CHEMISTRY LETTERS, pp. 2151-2154, 1991.

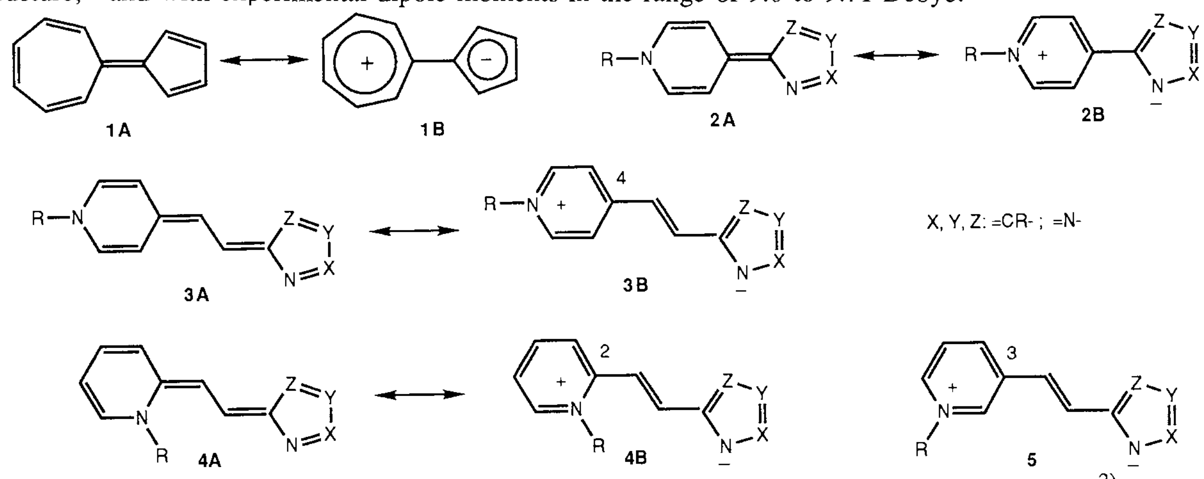
Aza-analogs of Stilbene with a Dipolar Character. (*E*)-1-Alkyl-[2-(azolyl-2-idene)etylidene]-dihydropyridines and (*E*)-2-[2-(1-Alkyl-3-pyridinium)vinyl]azolate Inner Salts

Ermitas ALCALDE,* Tomás ROCA, Jean Pierre FAYET,† and Marie Claire VERTUT†
Lab. Química Orgánica, Facultad de Farmacia, E-08028-Barcelona, Spain
†Lab. Chimie Organique Structurale URA-CNRS-1311, Université Paul Sabatier, F-31077-Toulouse Cédex, France

The first synthesis and characterization of several examples of the title compounds is described. Their physicochemical properties are discussed on the basis of the ^{1}H NMR data and the large experimental dipole moments 11.66 to 13.0 Debye. Furthermore, all the experimental results for (*E*)-1-alkyl-[2-(azolyl-2-idene)-etylidene]-dihydropyridines (**A**⟷**B**) favour the dipolar structure (**B**).

Due to their dipolar character, heterocyclic betaines have attracted significant interest from the point of view both of the molecular and the potential practical applications.

Recently, we have investigated an unusual class of aza-analogues of sesquifulvalene **1**, the 1-alkyl-4-(azolylidene)-1,4-dihydropyridines **2** with a betaine character, as shown by their electronic and molecular structure,[1] and with experimental dipole moments in the range of 9.0 to 9.71 Debye.



Pursuing our current search for novel organic substrates with large dipole moment values,[2] we have designed a novel ensemble of aza-analogs of stilbene **3**-**5** in order to ascertain the effect of a vinylene linkage between the pyridinium and azolate rings, leading to an expanded conjugated π system which contains extremely electron-deficient and electron-rich moities.

These structures are formally derived from (*E*)- stilbene and in **3** both rings are linked in a (*E*)-

stilbazolium fashion. Furthermore, the conjugated heterocycles **3** and **4** are satisfactorily represented by an uncharged covalent resonance form (**A**), whereas compounds **5** can be represented only by dipolar resonance forms, in which both the positive and negative charge are delocalized within the π-electron system.

We here report the first synthesis and characterization of examples of structures **3-5**, the (*E*)-1-alkyl-[2-(benzimidazolyl-2-idene)etylidene]-dihydropyridines **6-8** and the (*E*)-2-[2-(1-alkyl-3-pyridinium)vinyl]-benzimidazolate **9-11**. As mentioned before, compounds **6-8** should be considered as a novel class of push-pull stilbenes (**A**⟷**B**) and their physicochemical properties favour the dipolar canonical form **6B-8B**.

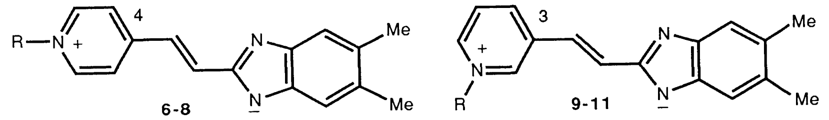
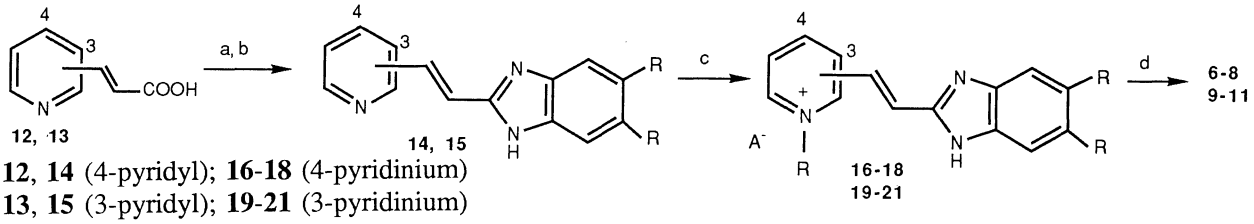


Fig. 1. Compounds **6-8** are represented in their dipolar resonance form **B**. (**6**, **9**) R= Me; (**7**, **10**) R= Bu; (**8**, **11**) R= n-$C_{10}H_{21}$.

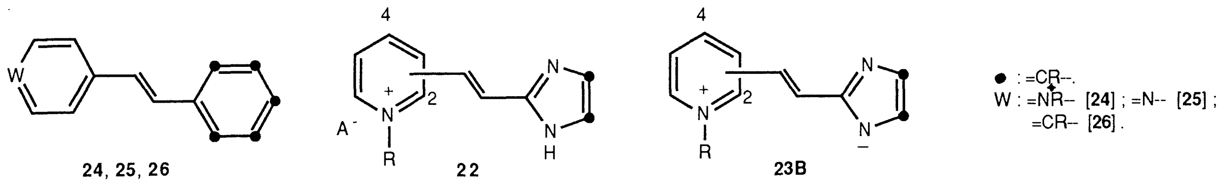
Compounds **6-8** and **9-11** were prepared by a three-step procedure (Scheme 1). Firstly, 2-(2-pyridylvinyl)-1*H*-benzimidazoles **14** and **15** were obtained by reaction of 4,5-dimethyl-1,2-phenylendiamine with the easily accesible (*E*)-3-pyridylacrylic acids **12** and **13**, using polyphosphoric acid as catalyst and solvent.[3] *N*-alkylation under neutral conditions gave the corresponding 1-alkyl-[2-(1*H*-benzimidazol-2-yl)vinyl]pyridinium salts **16-18** and **19-21** as the major products,[4] which were deprotonated using an anionic (OH^- form) ion-exchange resin to afford **6-8** and **9-11** in *ca.* 40% overall yields.



12, **14** (4-pyridyl); **16-18** (4-pyridinium)
13, **15** (3-pyridyl); **19-21** (3-pyridinium)

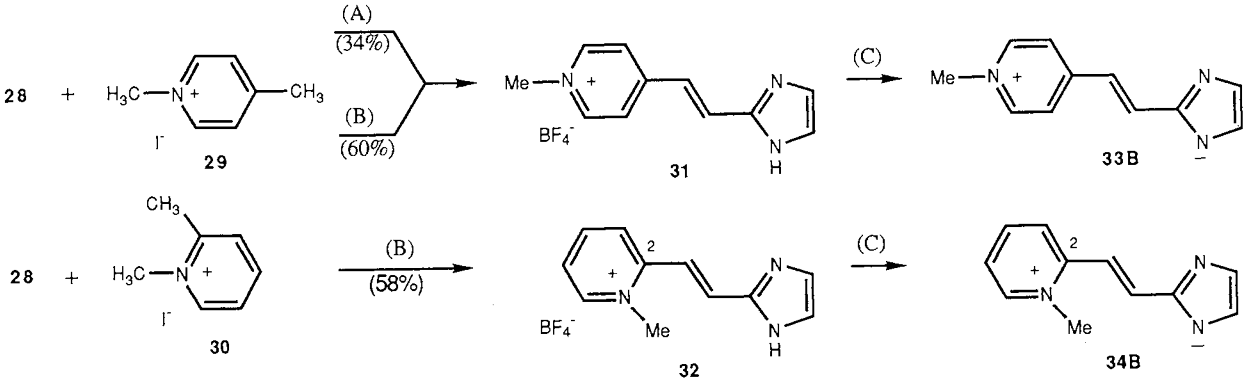
Scheme 1. Reagents and conditions: (a), 4,5-dimethyl-1,2-phenylendiamine in polyphosphoric acid, 170 °C, 1.5 h; (b), NH_4OH up to pH 7; (c), MeI, BuI or n-$C_{10}H_{21}$Br in anhyd acetonitrile or acetone; gentle reflux in an atmosphere of nitrogen; (d), anion-exchange Amberlite IRA 401 (OH^- form).[1] Overall yields: **6-8**>40% and **9-11**>37%.

During the course of this investigation, it became apparent that the (*E*)-imidazolyl-vinylpyridinium salts **22**, precursors of the unknown (*E*)-1-alkyl-[2-(imidazolyl-2-idene)etylidene]-dihydropyridines **23**, *a priori* could not be prepared in a satisfactory yield using existing methodology for preparation of stilbazolium salts **24**, stilbazoles **25** and stilbenes **26**.



A widely used procedure the Knoevenagel Condensation[5] would not appear to be an efficient method for synthesis of the title compounds, since the starting azole derivatives are less reactive, and are difficult to obtain. In this way, (*E*)-4-(2-phenylvinyl)-1-methylpyridinium iodide **27** was conveniently prepared using piperidine as catalyst as described in literature[6] (80% yield). Almost the same reaction conditions were applied for preparation of (*E*)-4-[2-(1*H*-imidazol-2-yl)vinyl]-1-methylpyridinium iodide **31** from 1*H*-2-imidazolcarbaldehyde[7] and compound **29**, yields being rather low (no more than 10%). After trial of a variety of conditions, and using the *N*-substituted-2-imidazolcarbaldehyde **28**,[7] the tetrafluoroborate of **31** was obtained in 34% yield (Scheme 2, method A).

We herein report an improved protocol for a Knoevenagel type reaction using a strongly basic ion-exchange resin, IRA-401 (OH^- form), which provides a facile entry into a variety of (*E*)-imidazolylvinylpyridinium salts **22**, with excellent yields for this type of reaction. Two (*E*)-imidazolylvinylpyridinium tetrafluoroborates **31** and **32** have been prepared (Scheme 2, method B), which were deprotonated to give the title (*E*)-1-alkyl-[2-(imidazolyl-2-idene)ethylidene]dihydropyridines **33-34**.



Scheme 2. *Reagents and Conditions: (A), Method A.* (1) Piperidine, MeOH, reflux 4 h; (2) 0.5M HBF_4-H_2O to pH 3, 50 °C, 4 h. (B), *Method B.* (1) A solution of compounds **29** or **30** in methanol previously treated with Amberlite IRA-401 (OH^- form)[1] was transferred into a solution of 1-(1-ethoxyethyl)-2-imidazolcarbaldehyde **28**[7] in methanol under an atmosphere of nitrogen; (2) Room temperature 0.25-0.5 h; (3) 0.5M HBF_4-H_2O to pH 3, 50 °C, 4 h. *(C), Method C.* Anion-exchange Amberlite IRA-401 (OH^- form),[1] yield 98%.

The novel aza-analogs of stilbene **6-8**, **9-11**, and **33**, **34** have been unambiguously characterized on the basis of their spectroscopic data, and all of them gave satisfactory elemental analysis. The ^{1}H NMR chemical shifts in $(CD_3)_2SO$ and in CD_3OD clearly indicated the dipolar resonance forms **6B-8B** and **33B**, **34B**, and the inner salt structure of **9-11**. The azolate ring protons were shifted to lower frequencies, and in the vinylene interannular group the α-CH proton to the π-excessive ring (azole) was shielded *ca.* 0.30 ppm, whereas the ß-CH proton was shielded *ca.* 0.05 ppm compared with the same positional protons of the corresponding precursors **16-18**, **19-21**, and **31**, **32**. On the other hand, comparison of the chemical shifts of **6-8** with the valuable data reported[1] for 1-alkyl-4-(benzimidazolylidene)-1,4-dihydropyridines **2**, left no doubt of the betaine character of these compounds. With regard to compounds **33** and **34**, the ^{13}C NMR chemical shifts[8] of the π-excessive moiety were in excellent agreement with data for the imidazolate ion itself.[9]

The electronic structure of compounds **6-8**, **9-11**, and **33**, **34** would be reflected in the dipole moment values. Table 1 shows the experimental dipole moments of anhydrous compounds **7** (11.94D) and **10** (13.00D). These values were extrapolated to infinite dilution to eliminate as far as possible, the perturbing influence of self-association (non-polar dimers), with consequent decrease of the measured dipole moments.[1, 10)]

Concerning the experimentally determining dipole moments of **33** and **34**, these compounds are strongly associated when the weight fraction is higher than 0.0005. Unfortunately, the experimental dipole moments could not be measured accurately.[10] It has however been possible to record the dipole moment of compound **34**, which is of 11.66 Debye. This large experimental value left no doubt that compounds **33**, **34** had a dipolar nature.

Table 1. Dipole Moments and Polarization data[1] in Dioxane at 298 K

Compd	α	ß	R_{MD}	$P_{2\infty}$	$\mu exp^{a)}$(D)
7	58.10	≈0	95.09	3008.42	11.94
10	68.75	≈0	95.09	3548.90	13.00
34	91.14	≈0	57.67	2836.47	11.66

a) Extreme dilution limits of measurement: **7**, ω<0.00006; **10**, ω <0.00008; **34**, ω<0.0001.

In conclusion, all the experimental data available on the hitherto unknown compounds **6-8** and **33**, **34** are consistent with a betaine character of these structures. The dipolar canonical form **6B-8B** and **33B**, **34B** can make an important contribution to the ground state, mainly due to the stability of the heteroaromatic electronic systems, both the pyridinium cation and the azolate anion.

This work has been supported by DGICYT (Pro. No: 89-0214). We are indebted to the Departament d'Ensenyament de la Generalitat de Catalunya for the postgraduate scholarship awarded (T.R.).

References

1) E.Alcalde, I.Dinarés, J.Frigola, C.Jaime, J.-P.Fayet, M.-C.Vertut, C.Miravitlles, and J.Rius, *J. Org. Chem.*, **56**, 4223 (1991).
2) E.Alcalde, L.Pérez, J.-P.Fayet, and M.-C.Vertut, *Chem. Lett.*, **1991**, 845.
3) P.N.Preston, *Chem. Heterocycl. Compds.*, **40** (Part. 1), 6 (1981).
4) *N*-Alkylation of compounds **14** and **15** under neutral conditions gave the corresponding pyridnium salts **16-18** and **19-21**, along with other products of polyalkylation. The desired compounds **16-18** and **19-21** were isolated after several recrystalizations.
5) G.Jones, *Org. React.*, **15**, Chap. 2 (1967).
6) A.P.Phillips, *J. Org. Chem.*, **14**, 302 (1949).
7) T.S.Manoharon and R.S.Brown, *J. Org. Chem.*, **53**, 1107 (1988).
8) The instability of compounds **6-8** and **9-11** in solution of $(CD_3)_2SO$ and CD_3OD precludes to record their ^{13}C-NMR spectra.
9) R.J.Pugmire and D.M.Grant, *J. Org. Chem.*, **93**, 1880 (1971).
10) It had not been possible to measure coherent experimental dipole moment value for compound **33**, as the effect of self-association was not completely eliminated, with consequent decrease of the measured values. For instance, the best recorded value were, for **33** 8.87D. Limit of measurement: ω<0.0005 for **33**.

(Received July 16, 1991)