Crystal Structure, Dissociation and Zwitterion Formation in 2,6-Diaryl-1(3)-oxo-3(1)-hydroxy-5(7)-imino-7(5)-amino-1H,5H-(3H,7H)-pyrazolo[1,2-a]pyrazoles

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Single crystal X-ray analysis and quaternization of 2,6-diphenyl-1(3)-oxo-3(1)-hydroxy-5(7)-imino-7(5)-1H,-5H(3H,7H)-pyrazolo[1,2-a]pyrazole is described. The dissociation constants are determined and compared with those of 4-phenyl-1,2-dimethyl-3(5)-oxo-5(3)-hydroxypyrazole and 4-phenyl-3,5-diaminopyrazole. The quaternization of the latter compound is also described. The influence of electron donating substituents at the cationic moiety on the electronic spectra of such paraionic systems is discussed. The title products exist in the solid state as zwitterions and probably as covalent species in solution.

Scheme I
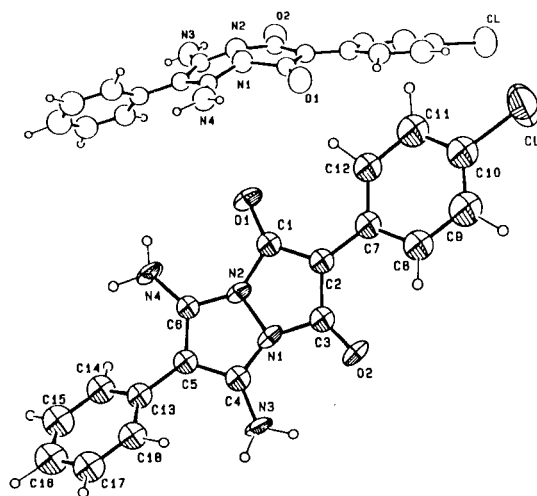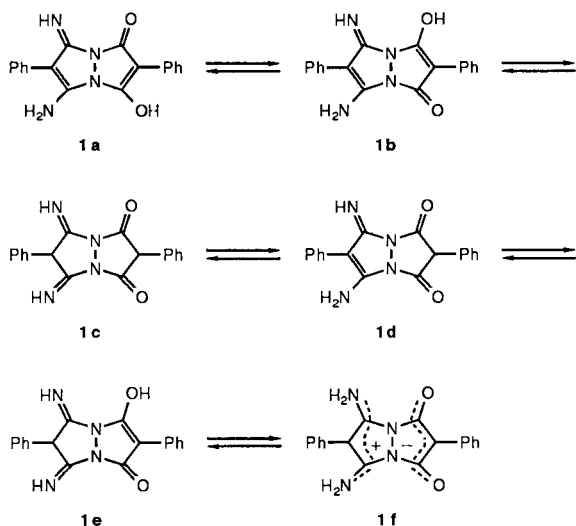

Figure 1. Zwitterionic structure of 2-(p-chlorophenyl)-6-phenyl-1(3)-oxo-3(1)-hydroxy-5(7)-imino-7(5)-amino-1H,5H(3H,7H)-pyrazolo[1,2-a]pyrazole by single crystal X-ray diffraction analysis.

The synthesis of 2,6-diphenyl-1(3)-oxo-3(1)-hydroxy-5(7)-imino-7(5)-amino-1H,5H(3H,7H)-pyrazolo[1,2-a]pyrazole (1) and some of its derivatives were described recently [1]. This polyfunctional system can exist in numerous covalent tautomeric forms, some of which are shown below, 1a-e, and a zwitterionic form 1f. The latter has an anion and a cation which are both stabilized separately by delocalization as in the case of the so called "paraionic compounds" [2]. However, while in the latter compounds the dipolar structure is fixed, in the present case tautomerism between the covalent forms and the zwitterionic structure is possible. Suggestions about the true structure which were made earlier [1] excluded the zwitterionic structure on the basis of comparison of the electronic spectrum in solution to that of a related paraionic substance. A covalent symmetric structure with intramolecular hydrogen bonding was suggested [1], based on the diffused carbonyl and OH absorptions in the infrared spectrum.
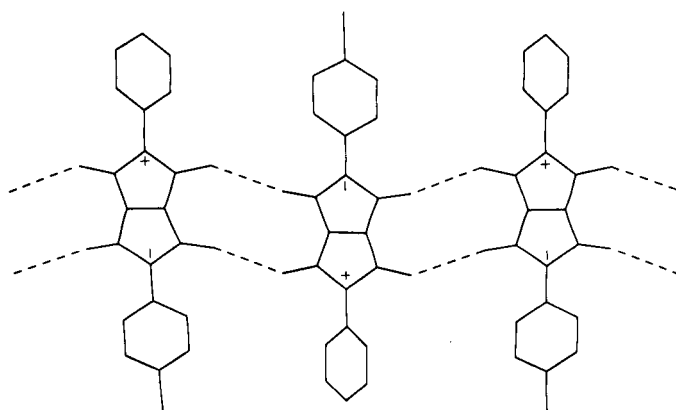

Figure 2. Molecular packing with intermolecular hydrogen bonding as obtained by X-ray diffraction.

At present, we have succeeded in crystallizing and analyzing by X-ray one of these derivatives (Figure 1). To our surprise the structure for the solid state was found to be zwitterionic. The X-ray study reveals that there are no intramolecular hydrogen bonds, but rather intermolecular (see Figure 2). They extend from the amino groups in the cationic part to the anionic oxygens forming a polymeric layer with alternating directions of the ions. It was possible to see that the anion is delocalized by resonance with the aromatic group. This is expressed by both the shortening of the C–C bond to the phenyl group and the coplanarity of the latter with the anionic ring (see Figure 1). This is less true for the ring attached to the cation which is rotated about 43°. An interesting feature is the angle of about 152° between the anionic and the cationic planes suggesting that the nitrogens which combine the anion and the cation exhibit a considerable sp^3 character. This is probably the result of the minor contribution of resonative forms in which these nitrogens are involved in the delocalization. This is in line with the long C–N bond inside the bicyclic system, especially in the anionic part (1.44 Å). The flexibility of similar systems was described [3] in a recent X-ray study of bimanes. The symmetric electron distribution both in the cation and the anion are well illustrated in the equally distributed bond lengths. These distances are in between double and single bonds, reminding those of aromatic values for C–C bonds.

The X-ray diffraction analysis was able to locate the hydrogen atoms at the proximity of the nitrogens. The bond distances of all four hydrogens from the nitrogens were in the range of 0.87-0.92, while the intermolecular distance from the hydrogens which are involved in the hydrogen bridging to the oxygen were about 2.02.

Whereas there is evidence for a zwitterionic structure in the solid state, it is still unclear whether it is the same in solution. Clarification of this problem was carried out by preparing a close analog with a fixed zwitterionic structure and studying its spectral properties. Another approach was to estimate the dissociation constants and try to compare that of the basic part with that of the acidic part of the molecule.

A fixed zwitterion (a paraionic betaine) was achieved by alkylation of **1** with methyl iodide in the presence of DMF and potassium carbonate. The tetramethylation product gave one ^{1}H nmr signal at δ 2.94 for all four methyl groups. The ultraviolet spectrum of the product does not change with the change of the pH, it does not show any NH or OH absorptions in the intrared. Its absorption at

Table 1

Positional Parameters (The estimated standard deviations are given in parentheses and refer to the last positions of the respective values)

Atom	X	Y	Z	Atom	X	Y	Z
Cl	.9572(1)	.3655(2)	.6569(4)	C(14)	.2066(4)	.4322(4)	.045(1)
O(1)	.5681(2)	.5316(2)	.2969(6)	C(15)	.1195(4)	.4317(5)	.028(1)
O(2)	.5624(2)	.2121(2)	.3121(6)	C(16)	.0721(5)	.3764(4)	.141(1)
N(1)	.4745(3)	.3256(3)	.2010(7)	C(17)	.1127(4)	.3193(4)	.271(1)
N(2)	.4768(3)	.4190(3)	.1928(7)	C(18)	.1197(4)	.3194(4)	.2936(9)
N(3)	.3741(3)	.2112(3)	.2170(7)				
N(4)	.3781(3)	.5367(2)	.1879(7)				
C(1)	.5552(3)	.4504(4)	.2802(8)	H(31) [a]	.411	.164	.246
C(2)	.6030(3)	.3713(4)	.3271(8)	H(32)	.325	.180	.238
C(3)	.5524(3)	.2932(4)	.2900(8)	H(41)	.407	.587	.180
C(4)	.3925(3)	.2985(4)	.2111(8)	H(42)	.319	.556	.176
C(5)	.3410(3)	.3748(3)	.1969(8)	H(8)	.689	.238	.485
C(6)	.3955(3)	.4497(3)	.1962(7)	H(9)	.829	.224	.606
C(7)	.6890(3)	.3697(4)	.4062(8)	H(11)	.858	.510	.477
C(8)	.7262(4)	.2906(4)	.4737(9)	H(12)	.719	.515	.411
C(9)	.8085(4)	.2888(5)	.552(1)	H(14)	.241	.465	−.948
C(10)	.8544(4)	.3665(4)	.557(1)	H(15)	.088	.476	−.076
C(11)	.8212(4)	.4475(4)	.491(1)	H(16)	.001	.377	.136
C(12)	.7390(4)	.4480(4)	.4127(8)	H(17)	.081	.283	.376
C(13)	.2487(3)	.3752(4)	.1800(8)	H(18)	.231	.274	.385

[a] All hydrogen atoms were located from the difference map and they were included in the final refinement cycles by using the riding model.

1710 cm^{-1} is consistent with absorption reported for betaines with similar structures [2]. Thus we were certain about having the needed betaine **2**.
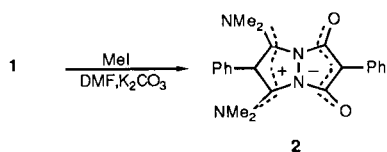
Compound **2** had two maxima in the ultraviolet spectrum in acetonitrile, at 295 and 267 nm, quite different from the unsubstituted material **1** which absorbs at 277 nm, suggesting that the latter probably does not exist in solution as a zwitterion. However, it was strange that compound **2**, being a paraion absorbs only in the ultraviolet range while the hitherto described [2] paraionic betaines absorb in the visible range, above 400 nm. But by examining the effect of substituents on the light absorption it was shown [2] that by replacing the hydrogens in positions 5 and 7 by two CH₃ groups there was a bathochromic shift of 10 nm. It was therefore worthwhile to find the dependence of the maxima on Hammett's σ function, in order to see whether substitution by two dimethylamino groups can lead to a shift of 139 nm. A key structure for such a study would be the 5,7-dimethoxy derivative **4**. The latter was synthesized here from 4-phenyl-3,5-dimethoxypyrazole **3** by the reaction with (α-chlorocarbonyl)phenylketene.
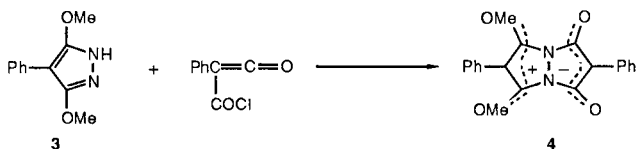
From Figure 3 it is possible to see that, indeed, by plotting the observed wavelength of the maxima as a function of the σ function for dissociation constants of substituted benzoic acid [4], the three substituents H, OCH₃ and
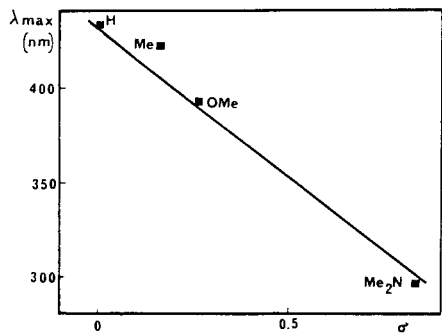

Figure 3.   Dependence of the long wavelength λ max in paraionic compounds on the Hammett's σ constant [4] (from the ionization of *para* substituted benzoic acids) of the substituents at positions 5 and 7 in the pyrazolo[1,2-*a*]pyrazolium system.

N(CH₃)₂ sit on the same straight line, there is only a slight deviation in the case of CH₃.

The large gap between the acidic and basic dissociation constant, in the order of 10^{10} which was found here ($pKa_1 = 1.6$, $pKa_2 = 11.6$), leads to the conclusion that there is one predominant tautomer. However, in order to know whether it is a covalent tautomer, represented in the scheme below in structure **C**, or it is a zwitterionic tautomer which is represented below in structure **B**, it must be determined which one of the hydrogens is eliminated first from the cation which is presented by structure **D**, by the addition of base. In other words, it is to determine which is the more basic side in anion **A**:

Scheme II
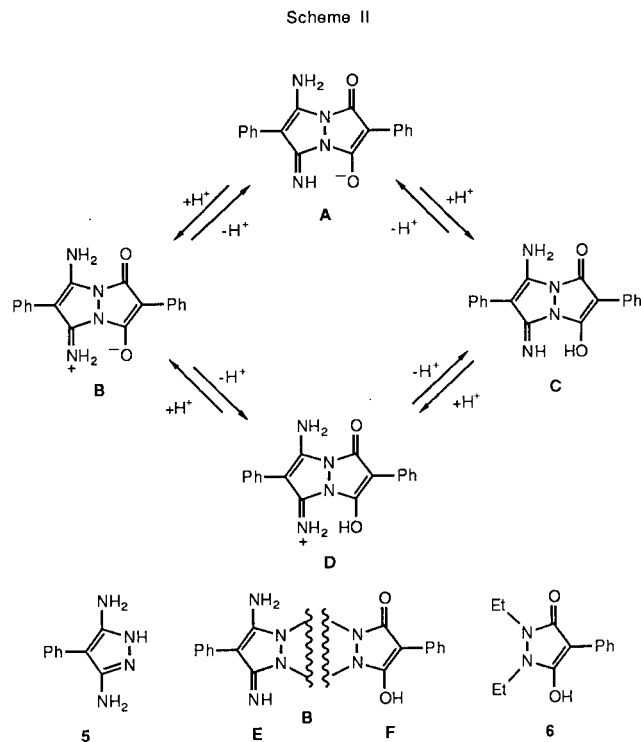
In order to determine that, we needed two models that would correspond to the two halves of the molecule, **E** and **F**. The closest models available were 4-phenyl-3,5-diaminopyrazole (**5**) [5] which corresponds to part **E** and 4-phenyl-1,2-dimethyl-3(5)-oxo-5(3)-hydroxy-3*H*(5*H*)-pyrazole (**6**) which corresponds to part **F**. The latter compound was synthesized here by alkylation of **7** with diethyl sulfate in aqueous sodium bicarbonate. Spectral evidence for the structure of this *N,N*-dimethyl derivative **6** is dealt with in the following article [9].
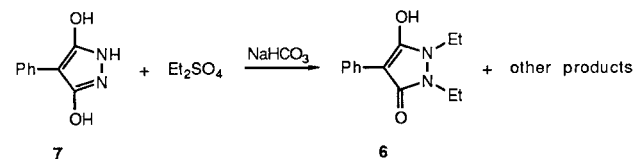
Table 2

Important Inter-Atomic Distances [a] (Å)

O(1)-C(1)	1.223(6)	C(2)-C(3)	1.424(7)
O(1)-N(3)	2.813(5)	C(2)-C(7)	1.450(7)
O(1)-H(31)	2.017(5)	C(4)-C(5)	1.395(7)
O(2)-C(3)	1.219(6)	C(5)-C(6)	1.405(7)
O(2)-N(4)	2.761(4)	C(5)-C(13)	1.465(7)
O(2)-H(41)	1.922(4)	C(7)-C(8)	1.384(8)
N(1)-N(2)	1.383(6)	C(7)-C(12)	1.403(8)
N(1)-C(3)	1.442(7)	C(8)-C(9)	1.394(8)
N(1)-C(4)	1.364(7)	C(9)-C(10)	1.361(9)
N(2)-C(1)	1.440(7)	C(10)-C(11)	1.378(9)
N(2)-C(6)	1.368(7)	C(11)-C(12)	1.394(8)
N(3)-C(4)	1.325(7)	C(13)-C(14)	1.401(8)
N(3)-H(31)	0.920(7)	C(13)-C(18)	1.386(8)
N(3)-H(32)	0.926(7)	C(14)-C(15)	1.383(9)
N(4)-C(6)	1.318(6)	C(15)-C(16)	1.36(1)
N(4)-H(41)	0.868(5)	C(16)-C(17)	1.37(1)
N(4)-H(42)	0.980(7)	C(17)-C(18)	1.383(9)
C(1)-C(2)	1.426(7)	Cl -C(10)	1.746(6)

[a] The estimated standard deviations are given in parentheses and refer to the last positions of the respective values.

The pKa found for compound **6** was 8.8. Compound **5** had two pKa values, 2.0 and 5.5, respectively. We think, therefore, that the addition of a proton to Structure **A** (in Scheme II) will be first at the negative oxygen, suggesting that the predominant tautomer in solution is not zwitterionic but rather covalent, be it structure **C** or any other covalent form or a mixture of a few of them.

EXPERIMENTAL

The uv spectra were taken with a Varian Techtron Model 635 spectrophotometer and the ir with a Perkin Elmer Model 157. The nmr spectra were recorded with a Bruker WH-300-Aspect 2000 spectrometer. Melting points were observed with a Thomas Hoover apparatus and are uncorrected. Determination of dissociation constants was carried out either by studying the uv spectra in buffered solutions and calculating the pKa values as described earlier [6], or by potentiometric titration [7]. Single crystal X-ray structure analysis data were measured on PW 1100/20 Philips Four-Circle Computer-Controlled Diffractometer, MoKα >0.71069 Å) radiation with a graphite crystal monochromator in the incident beam was used. The unit cell dimensions were obtained by a least-squares fit of 20 centered reflections in the range of $10 \leq \theta \leq 14°$. Intensity data were collected using the $\omega - 2\theta$ technique to a maximum of 2θ of 45°. The scan width, $\Delta\omega$, for each reflection was 1° with a scan spped of 0.05 degree/minute. Backqround measurements were made for a total of 20 seconds at both limits of each scan. Three standard reflections were monitored every 60 minutes. No systematic variations in intensities were found.

Table 3

Important Angles (Degrees) [a]

N(2)-N(1)-C(3)	109.04(4)
N(2)-N(1)-C(4)	108.8(4)
O(3)-N(1)-C(4)	133.3(5)
N(1)-N(2)-C(1)	109.3(4)
N(1)-N(2)-C(6)	107.7(4)
C(1)-N(2)-C(6)	133.5(4)
O(1)-C(1)-N(2)	119.7(5)
O(1)-C(1)-C(2)	134.4(5)
N(2)-C(1)-C(2)	105.9(4)
C(1)-C(2)-C(3)	109.5(5)
C(1)-C(2)-C(7)	125.7(5)
C(3)-C(2)-C(7)	124.8(5)
O(2)-C(3)-N(1)	119.0(5)
O(2)-C(3)-C(2)	134.9(5)
N(1)-C(3)-C(2)	106.0(4)
N(1)-C(4)-N(3)	119.9(5)
N(1)-C(4)-C(5)	108.3(5)
N(3)-C(4)-C(5)	131.5(5)
C(4)-C(5)-C(6)	106.3(5)
C(4)-C(5)-C(13)	126.2(5)
C(6)-C(5)-C(13)	127.5(5)
N(2)-C(6)-N(4)	121.3(5)
N(2)-C(6)-C(5)	108.5(4)
N(4)-C(6)-C(5)	130.1(5)
C(2)-C(7)-C(8)	121.6(5)
C(2)-C(7)-C(12)	121.4(5)

Plane	Plane	Angle
C(1),C(2),C(3)	C(7)-C(12)	9.35(5)
C(4),C(5),C(6)	C(13)-C(18)	137.09(5)
C(1),N(1),N(2),C(3)	C(4),N(1),N(2),C(6)	151.74(5)

Intensities were corrected for Lorentz and polarization effects. All non-hydrogen atoms were found by using the results of the SHELX 86 program (a Fortran-77 Program for the solution of crystal structure from diffraction data, University of Goettingen, Germany). All crystallographic computing was done on a CYBER 855 computer, using the SHELX 1977 structure determination package. After several cycles of refinements the positions of the hydrogen atoms were found and added with a constant isotropic temperature factor of 0.05 Å^2 to the refinement process. Refinement proceeded to convergence by minimizing the function Ew(| F$_o$ | - | F$_o$ |)^2. A final difference peaks less than 0.4 e/Å^{-3} scattered about the unit cell without a significant feature.

Crystallographic data:

Chemical formula: $C_{18}H_{13}ClN_4O_2$

Molecular weight: 352.8

Space group: P2₁/C

Unit cell dimensions:

a = 15.853

b = 14.793

c = 6.821

β = 91.78°

v = 1599.4 Å³

Number of molecules in unit cell: 4

Density (calculated): ρ = 1.465 g cm⁻³

Linear absorption coefficient: μ(MoKα) = 2.12 cm⁻¹

Number of unique reflections: 2046

Reflections with I ≥ 25(I): 1421

Disagreement index R: 0.072

Weighted disagreement index Rw: 0.093

w = $(\sigma_F^2 + 0.00117 \cdot F^2)^{-1}$

Anhydro-2,6-diphenyl-1-oxo-3-hydroxy-5,7-bis(dimethylamino)pyrazolo[1,2-a]pyrazolium Hydroxide (2).

To a solution of 2,6-diphenyl-1(3)-oxo-3(1)-hydroxy-5(7)-imino-7(5)-amino-1H,5H(3H,7H)-pyrazolo[1,2-a]pyrazole (1) (0.32 g) in dimethylformamide (1 ml), potassium carbonate (0.7 g) and methyl iodide (8 ml) were added and the reaction mixture was stirred and refluxed for 48 hours. After evaporation in vacuum the residue was dissolved in water (8 ml) and extracted three times with ethyl acetate. The combined organic layers were dried over sodium sulfate and the solvent removed by evaporation in vacuum. The residue was crystallized from a small amount of ethanol and recrystallized from ethanol (0.1 g). The product was dried in vacuum over phosphorus pentoxide at 125°, mp 240°; ir (Nujol): ν max 1710, 1580, 1500, 1330, 1290, 1130, 870, 770, 720, 690 cm⁻¹. ¹H nmr (deuteriochloroform): δ 8.07 (dd, 2H at the *ortho*-position in the anionic phenyl ring), 7.38-7.20 (m, 7H aromatic), 7.00 (s, 1H at *para*-position of the anionic phenyl ring), 2.94 (s, 12H of 4CH₃); uv (acetonitrile): λ max 303 mm (shoulder), 295 mm (ϵ = 24300), 266 mm (20600).

Anal. Calcd. for $C_{22}H_{22}N_4O_2$: C, 70.57; H, 5.92; N, 14.96. Found: C, 70.51; H, 5.97; N, 14.58.

4-Phenyl-1,2-diethyl-3(5)-oxo-5(3)-hydroxy-3H(5H)-pyrazole (6).

4-Phenyl-3,5-dihydroxypyrazole [2,8] (1.76 g) was dissolved in 5% aqueous sodium bicarbonate (100 ml) and diethylsulfate (10 ml) was added. The reaction mixture was stirred and heated at 80° for 3 hours and left overnight at room temperature. The precipitate (0.25 g) contained 4-phenyl-3,5-diethoxypyrazole [9] and the desired product 6. The latter was isolated by fractional crystallization from ethanol, in which it crystallizes first. Recrystallized from ethanol (0.1 g), mp 175°; ir (Nujol): ν max 1610, 1540, 1500, 1350, 1310, 1090, 1050, 1020, 770, 690 cm⁻¹; ¹H nmr (deuteriochloroform): δ 7.65 (dd, 2H *ortho*), 7.31 (tt, 2H *meta*), 7.12 (tt, 1H

para), 3.91 (q, CH₂), 3.87 (q, CH₂), 1.35 (t, CH₃), 1.24 (t, CH₃).

Anal. Calcd. for $C_{13}H_{16}N_2O_2$: C, 67.24; H, 6.89; N, 12.06. Found: C, 67.17; H, 6.66; N, 11.73.

Anhydro-2,6-diphenyl-1-oxo-3-hydroxy-5,7-dimethoxypyrazolo[1,2-a]pyrazolium Hydroxide (4).

4-Phenyl-3,5-dimethoxypyrazole [9] (0.2 g) was dissolved in dry ether (8 ml). A solution of (chlorocarbonyl)phenylketene [10] (0.5 g) in ether (2 ml) was added with stirring for 5 minutes. The reaction mixture was stirred for additional 15 minutes and the orange precipitate which was collected was triturated in aqueous 5% sodium bicarbonate (10 ml) and filtered. The product was recrystallized from acetonitrile (0.15 g), mp 150°; ir (Nujol): ν max 1680, 1520, 1490, 1300, 1120, 770, 690 cm⁻¹; ¹H nmr (deuteriochloroform): δ 8.30-7.20 (m, 10H aromatic), 4.53 (s, 6H, 2CH₃); uv (acetonitrile): λ max 393 nm (ϵ = 5580), 273 nm (ϵ = 25480).

Anal. Calcd. for $C_{20}H_{16}N_2O_4$: C, 68.96; H, 4.63; N, 8.04. Found; C, 68.86; H, 4.63; N, 8.32.

4-Phenyl-1,2-dimethyl-3,5-bis(dimethylamino)pyrazolium Iodide (8).

4-Phenyl-3,5-diaminopyrazole (5) (0.35 g) was dissolved in acetone (20 ml). Methyl iodide (15 ml) and potassium carbonate (0.84 g) were added and the reaction mixture refluxed overnight. The precipitate was filtered off and the solution evaporated to dryness. The residue was dissolved in methylene chloride filtered from impurities, the solution was concentrated in vacuum and subjected to silica gel preparative layer chromatography (plc) in chloroform-petroleum ether (1:1). The stain which remained close to the origin was extracted with chloroform and recrystallized from chloroform-cyclohexane (0.2 g), mp 237°; ir (Nujol): ν max 1560, 1410, 1320, 1070, 1000, 820, 770, 710 cm⁻¹; ¹H nmr (deuteriochloroform): δ 7.35-7.22 m (5H, Ph), 3.78 (6H, 2CH₃), 2.70 (12H, 4CH₃); uv (ethanol): λ max 287 nm (ϵ = 13700), 221 nm (ϵ = 18400).

Anal. Calcd. for $C_{15}H_{23}IN_4$: C, 46.63; H, 5.96; N, 14.50. Found: C, 45.94; H, 5.72; N, 14.18.

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