Zwitterionic 2,4-Dioxopyrrolidines

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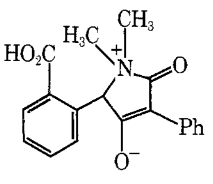
In the course of the development of the fluorogenic amine reagent fluorescamine,[2,3] we encountered the unusual ammonium acylides[4] 1 and 2. The key step in the synthesis of fluorescamine (3) entails the formylation of *o*-(α-hydroxycinnamoyl)benzoic acid with *N*,*N*-dimethylformamide dimethyl acetal.[3] Presumably, a diketoenamine 4 (R = CH_3) is formed in this reaction, and is transformed during acidic work-up either directly (cf. 4, arrows) or via the carbinolamine 5 (R = CH_3) to the spirolactone 6 (R = CH_3) and subsequently to the desired 3. A minor by-product of this reaction sequence is the enol betaine 1. The analogous reaction of *o*-(α-hydroxycinnamoyl)benzoic acid with tripiperidinomethane[5] affords only a small amount of the expected 3, while the major product, obtained after hydrolysis, is the piperidinium acylide 2. This compound is also formed when fluorescamine (3) is allowed to react with excess piperidine and subsequently with aqueous acid.



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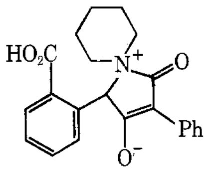
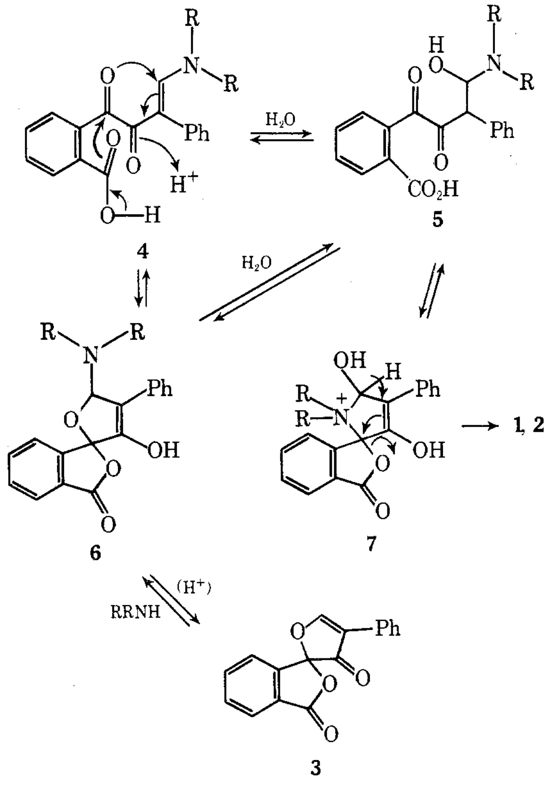
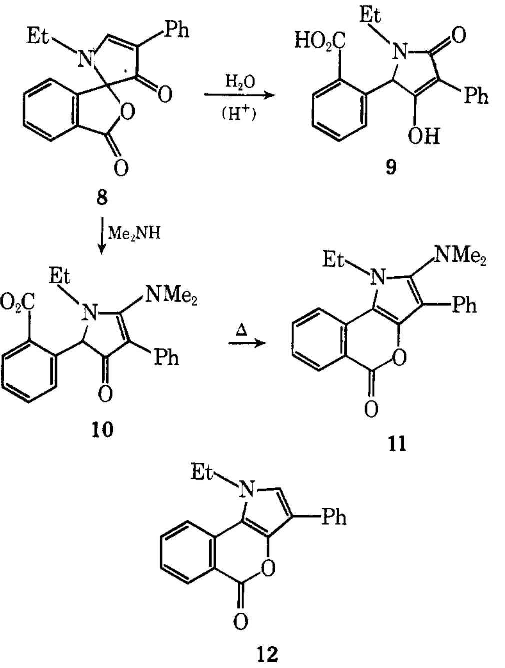


2

It thus appears that the proposed carbinolamine intermediate of type 5 can follow an alternative mode of cyclization leading to an intermediate of type 7 (instead of 6), which upon intramolecular disproportionation gives rise to the observed products 1 and 2. A first indication as to the structural nature of 1 and 2 was obtained from spectral comparisons of these materials with the related tetramic acid 9, which was previously isolated from an acid catalyzed rearrangement of the spirolactone 8.[6] For example, the ultraviolet spectra of 1 and 2 (measured in 0.1 *N* KOH) have an absorption maximum at 262 (ϵ 16500) and 263 nm (16800), respectively, while 9 (in 0.1 *N* KOH) absorbs maximally at 265 nm (ϵ 14500). Complete structure proof was furnished by an x-ray crystal structure analysis of 2, the details of which are reported in the Experimental Section (cf. Figure 1).





In this connection, it is also interesting that 8[6] rapidly reacts with dimethylamine at room temperature to afford the aminopyrrolinone 10, a process which is strongly reminiscent of the reactions described above. At elevated temperatures, 10 is readily converted to the enol lactone 11. The ultraviolet spectrum of 11 is remarkably similar in shape to that of 12,[6] the first one having maxima (in methanol) at 233 (ϵ 27500), 313 (18500), and 390 nm (6200), the latter at 240 (ϵ 29750), 291 (19800), and 372 nm (5800). An x-ray crystal structure analysis of 10 (Figure 2) fully corroborated its assigned structure, thus securing also that of 11.

Experimental Section

General. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer 621 or a Beckman IR-9 spectrometer. Ultraviolet spectra were recorded on a Carey Model 16 spectrophotometer. ^{1}H NMR spectra were measured on a Varian HA-100 instrument and are reported in parts per million downfield from internal tetramethylsilane.

5-(*o*-Carboxyphenyl)-1,1-dimethyl-2-oxo-4-oxy-3-phenylpyrrolidinium Inner Salt (1). A reaction of 16.08 g of *o*-(α-hydroxycinnamoyl)benzoic acid with 30 ml of *N*,*N*-dimethylformamide dimethyl acetal was carried out and worked up as described in the preceding paper[3] for the preparation of fluorescamine. The aqueous sodium bicarbonate washings (500 ml, 1% w/v), obtained in this process, were acidified with 1 *N* HCl. The resulting precipitate was extracted into chloroform, and the organic extract was washed with water, dried over Na_2SO_4, and evaporated to dryness under reduced pressure. The solid residue was crystallized from chloroform to afford 580 mg (3%) of the acylide 1 (as crystals containing ½ equiv of $CHCl_3$): mp 251–253°; uv max (0.1 *N* KOH) 262 nm (ϵ 16500); ir (KBr) 1770, 1690 cm^{-1}; NMR (Me_2SO-d_6) δ 2.54

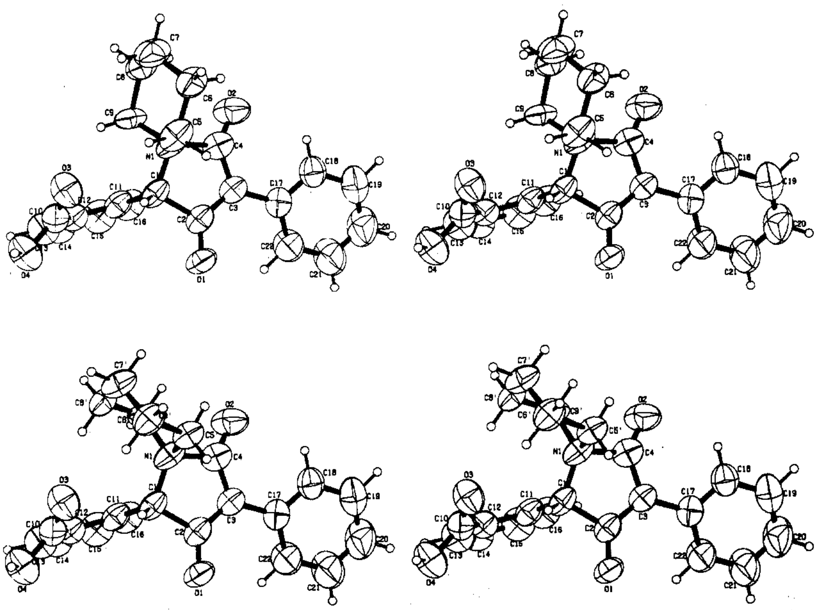


Figure 1. Computer-generated stereodrawing of **2**. The two conformers present in the crystal differ only in the conformation of the six-membered heterocyclic ring.

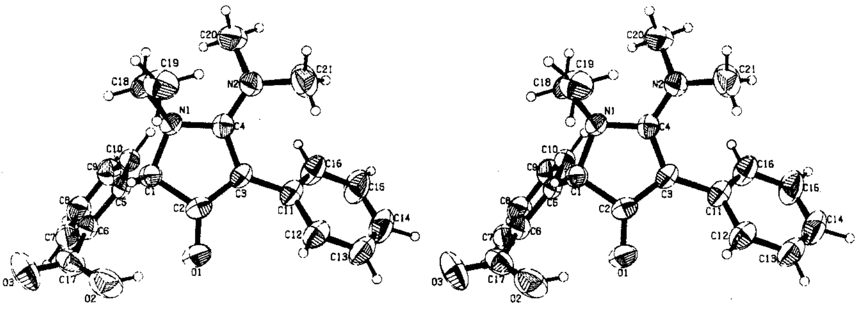


Figure 2. Computer-generated stereodrawing of **10**.

(3, s, NCH_3), 3.45 (3, s, NCH_3), 5.67 (1, s, benzylic CH), 7.0–8.4 (9, m, aromatic).

Anal. Calcd for $C_{19}H_{17}NO_4 \cdot \frac{1}{2}CHCl_3$: C, 60.36; H, 4.55; N, 3.60. Found: C, 60.60; H, 4.42; N, 3.57.

4-(*o*-Carboxyphenyl)-1-oxo-3-oxy-2-phenyl-5-azoniaspiro[4.5]decane Inner Salt (2). A. To a solution of 1.34 g of *o*-(α-hydroxycinnamoyl)benzoic acid in 10 ml of *N,N*-dimethylformamide was added dropwise with stirring a solution of 2.0 g of tripiperidinomethane[5] in 5 ml of ether. The mixture was kept at room temperature for 16 hr and was then poured into 100 ml of ice-cold 1% HCl. The resulting precipitate was extracted into methylene chloride and the organic phase was extracted with 250 ml of 2% sodium bicarbonate. After drying and evaporation, the organic layer yielded 357 mg of fluorescamine (**3**).[3] The sodium bicarbonate phase was acidified and extracted with chloroform and the extract was washed with water, dried (Na_2SO_4), and evaporated in vacuo. Recrystallization of the solid residue from methylene chloride–ether afforded 1.12 g (61%) of the acylide **2**, mp 233°.

B. To a mixture of 15 ml of piperidine and 5 ml of water was added, in small portions, 1.39 g of fluorescamine (**3**). The resulting solution was left at room temperature for 5 hr and then poured onto crushed ice. Acidification with 2 *N* HCl produced a precipitate which was taken up in methylene chloride and the organic phase was then extracted with saturated sodium bicarbonate. After evaporation of the methylene chloride, 840 mg (60%) of fluorescamine was recovered. The bicarbonate extract was acidified and extracted with chloroform. The chloroform solution was dried (Na_2SO_4) and evaporated in vacuo. Recrystallization of the residue from methylene chloride–ether gave 294 mg (16%) of the acylide **2** (44%, based on unrecovered **3**): mp 233°; uv max (0.1 *N* KOH) 263 nm (ε 16800); ir (KBr) 1765, 1705 cm^{-1}; NMR (Me_2SO-d_6) δ 1.1–2.5 [6, m, $(CH_2)_3$], 3.3–3.9 (4, m, NCH_2), 6.29 (s, 1, benzylic CH), 7.0–8.1 (9, m, aromatic).

Anal. Calcd for $C_{22}H_{21}NO_4 \cdot \frac{1}{2}CH_2Cl_2$: C, 66.58; H, 5.46; N, 3.45; Cl, 8.74. Found: C, 66.60; H, 5.45; N, 3.43; Cl, 8.90.

1-Ethyl-2-dimethylamino-3-phenyl-5-(2-carboxyphenyl)-2-pyrrolin-4-one (10). To 4.50 g of 1′-ethyl-3′-phenylspiro[phthalan-1,5′(2)-pyrroline]-3,4′-dione (**8**)[6] in 200 ml of methylene chloride was added slowly, with ice cooling and stirring, 150 ml of a freshly prepared solution (10% w/v) of dimethylamine in methylene chloride. The mixture was kept in an ice bath for 30 min. Excess amine and solvent were then removed under reduced pressure and the residual oil was purified by chromatography on silica gel with chloroform–methanol (95:5) as the eluent. Fractions containing **10** were combined and concentrated at low temperature to a volume of 20 ml. After addition of 20 ml of methanol, the volume was further reduced in vacuo until the desired product started to crystallize. After refrigeration, there was collected 4.27 g (81%) of the pyrrolinone **10**: mp 197–200° dec; uv max (MeOH) 243 nm (ε 16400) and 302 (13650); ir (KBr) 1725 cm^{-1}; NMR (Me_2SO-d_6) δ 1.02 (3, t, NCH_2CH_3), 2.93 [6, s, $N(CH_3)_2$], 3.34 (2, q, NCH_2CH_3), 5.77 (1, s, benzylic CH), 7.02–7.85 (9, m, aromatic).

Anal. Calcd for $C_{21}H_{22}N_2O_3$: C, 71.98; H, 6.33; N, 7.99. Found: C, 71.97; H, 6.44; N, 8.02.

1-Ethyl-2-dimethylamino-3-phenyl[2]benzopyrano[4,3-*b*]pyrrol-5(1*H*)-one (11). A sample (600 mg) of **10** was melted in a pyrolysis tube by heating to 200°C. The melt was allowed to cool to room temperature and was then dissolved in methylene chloride. The solution was concentrated in vacuo and applied to preparative TLC plates (2 mm silica gel). The plates were developed in methylene chloride and a major band was collected by eluting with the same solvent. The eluate was evaporated and the residue was crystallized from ether to give 383 mg (67%) of the lactone **11**: mp 152–154°C; uv max (MeOH) 233 nm (ε 27500), 313 (18500), and 390 (6200); ir ($CHCl_3$) 1710, 1610, 1525, 1515 cm^{-1}; NMR ($CDCl_3$) δ 1.41 (3, t, NCH_2CH_3), 2.76 [6, s, $N(CH_3)_2$], 4.82 (2, q, NCH_2CH_3), 7.15–7.80 (9, m, aromatic).

Anal. Calcd for $C_{21}H_{20}N_2O_2$: C, 75.88; H, 6.07; N, 6.43. Found: C, 75.93; H, 6.09; N, 6.41.

Crystallography. Three-dimensional intensity data for **2** and

10 were measured on a Hilger-Watts four-circle diffractometer (θ–2θ scans, Ni-filtered Cu Kα radiation, pulse height discrimination). The data for **2** were corrected for absorption, but the data for **10** were not. Both structures were solved by a multiple solution procedure.[7] All refinements were carried out by full-matrix least square (FMLS). The unweighted discrepancy index is given by $R = \Sigma||F_0| - |F_c|/\Sigma|F_0|$ and the weighted index by $R_w = [\Sigma w||F_0| - |F_c|^2/\Sigma w|F_0|^2]^{1/2}$.

Crystal data for **2** ($C_{22}H_{21}NO_4 \cdot \frac{1}{2}CH_2Cl_2$) follow: monoclinic, space group $C2/c$ or Cc, $a = 14.262$ (8), $b = 11.305$ (6), $c = 25.813$ (15) Å, $\beta = 99.80$ (4)°, $d_{obsd} = 1.31$ (2), $d_{calcd} = 1.314$ g cm^{-3} for $Z = 8$, μ (Cu Kα) = 18.9 cm^{-1}. Of 3884 accessible reflections with $\theta < 70°$, 2238 had intensities significantly greater than background [$I > 2.5\ \sigma\ (I)$]. The structure was obtained while working in the centrosymmetric space group $C2/c$. In the process of solving the structure, it was found that the crystal contains two different conformers of **2** which differ significantly only in the conformation of the heterocyclic six-membered ring. The presence of two conformers suggested the possibility that the space group was actually the noncentrosymmetric one, Cc. Since this space group has only four symmetry operations, the unique part of the unit cell would contain two independent molecules whose conformations need not be the same. The attempt to distinguish between $C2/c$ and Cc is described below.

The initial refinement of the structure was done in space group $C2/c$. The five carbon atoms of the heterocyclic six-membered ring were resolved into two sets of half-atoms corresponding to the two conformations of this ring. It was assumed that there are equal numbers of the two conformers in the crystal and that the two conformers are randomly distributed throughout the crystal, thus giving rise to a disordered structure. Isotropic temperature factors were used for the first few cycles of FMLS which were followed by several cycles of FMLS in which all atoms had anisotropic thermal parameters.

At this point the space group Cc was considered. There are two possible arrangements in Cc: (1) one independent molecule has conformation A and the other independent molecule has conformation B, and (2) vice versa. Refinements (isotropic temperature factors) of both arrangements were carried out. Both showed modest decreases in their R indices (R, R_w = 0.175, 0.228 and 0.174, 0.226 for the two trial structures in Cc) as compared to the corresponding values for the $C2/c$ refinement (R, R_w = 0.176, 0.240). Some decrease is expected because the number of independent variables is nearly doubled in Cc. Further refinement of these trial structures in space group Cc was not done because the reductions in the R values did not appear to be significant, particularly since both models showed almost equal decreases. Furthermore, the disordered model in $C2/c$ is more than adequate to establish the chemical structure.

The final refinement of the structure was carried out on the disordered model in space group $C2/c$. A difference Fourier calculated at the end of the anisotropic refinement showed peaks at reasonable positions for almost all the hydrogen atoms including those for the half-atoms. The idealized positions for all the hydrogen atoms were calculated and the hydrogen atoms were included in all subsequent calculations. In the final refinement, the hydrogen atoms were included in the structure factor calculations but their parameters were not refined. The final discrepancy index is $R = 0.099$ for the 2238 observed reflections. The final difference Fourier has only three features greater than 0.2 e Å^{-3} in magnitude. These are three peaks of about 0.5 e Å^{-3} which are located at 0.5–0.8 Å from the Cl atom of the solvent molecule. Stereodrawings of the two conformers of **2** are shown in Figure 1.

Crystal data for **10** ($C_{21}H_{22}N_2O_3$) follow: monoclinic, space group $P2_1/c$, $a = 10.901$ (5), $b = 12.230$ (5), $c = 14.769$ (12) Å, $\beta = 112.09$ (5)°, $d_{calcd} = 1.275$ g cm^{-3} for $Z = 4$, μ (Cu Kα) = 7.03 cm^{-1}. Of the 3716 accessible reflections with $\theta < 76°$, 2187 were considered observed [$I > 2.5\sigma\ (I)$]. The structure was solved by a multiple solution procedure as implemented in the computer program MULTAN.[8] The structure was not found on any E map calculated from phase sets based on an expansion of eight reflections (three origin defining reflections and five reflections of unknown phases). The number of starting reflections was increased to 11 and the resulting 256 phase sets were generated. An E map calculated from the phase set with the highest absolute figure of merit (FOM = 1.132, Karle R factor 30.8%) revealed all atoms except the hydrogens. The hydrogen atoms were located from a difference Fourier calculated after refinement of the heavier atoms. For the final refinement, anisotropic thermal parameters were used for the heavier atoms and isotropic temperature factors were used for the hydrogens; the hydrogen atom parameters were refined. The final R is 0.050 for the 2187 observed reflections. There are no features on the final difference Fourier of intensity greater than ±0.1 e Å^{-3}.

Registry No.—**1**, 57109-19-0; **2**, 57109-20-3; **3**, 38183-12-9; **8**, 36777-62-5; **10**, 57109-21-4; **11**, 57109-22-5; *o*-(α-hydroxycinnamoyl)benzoic acid, 43053-07-2; *N,N*-dimethylformamide dimethyl acetal, 4637-24-5; tripiperidinomethane, 22630-08-6; piperidine, 110-89-4.

Supplementary Material Available. Tables of the positional and thermal parameters for the structures of **2** and **10** (5 pages) will appear following these pages in the microfilm edition of this volume of the journal.

References and Notes

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Substituent Effects on the Electronic Nature of Carbon-Bonded Fluorine[1]

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We recently reported the surprising observation that certain lanthanide β-diketonates induce substantial shifts in the ^{1}H NMR spectrum of simple alkyl fluorides.[2] Here we wish to present results relevant to the nature of this interaction and describe its use to probe the electronic nature of organic fluorides.

Table I lists the magnitudes of selected ^{1}H and ^{19}F chemical shift, line width, and coupling constant differences induced by the addition of Yb(fod)$_3$ to a variety of alkyl fluorides. An examination of these results reveals that only relatively minor changes occur in the magnitude of the induced chemical shifts and spectral line widths as the steric bulk of adjacent centers is increased. Thus, steric factors do not have an overwhelming influence in determining the extent of substrate–lanthanide interaction. It is apparent, however, that the introduction of a second electronegative atom at the carbon bearing the fluorine atom produces a very significant *decrease* in both the induced chemical shifts and line widths while addition of Yb(fod)$_3$ has essentially no effect on the ^{1}H or ^{19}F spectra of compounds that contain two additional electronegative atoms at the fluorine-bearing carbon. Taken together, these results militate against a lanthanide–substrate interaction resulting from a principally electrostatic interaction between the electropositive lanthanide center and the electronegative end of the substrate molecular dipole since such an interaction, in contrast to what is observed, would be expected to increase as the resultant dipole moment of the substrate increases.