Heterocyclic Betaines. XVI. Properties of (*E*)-1-Alkyl(or Aminoalkyl)-4-[2-(1*H*-benzimidazol-2-yl)vinyl]pyridinium Salts

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***N*-Alkylation of (*E*)-2-[2-(4-pyridyl)vinyl]-1*H*-benzimidazole (10), obtained by two different approaches, affords the title salts 4—6, deprotonation of which results in the new (*E*)-1-alkyl-4-[2-(benzimidazolyl-2-idene)ethylidene]-1,4-dihydropyridines (7 and 8) with a betaine character. Their biological properties have also been examined.**

Keywords aza-analogue; (*E*)-stilbene; heterocyclic betaine; antisecretory activity

As part of a search for organic substrates with a dipolar nature in the field of heterocyclic betaines,[1-3] we recently reported several examples of (*E*)-azolylvinylpyridinium salts (**1**),[3,4] precursors of a novel ensemble of aza-analogues of (*E*)-stilbene with a betaine character **2** (A↔B).[3] On the other hand, Sanfilippo *et al.*[5] have found that a series of structurally related (*E*)-2-(alkylaminoaryloxyvinyl)benzazoles **3** are potent (H^+-K^+)-sensitive ATPase enzyme inhibitors.

The present study originated from those results,[3,5] and the simple title salts **4—6** were selected as model compounds to generate the new aza-analogues of (*E*)-stilbene with a betaine character **7—9** for testing of their antisecretory activity.

(*E*)-2-[2-(4-Pyridyl)vinyl]-1*H*-benzimidazole (**10**) appeared to be the key intermediate for synthesis of the new compounds **4—6**. As outlined in Chart 1, preparation of compound **10** was accomplished by two approaches in order to assess which was more convenient. Firstly, condensation of 1,2-phenylenediamine and (*E*)-3-(4-pyridyl)acrylic acid was conducted by application of either Hein's benzimidazole synthesis[6] (method A) or the classical Phillips synthesis (method B). Secondly, dilithio 2-methyl-1*H*-benzimidazole was used as a synthetic intermediate for preparation of 2-[2-hydroxy-2-(4-pyridyl)ethyl]-1*H*-benzimidazole (**11**) (method C),[7] which was transformed to compound **10**. Method A gave the best result.

N-Alkylation of compound **10** with alkyl halides under neutral conditions afforded the corresponding title compounds **4—6**, which were deprotonated by using an anion-exchange resin (OH^- form).[1a] The new azaanalogues of (*E*)-stilbene **7** and **8** were obtained in appropriate yield (Chart 2). Unfortunately, compound **9** could not be isolated, probably because of its instability (see Experimental).

Physical data for all new compounds, **4—8** and **10**, **11**, are listed in Table I. The structures of all of them have been unambiguously characterized on the basis of their ^{1}H-NMR data and all of them gave satisfactory elemental analyses.

The novel (*E*)-1-alkyl-4-[2-(benzimidazolyl-2-idene) ethylidene]-1,4-dihydropyridines (**7** and **8**) are air- and light-sensitive and are easily altered or decomposed, even in the solid state.[9a] As shown in Table I, the ^{1}H-NMR chemical shifts of **7B** and **8B**, indicate their dipolar nature in solution. The benzimidazolate ring protons were shifted

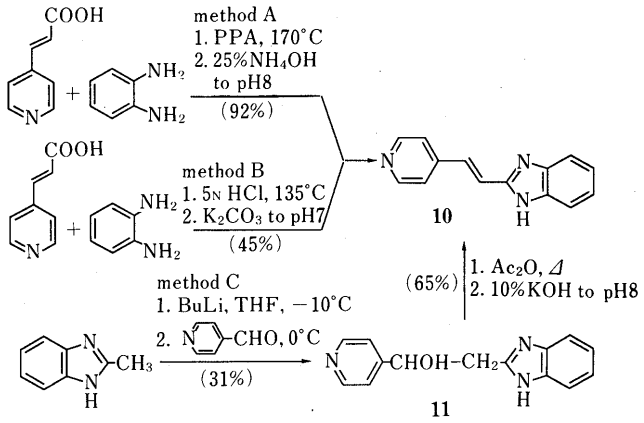
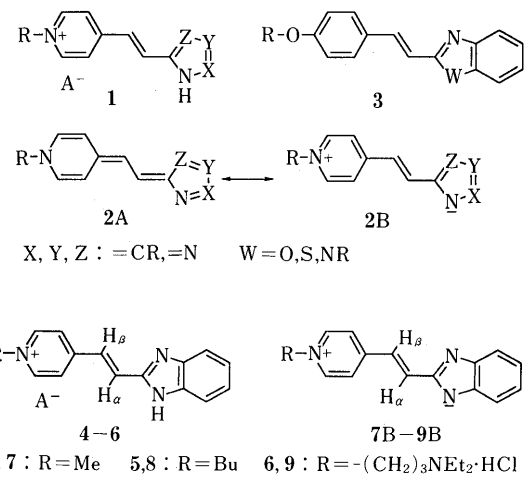


Chart 1



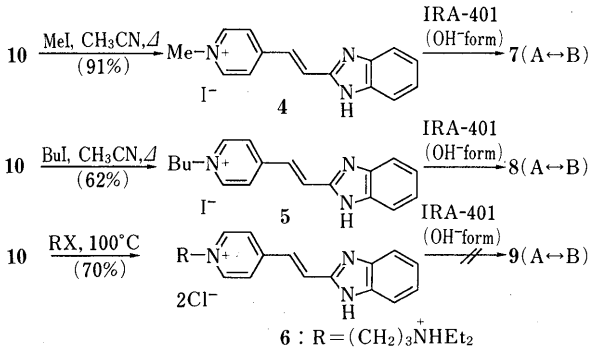


Chart 2

TABLE I. Preparation and Properties of Compounds **10**, **11** and **4**—**8**

Compd. No.	Method	Yield[a] (%)	Time (h)	mp (°C)[b] [Recryst. solv.]	Formula[c]	^{1}H-NMR (DMSO-d_6/TMS)[d]						
						H-2,6	H-3,5	H-α[e]	H-β	H-4′,7′	H-5′,6′	R
4	E	83	7	269[f]	$C_{15}H_{14}IN_3$	8.91	8.34	7.90	7.75	7.63	7.27	4.28
7	H	96	—	242[f]	$C_{15}H_{13}N_3$	8.63	8.11	7.91	7.56	7.36	6.79	4.14
$\Delta\delta$[g]						−0.28	−0.23	+0.01	−0.19	−0.27	−0.48	−0.14
5	F	62	7	230[f]	$C_{18}H_{20}IN_3$	9.03	8.37	7.93	7.78	7.62	7.27	4.54[h]
8	H	98	—	285[f]	$C_{18}H_{19}N_3$	8.73	8.15	7.96	7.58	7.36	6.78	4.38[h]
$\Delta\delta$[g]						−0.30	−0.22	+0.03	−0.20	−0.26	−0.49	−0.16
6	G	70	1	227 [CH_3CN]	$C_{21}H_{28}Cl_2N_4$	9.27	8.36	8.17	7.90	7.66	7.32	4.84[h]
10	A	92	2	230 [CH_3CN]	$C_{14}H_{11}N_3$	8.61	7.62	7.61	7.49	7.58	7.20	—
10	B	45	14	228—229[f]	$C_{14}H_{11}N_3$							
11	C	31	i)	185—187[f]	$C_{14}H_{13}N_3O$	8.14	7.01	4.81	5.55	7.22	6.51	—
10	C	65	i)	228—229[f]	$C_{14}H_{11}N_3$							

a) Yields were not optimized. *b*) Uncorrected measured with a CTP-MP hot-plate melting point apparatus. *c*) Satisfactory microanalysis was obtained: C ± 0.4, H ± 0.4, N ± 0.4. *d*) Recorded on a Bruker AM-100 spectrometer (100 MHz). ^{1}H-NMR chemical shifts are reported in ppm (δ) downfield from TMS in DMSO-d_6. *e*) α-CH proton to the benzimidazole nucleus. $J_{H\alpha,H\beta} \approx 16.4$ Hz. *f*) Recrystallization was not necessary. *g*) $\Delta\delta$: difference in observed chemical shifts between compounds **7**, **8** and their precursors **4**, **5**. *h*) Only δ values for the α-protons to nitrogen are listed. *i*) See Experimental.

to lower frequencies, and in the vinylene interannular moiety the α-CH proton of the π-excessive ring (bezimidazolate) was shielded by *ca.* 0.02 ppm, whereas the β-CH proton was shielded by *ca.* 0.20 ppm compared with the same positional protons of the corresponding precursors **4** and **5**. The ^{1}H-NMR parameters of **7** and **8** agree with data for anionic species (benzimidazolates),[2b,11] quaternary pyridinium compounds, and the useful data obtained from 1-alkyl-4-(benzimidazolydene)-1,4-dihydropyridines with betaine character.[11]

The biological properties of the model compounds **4**—**6** were examined[12] and none of them showed activity deserving of further study. It has, however, been possible to prepare the novel (*E*)-1-alkyl-[(2-benzimidazol-2-idene)ethylidene]dihydropyridines (**7** and **8**) and their physicochemical properties are consistent with the betaine character of these compounds. Thus, the dipolar resonance forms **7B** and **8B** make an important contribution to the ground state, leading to an unconventional extended π-system which contains both extremely π-deficient (pyridinium cation) and π-excessive (benzimidazolate anion) heteroaromatic systems.

Experimental

General Methods Melting point (uncorrected): CTP-MP 300 hot-plate apparatus (data in Table I). IR (KBr discs): Perkin-Elmer 1430 spectrophotometer. ^{1}H-NMR: Bruker AM-100 or Perkin-Elmer R-24B spectrometer (100 and 60 MHz respectively). ^{13}C-NMR: Bruker AM-100 Fourier transform spectrometer (25.1 MHz). HETCOR[9b]: Varian VXR-500 spectrometer. NMR spectra were determined in dimethylsulfoxide-d_6 (DMSO-d_6), and chemical shifts are expressed in parts per million (δ) relative to tetramethylsilane (TMS) as an internal standard or to the central peak of DMSO-d_6. TLC: Merck Silica gel 60F_{254} plates; detection under UV light. Ion-exchange chromatography: Amberlite IRA-401 (OH-form).[11] If necessary, the compounds were dried by heating overnight at 25 °C in a vacuum oven. Microanalyses were obtained using a Carlo Erba model 1106 element analyzer.

Materials 2-Methyl-1*H*-benzimidazole, 4-pyridylcarbaldehyde and 1,2-phenylendiamine are commercially available. (*E*)-3-(4-Pyridylic)acrylic acid[4] was prepared as described in the literature.

Preparation of (*E*)-2-[2-(4-Pyridyl)vinyl]-1*H*-benzimidazole (10) (Table I). Method A A stirred suspension of 1,2-phenylenediamine (1.8 g, 16.3 mmol) and (*E*)-3-(4-pyridyl)acrylic acid (2.6 g, 17.3 mmol) in polyposphoric acid (17 g) under an atmosphere of nitrogen was maintained at 170 °C (bath temperature) for 2 h. The cooled mixture was poured onto ice (50 ml) and then slowly neutralized with a solution of concentrated ammonium hydroxide to pH 8. The yellow precipitate was collected by filtration, washed with water (2 × 20 ml), dried and recrystallized (Table I). *Anal.* Calcd for $C_{14}H_{11}N_3$: C, 76.0; H, 5.0; N, 19.0. Found: C, 76.1; H, 5.0; N, 18.95.

TABLE II. Reaction Conditions for Preparation of **6**

Ratio molar RX/**10**	Solvent	Temp (°C)	Time (h)	**6** (% Yield[a])
5	Acetonitrile	Reflux	168	15
5	DMF	100	24	5[b]
5	—	130—40	1	8[c]
5	—[d]	100	1	70

a) Yield of isolated product. *b*) An aliquot of the reaction mixture was shown by ^{1}H-NMR to contain *ca.* 70% of **6**. However, when the reaction mixture was worked up, only 5% of **6** was isolated. *c*) The reaction mixture was shown by TLC to contain **6** along with unidentified products of decomposition. *d*) In a sealed tube, see Experimental (method G).

Method B A stirred suspension of 1,2-phenylenediamine (4.0 g, 37.0 mmol) and (*E*)-3-(4-pyridyl)acrylic acid (5.5 g, 37.0 mmol) in 5 N HCl (30 ml, 148 mmol) was maintained in a bath at 135 °C for 14 h. The resulting reddish solution was neutralized with solid potassium carbonate and the yellow precipitate was collected by filtration, washed with water (3 × 20 ml) and dried (Table I).

Method C BuLi (*ca.* 1.6 M in hexane, 57.8 ml, 92.5 mmol) was transferred *via* a cannula into a stirred solution of 2-methyl-1*H*-benzimidazole (5.8 g, 44.0 mmol) in anhydrous THF (100 ml) at −10 °C under an atmosphere of nitrogen and the mixture was stirred at −10 °C for 2 h. A solution of 4-pyridylcarbaldehyde (21.8 ml, 220.0 mmol) in anhydrous. THF (50 ml) was then added at −5 °C. The resulting reaction mixture was stirred at ≈0 °C for 3 h and a saturated aqueous solution of ammonium chloride was added. The whole was extracted with diethyl ether (3 × 50 ml). The combined organic layers were dried and evaporated to dryness. The oily residue was triturated with dichloromethane (50 ml) to yield 2-[2-hydroxy-2-(4-pyridyl)ethyl]-1*H*-benzimidazole (**11**) (Table I). *Anal.* Calcd for $C_{14}H_{13}N_3O$: C, 70.3; H, 5.5; N, 17.6. Found: C, 70.1; H, 5.6; N, 17.5.

A stirred solution of compound **11** (1.5 g, 6.2 mmol) in acetic anhydride (30 ml) and acetic acid (2 ml) was refluxed for 5 h. The reaction mixture was concentrated to dryness and neutralized with 10% potassium hydroxide to pH 8, and then ethanol (*ca.* 30 ml) was added to dissolve the solid materials. The solution was stirred overnight and an ocher solid slowly precipitated. Compound **10** was collected by filtration, washed with water (2 × 5 ml) and dried (Table I).

Preparation of (*E*)-1-Alkyl-4-[2-(1*H*-benzimidazol-2-yl)vinyl]pyridinium Salts (4—6) (Table I). Method E A solution of methyl iodide (2.7 ml, 43.0 mmol) in dry acetonitrile (5 ml) was added dropwise at 0 °C to a stirred solution of compound **10** (1.9 g, 8.6 mmol) in dry acetonitrile (70 ml) under an atmosphere of nitrogen, and the mixture was refluxed for 7 h. The crude

TABLE III. ^{13}C-NMR Data for Compounds **10**, **11**, and **4**—**6**[9]

Compd. No.	^{13}C-NMR (DMSO-d_6)[a] δ (ppm)									
	C-2,6	C-3,5	C-4	C-α[b]	C-β	C-2′	C-3′, 7a′	C-4′, 7′	C-5′, 6′	R
4	145.2	124.2	150.8	128.5	128.2	148.7	139.2	115.5	123.2	47.3
5	144.3	124.5	151.1	128.8	128.1	148.7	139.2[c]	115.5[c]	123.1	59.7; 32.4; 18.7; 13.3
6	144.9	124.9	151.0	130.8	126.6	147.9	137.0	115.1	124.3	57.3; 47.3; 46.5; 25.1
10	150.2	121.1	143.0	131.6	122.2	150.0	139.3	115.5	122.4	—
11	149.5	121.0	153.6	38.4	70.2	152.2	138.7	114.6	121.3	—

a) Recorded on a Bruker AM-100 spectrometer (25.1 MHz). ^{13}C-NMR chemical shifts are reported in ppm (δ) downfield from the central peak of DMSO-d_6. *b*) α-CH carbon to the benzimidazole nucleus. *c*) Broad signal due to prototopic annular tautomerism.

yellow compound **4** was obtained by filtration from the cooled reaction mixture and washed with acetonitrile (2 × 5 ml). A suspension of the crude product in acetone (30 ml) was vigorously stirred at 30 °C for 0.5 h, and filtered to yield pure compound **4** (Table I). *Anal* Calcd for $C_{15}H_{14}IN_3$: C, 49.6; H, 3.9; N, 11.6. Found: C, 49.8; H, 3.7; N, 11.5.

Method F *n*-Butyl iodide (5.7 ml, 49.8 mmol) was added to a stirred solution of compound **10** (2.2 g, 9.95 mmol) in dry acetonitrile (80 ml) under an atmosphere of nitrogen and the mixture was refluxed for 7 h. After cooling, the yellow precipitate was collected by filtration, washed with acetonitrile (2 × 10 ml) and dried to give pure compound **5** (Table I). *Anal.* Calcd for $C_{18}H_{20}IN_3$: C, 53.4; H, 5.0; N, 10.4. Found: C, 53.3; H, 5.1; N, 10.5.

Method G A mixture of compound **10** (0.5 g, 2.3 mmol) and 3-chloro-*N*,*N*-diethylpropylamine hydrochloride (1.8 g, 11.3 mmol), in a sealed tube, was heated in a bath at 100 °C and stirred until a yellow precipitate prevented further stirring (*ca.* 1 h). After the mixture had cooled, acetone (20 ml) was added to give a solid, which was collected by filtration and washed with acetone (5 × 5 ml). The crude product **6** was dissolved in water (60 ml) and washed with chloroform (6 × 20 ml). The aqueous layer was evaporated to dryness and the residue of **6** was recrystallized (Table I). *Anal.* Calcd for $C_{21}H_{27}ClN_4 \cdot HCl$: C, 61.9; H, 6.9; N, 13.75. Found: C, 61.8; H, 6.95; N, 13.6.

For the preparation of compound **6**, different reaction conditions were assayed (Table II) and the best result was obtained by method G (described above).

(*E*)-1-Alkyl-4-[2-(benzimidazolyl-2-iden)ethylidene]-1,4-dihydropyridines (7 and 8) (Table I). Method H A column packed with anion-exchange Amberlite resin IRA-401 (OH^-) form was prepared according to the procedure previously reported.[11]

A solution of the corresponding precursor **4** or **5** (130 mg or 170 mg) in 80% ethanol (300 ml or 50 ml) was passed through the column. The neutral eluates were concentrated on a rotatory evaporator at 25 °C to yield compound **7** or **8**, respectively (Table I). *Anal.* Compound **7**: Calcd for $C_{15}H_{13}N_3 \cdot H_2O$: C, 71.1; H, 6.0; N, 16.6. Found: C, 70.8; H, 6.3; N, 16.4. *Anal.* Compound **8**: Calcd for $C_{18}H_{19}N_3 \cdot H_2O$: C, 73.2; H, 7.2; N, 14.2. Found: C, 73.0; H, 7.2; N, 14.3.

In a similar manner, compound **6** was passed through the column but compound **9** could not be isolated. An aliquot of the residue was shown by ^{1}H-NMR to contain products of alteration or decomposition, which were not further studied.

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References and Notes

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