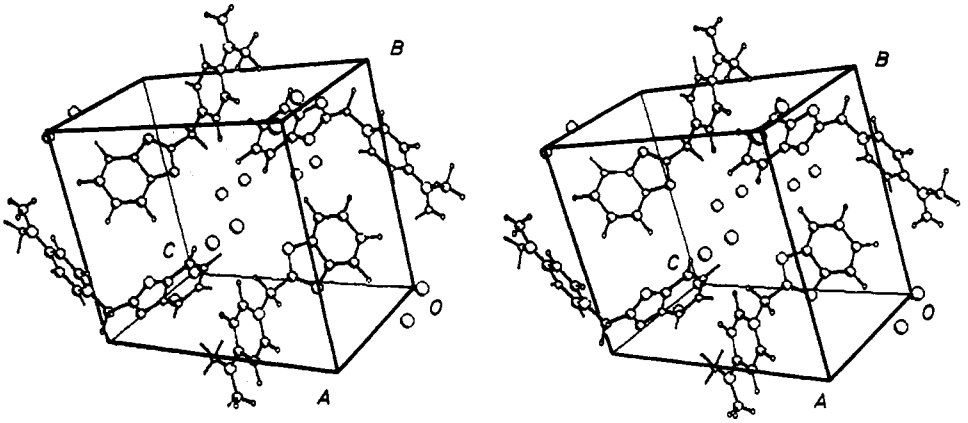
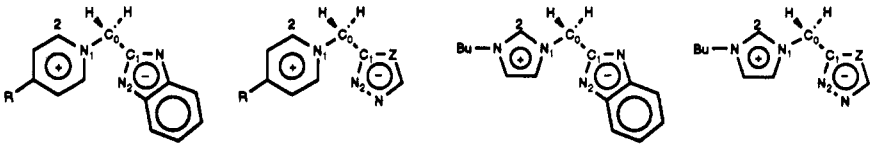


Figure 4.

Table X. MNDO and AM1 Semiempirical Calculations of Methylenepyridinium Azolate Betaines 5, 7, 9, 10, and 32 and Methyleneimidazolium Azolate Betaines 13, 16, and 33



5 R=H
7 R=NMe$_2$

9 R=H; Z:N
10 R=NMe$_2$; Z:N
32 R=NMe$_2$; Z:CH

13

16 Z:N
33 Z:CH

	ΔH_f[a]		C_1–C_0–N_1[b]		$\varphi_{A,min}$[b,c]		$\varphi_{B,min}$[b,c]		C_0–N_1[d]		C_0–C_1[d]		μ_{calcd}[e]		
compd	AM1	MNDO	AM1	MNDO	AM1	MNDO	AM1	MNDO	AM1	MNDO	AM1	MNDO	AM1	MNDO	μ_{exp}[e,f]
5	637.35	511.79	109.8	107.6	68.6	86.5	96.7	95.2	1.494	1.546	1.479	1.473	14.32	14.34	
7	642.95	532.08	110.5	108.3	64.2	86.3	92.9	92.7	1.484	1.534	1.484	1.478	17.85	17.13	12.34
9	624.00	455.47	111.6	108.7	102.9	86.2	80.9	88.6	1.506	1.558	1.459	1.457	13.43	13.70	
10	631.53	476.93	110.2	108.7	96.8	85.9	79.0	87.9	1.495	1.544	1.464	1.462	16.52	16.40	14.82
32	605.22	508.90	111.4	108.8	106.5	86.9	69.6	72.3	1.501	1.555	1.453	1.456	16.21	15.59	
13	616.47	428.40	110.5	108.2	57.7	73.6	115.2	102.7	1.467	1.523	1.488	1.478	15.73	15.76	12.56
16	605.76	373.59	111.6	108.7	40.7	67.6	109.3	101.5	1.476	1.532	1.467	1.463	15.39	15.49	15.34
33	590.11	403.34	110.8	110.4	110.3	13.9	78.6	72.3	1.491	1.541	1.449	1.457	15.93	14.34	

[a] In kilojoules per mole. [b] In degree. [c] $\varphi_A(C_2–N_1–C_0–C_1)$ and $\varphi_B(N_1–C_0–C_1–N_2)$. [d] In angstroms. [e] In deybe; 1 D = $3.34 \times 10^{3-}$ Cm. [f] μ_{exp} as in ref 4.

constructed in CHEMX[12a] and fully optimized at the RHF, closed-shell, ground-state level using both the MNDO SCF-MO[12b] and the AM1 SCF-MO[12c] models as implemented in the AMPAC program package.[12d]

The 2-(1-pyridinomethyl)benzimidazolate (**5**) was selected as the model compound studying of the AM1 conformational space of these structures. Five local minima were found, all of them being within a range of less than 5 kcal/mol of the absolute minimum and having close values of dipole moment (14.3–15.8 D). Similar results could be obtained using the MNDO method. It is worth noting that the minimum energy conformation found theoretically for compound **5** is the same as that which compound **7** adopts in its crystal structure. All the betaines included in this theoretical study were calculated in this conformation. Relevant results are collected in Table X (see Table XI and Figure 5 in supplementary material).

Comparison of the calculated molecular geometries (bond lengths, bond angles) of compound **7** with those obtained from its single-crystal X-ray diffraction analysis shows that AM1 methodology provides a good description of the structure which is slightly better than by the MNDO method as shown in Figures 6 and 7 (see the supplementary material). This result validates the present theoretical study from a geometrical point of view.

With regard to the dipole moments, the AM1 method predicts values closer to those experimentally determined than does the MNDO method. We may thus conclude that the AM1 method is better suited to predict experimentally observed trends of the title betaines **3** and **4** than the MNDO method. In this connection, AM1 method has recently been used in the calculation of some pyridinium *N*-phenoxide betaines of the Reichardt type.[13]

For 3-[(3-butyl-1-imidazolio)methyl]-1,2,4-triazolate (**16**), there is an excellent agreement between μ_{exp} and μ_{calcd}. A different situation exists with regard to the values obtained for the betaines **7**, **10**, and **13**, since their calculated dipolar moments are higher than their experimental ones (see Table X and Figure 8 in the supplementary material). The fact that a similar behavior has been found for the azolium azolate inner salts **2**, i.e. compound **35**[3a] in Figure 8, is noteworthy (see Dipole Moments).

Theoretical MO calculations of the title betaines **3** and **4**, using AM1 and MNDO methods, have produced data which correlated well with the experimental physicochemical properties i.e. molecular geometries (X-ray) and

(12) (a) CHEMX, developed and distributed by Chemical Design Ltd., Oxford, England. (b) Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4899. (c) Dewar, M. J. S.; Zoebich, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902. (d) AMPAC program package: QCPE No. 506. *QCPE Bull.* **1986**, *6*, 24.

(13) Paley, M. S.; Harris, J. M. *J. Org. Chem.* **1991**, *56*, 568.

dipole moments (dipolarimetry).

Conclusions

The novel betaines of methylenepyridinium(azolium) azolate **3** and **4** constitute an ensemble of organic substrates with an interest worthy of development. The experimental results discussed in terms of ^1H and ^{13}C NMR data, a monocrystal diffraction analysis, and dipole moments are consistent with the highly dipolar structure of **3** and **4**. The MO calculations using the AM1 Hamiltonian sheds light on their intrinsic high dipolar character.

Experimental Section

General Methods. Melting point: CTP-MP 300 hot-plate apparatus in ASTM 2C thermometer, (given in Tables I and II). IR (KBr disks): Perkin-Elmer 1430 spectrophotometer. ^1H NMR: Varian XL-200, Bruker AM-100 or Perkin-Elmer R-24B spectrometer (200, 100, and 60 MHz respectively). ^{13}C NMR: Bruker AM-100 Fourier transform spectrometer (25.1 MHz). NMR spectra were determined in dimethyl-d_6 sulfoxide, and chemical shifts are expressed in parts per million (δ) relative to TMS as internal standard or the central peak of dimethyl-d_6 sulfoxide. TLC: Merck silica gel 60 F_{254} plates; detection by UV light. Ion-exchange chromatography: Amberlite IRA-401 (OH^- form).[14] In general, the compounds were dried by heating overnight at 25 °C in a vacuum oven. Microanalyses of compounds **5–28** (Table XVI) were performed on a Carlo Erba 1106 analyzer.

Materials. DMAP, 1-methylimidazole, and 1-*n*-butylimidazole are commercially available. 2-(Chloromethyl)benzimidazole, **29**,[6a,b] 2-(chloromethyl)-5,6-dimethylbenzimidazole, **30**,[6a,b] and 3(5)-(chloromethyl)-1,2,4-triazole, **31**,[6c] were prepared according to literature procedures.

Preparation of *N*-(Azolylmethyl)pyridinium Salts 17–22 and *N*-(Azolylmethyl)imidazolium Salts 23–28 (Tables I and II). Method A. A stirred solution of the 2-(chloromethyl)-benzimidazole, **29**, or **30** (10 mmol) and anhyd pyridine (7.4 mL, 91.8 mmol), under an atmosphere of nitrogen, was heated on a bath at 135 °C for the time specified in Table I. After cooling, acetonitrile (ca. 40 mL) was added to give an orange solid, **17** or **18**, which was then filtered, washed with acetonitrile (2 × 20 mL), and recrystallized (Table I).

Method B. A stirred solution of the 2-(chloromethyl)azole, **29**, **30**, or **31** (10 mmol) and DMAP (3.6 g, 30 mmol) in anhyd DMF (15 mL), under an atmosphere of nitrogen, was heated on a bath at 130 °C for the time specified in Table I. To the cooled reaction mixture was added acetone (50 mL), and the resulting yellow solid **19** or **20** was filtered, washed with acetone (2 × 25 mL), and recrystallized (Table I).

The crude compound **22** was obtained by filtration from the cooled reaction mixture and washed with anhyd DMF (3 × 5 mL). Then, a suspension of the crude material in anhyd DMF (150 mL) was vigorously stirred for 2 h and then filtered to afford pure 1*H*-1,2,4-triazol-3(5)-ylpyridinium salt **22** (Table I).

Method C. A stirred solution of the 2-(chloromethyl)azole, **29**, **30**, or **31** (6 mmol) and anhyd pyridine or anhyd *N*-alkylimidazole (18 mmol), under an atmosphere of nitrogen, was heated on a bath at 130 °C for the time specified in Tables I and II. The reaction mixture was cooled, and the crude compound **21**, **23**, **24**, **25**, **26**, or **27** was filtered after addition of anhyd acetone (15 mL) for **21**, **23**, or **24**, diethyl ether (10 mL) for **25** or **26**, and acetonitrile (10 mL) for **27**, respectively. In the case of the diethyl ether suspension of compound **25**, it was triturated thoroughly before filtration. Then, the crude salts **21**, **23–27** were washed with acetone (2 × 5 mL) for **21**, **23**, and **24**, diethyl ether (2 × 25 mL) for **25** and **26**, and acetonitrile (3 × 25 mL) for **27** and recrystallized (Tables I and II).

Preparation of Methylenepyridinium Azolate Inner Salts 5–10 and Methyleneimidazolium Azolate Inner Salts 11–16 (Tables I and II). Method D. An aqueous suspension of Amberlite resin IRA-401 hydroxide form was prepared according to the companion paper.[14] A column (5-in. diameter) was packed with this aqueous suspension of IRA-401 (OH^- form) up to a height of 8 in., and the column bed was equilibrated with the following eluants: water (20 mL), 50% ethanol (20 mL), and 85% ethanol (20 mL).

A solution of the corresponding *N*-(azolylmethyl)pyridinium salts **17–22** or *N*-(azolylmethyl)imidazolium salts **23–28** (ca. 250 mg) in 85% ethanol (50 mL) were passed through the column. The neutral eluates were concentrated on a rotary evaporator at 25 °C to afford the methylenepyridinium azolate inner salts **5–10** (Table I) or methyleneimidazolium inner salts **11–16**, respectively (Table II).

1-Butyl-3-(1*H*-1,2,4-triazol-3(5)-ylmethyl)imidazolium Tetrafluoroborate (28). Method E. A stirred solution of 3-(5)-(chloromethyl)-1,2,4-triazole (**31**) (0.96 g, 6.2 mmol) and anhyd 1-butylimidazole (2.5 mL, 18.7 mmol), under an atmosphere of nitrogen, was heated on a bath at 130 °C for 0.5 h. To the cooled reaction mixture was added dichloromethane (20 mL) and left overnight under vigorous stirring. Thus, a solid slowly precipitated which was filtered, washed with dichloromethane (2 × 3 mL), and dissolved in 85% ethanol (20 mL). Then, the ethanolic solution was passed through a column packed with Amberlite IRA-401 (OH^- form); see above. The eluate was acidified with 54% tetrafluoroboric acid–diethyl ether (2 mL) and concentrated to dryness. The oily residue was triturated thoroughly with anhyd acetone (20 mL). The triturate was filtered, washed with two 3-mL portions of acetone–diethyl ether (2:1), and dried to afford compound **28** (Table II).

Single-Crystal X-ray Structure Determination of Compound 7. Crystal data for compound **7**: $C_{15}H_{16}N_4 \cdot 2H_2O$, M = 288.35, monoclinic, space group $P2_1/n$, a = 8.395 (2), b = 11.493 (1), c = 15.740 (5), β = 96.24 (2), U = 1510 Å^3 (by least-squares refinement on diffractometer angles for 25 automatically centred reflections), λ = 0.710 69 Å, Z = 4, D_c = 1.27 g cm^{-3}. Colorless, 0.30 × 0.25 × 0.20 mm^3, μ(Mo Kα) = 0.813 cm^{-1}, F(000) = 616. All crystallographic measurements were made on a CAD4 diffractometer, $\omega - 2\theta$ mode with ω scan width = 2.40 + 1.05 tan θ, ω scan speed 1.5–6.7 deg min^{-1}, graphite-monochromated Mo Kα radiation; 2651 unique reflections [$1.0 \le \theta \le 23.5°$, $-9 \le h \le 9$, $0 \le k \le 13$, $0 \le l \le 18$; 1928 observed reflections with $I > 2.5\theta(I)$]. Stability of intensity control, ca. 1%. The structure was solved by multisolution direct methods using the Ω tangent formula.[15c] Full-matrix least-squares refinement with all non-H atoms anisotropic. All the H-atoms except those of the water molecules were experimentally determined. Final R and R_w values are 0.055 and 0.063; the weighting scheme is $w = 4.82/[\sigma^2(F_o) + 0.0006F_o^2]$ with $\theta(F_o)$ from counting statistics. Highest and lowest peaks in final ΔF map (e Å^{-3}) 0.30 and −0.22. Programs used and sources of scattering factor data are given in ref 15. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (see Notice to Authors, Issue No. 1).

Acknowledgment. This research was supported by the DGIGYT (Grant No PB 89-0214), Spain. We are grateful to the referees for constructive criticism.

Supplementary Material Available: Observed chemical shift (ppm) difference between the betaines **5**, **13**, **34**, and **36** and their corresponding precursors the *N*-benzimidazolylpyridinium(imidazolium) salts and compounds **17**, **25** (Figure 1), methylene interannular linkage mean values of the observed δ ^1H and δ ^{13}C of betaines **5–16** and their corresponding precursors **17–28** (Figure 2), AM1 energy-minimized structures of betaines **16** and **33** constructed in Chem X (Figure 5), X-ray crystal structure of betaine **7** superimposed with the AM1 optimized conformation for **7** constructed in Chem X (Figure 6), X-ray crystal structure of betaine **7** superimposed with the MNDO optimized conformation for **7** constructed in Chem X (Figure 7), experimental and calculated dipolar moment values for betaines **7**, **10**, **13**, and **16** (Figure 8), ^1H NMR spectroscopic data of methylenepyridinium

(14) Alcalde, E.; Roca, T. *J. Org. Chem.*, following paper in this issue.

(15) (a) Rius, J.; Miravitlles, C. *Acta Crystallogr.* **1989**, *A45*, 490. (b) *International Tables for X-ray Crystallography*; Kynoch Press: Birmingham (present distributor D. Reidel, Dordrecht), 1974; Vol. IV, pp 99 and 149. (c) Scheldrick, G. M. SHELX-76, University of Cambridge. (d) Rius, J. CELGRAF-90, Institut de Ciencia de Materials de Barcelona (CSIC).

azolate inner salts 5-10 and their corresponding (azolylmethyl)pyridinium salts 17-22 (Table V), ^{13}C NMR spectroscopic data of methylenepyridinium azolate inner salts 5-10 and their corresponding (azolylmethyl)pyridinium salts 17-22 (Table VI), ^{1}H NMR spectroscopic data of methyleneimidazolium azolate inner salts 11-16 and their corresponding (azolylmethyl)-imidazolium salts 23-28 (Table VII), ^{13}C NMR spectroscopic data of methyleneimidazolium azolate inner salts 11-16 and their corresponding (azolylmethyl)imidazolium salts 23-28 (Table VIII), selected conformers of 2-(1-pyridiniomethyl)benzimidazolate 5, heats of formation, torsion angles (θ_A and θ_B), and dipole moments (Table XI), bond angles (Å) with esd's in parentheses (Table XII), final positional parameters ($\times 10^4$) for non-hydrogen atoms and equivalent isotropic temperature coefficients (Å^2) with esd's in parentheses (Table XIII), positional parameters ($\times 10^4$) of the H atoms (Table XIV), thermal anisotropic coefficients ($\times 10^4$) for non-H atoms with their esd's (Table XV), elemental analyses of compounds 5-28 (Table XVI), AM1 and MNDO data of betaines 5, 7, 9, 10, 13, 16, 32, and 33 AM1 and MNDO Mulliken charges and dipole direction of betaines 5, 7, 9, 10, 13, 16, 32, and 33 (58 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Heterocyclic Betaines. 14.[1] (*E*)-1-Alkyl-[2-(imidazol-2-ylidene)ethylidene]dihydropyridines with a Betaine Character. An Improved Protocol for a Knoevenagel-Type Condensation for Synthesis of (*E*)-1-Alkyl-[2-(1*H*-imidazol-2-yl)vinyl]pyridinium Salts

Ermitas Alcalde* and Tomás Roca

Laboratorio de Química Orgánica, Facultad de Farmacia, Universidad de Barcelona, E-08028-Barcelona, Spain

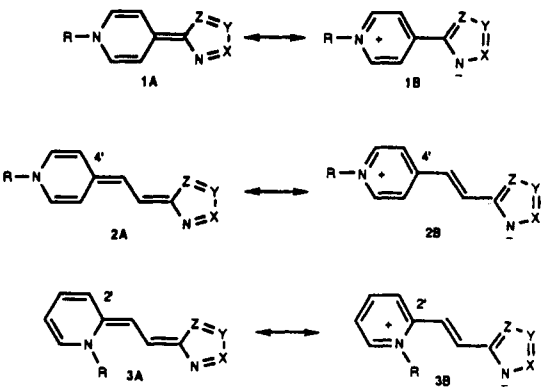
Received December 2, 1991

A novel class of aza analogues of (*E*)-stilbene, the (*E*)-1-alkyl-[2-(imidazol-2-ylidene)ethylidene]dihydropyridines **4A ↔ 4B, 5A ↔ 5B**, have been studied. They were synthesized by a convenient two-steps procedure. In each of the steps, the necessary basic reaction medium has been generated by a strong basic ion-exchange resin (OH^- form). Thus, a modified protocol of the Knoevenagel condensation has been applied to preparation of the title (imidazolylvinyl)pyridinium salts, deprotonation of which yields several examples of compounds **4** and **5**. The betaine character of **4** and **5** is well reflected by their physicochemical properties and reactivity toward electrophiles (MeI).

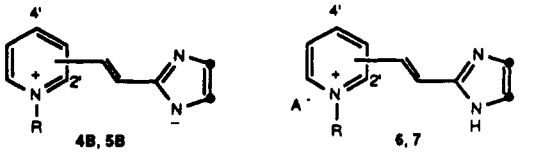
Introduction

Pursuing our research project in the quest for novel organic substrates with a dipolar character in the context of heterocyclic betaines and molecules with a betaine character, we have recently studied[2] an unusual class of aza analogues of sesquifulvalene, the 1-alkyl-4-azolylidene-1,4-dihydropyridines **1 (A ↔ B)**. Their electronic and molecular structure are consistent with the betaine character of these compounds. A logical extension of the preceding study leads to the development of a novel ensemble of aza analogues of (*E*)-stilbene, the (*E*)-1-alkyl-[2-(azol-2-ylidene)ethylidene]dihydropyridines **2(A ↔ B)** and **3(A ↔ B)** in which both rings are linked by a vinylene group leading to an extended π-system which contains extremely π-deficient and π-excessive moities.[3]

This paper describes the first synthesis and characterization of several examples of the title compounds **4(A ↔ B)** and **5(A ↔ B)** with a dipolar nature. Furthermore their immediate precursors, the (*E*)-1-alkyl-[2-(1*H*-imidazol-2-yl)vinyl]pyridinium salts **6** and **7** have been prepared by



an efficient modification of Knoevenagel condensation.



4, 6 (4-pyridinio)
5, 7 (2-pyridinio)

Results and Discussion

Synthesis. The unknown (*E*)-(imidazolylvinyl)-pyridinium salts **6** and **7**, a priori could not be prepared in a satisfactory yield using existing methodologies for preparation of (*E*)-stilbazolium salts, (*E*)-stilbazoles, and

(1) (a) Part 13: Alcalde, E.; Pérez-García, Ll.; Miravitlles, C.; Rius, J.; Valentí, E. *J. Org. Chem.* previous paper in this issue. (b) Abstracted from the Ph.D. Thesis of Tomás Roca, Facultad de Farmacia, Universidad de Barcelona, 1992.

(2) Alcalde, E.; Dinarés, I.; Frigola, J.; Jaime, C.; Fayet, J.-P.; Vertut, M.-C.; Miravitlles, C.; Rius, J. *J. Org. Chem.* **1991**, *56*, 4223 and references quoted therein.

(3) For an earlier report on several examples of compounds **2** and **3**, see: Alcalde, E.; Roca, T.; Fayet, J.-P.; Vertut, M.-C. *Chem. Lett.* **1991**, 2151.

0022-3263/92/1957-4834$03.00/0