A New Class of Heterocyclic Betaines: 1,1-Dimethyl-3-phenylpyrazolium-5-oxide (1)

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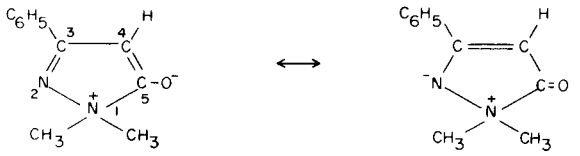
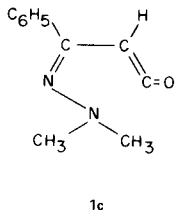
1,1-Dimethyl-3-phenylpyrazolium-5-oxide (**1**) was isolated as a minor product (3%) in the reaction of ethyl benzoylacetate with 1,1-dimethylhydrazine and also was obtained as the major product (58%) from the reaction of methyl *p*-toluenesulfonate with ethyl benzoylacetate dimethylhydrazone. The structural assignment was made on the basis of chemical reactions and spectral data and the formula is represented by a resonance structure for which there are two principal canonical forms. Reaction of **1** with methanol at room temperature afforded methyl benzoylacetate dimethylhydrazone. Ethyl benzoylacetate dimethylhydrazone was shown to exist as a tautomeric mixture containing 65% of the imine form at room temperature.

1,1-Dimethyl-3-phenylpyrazolium-5-oxide represents the first reported member of a new class of heterocyclic betaines. The evidence from elemental and spectrographic analyses and from chemical reactions is consistent with the assignment of a resonance structure for which there are two canonical forms (**1a** ↔ **1b**). The molecular structure of **1** is confirmed by a single crystal x-ray diffraction study (3). The contribution of a "ketene" structure in which one of the ring bonds does not exist (**1c**), proposed by DeCamp and Stewart to explain the unusually long C(5)–N(1) bond length (1.565 Å) and the large C(4)–C(5)–O bond angle (140.3°), is also consistent with the very facile cleavage of the C(5)–N(1) bond with methanol. It is of interest that **1** is a structural isomer of the antipyretic drug antipyrine (4).



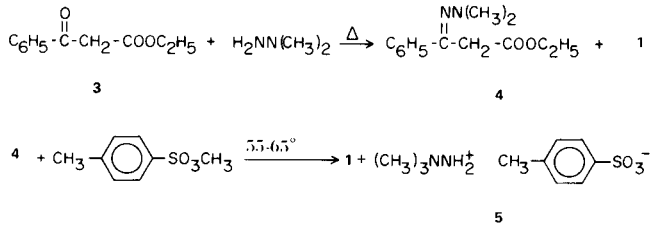
1a ⟷ **1b**



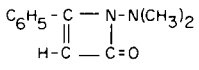
1c

Results and Discussion.

Compound **1**, m.p. 135°, was formed as a minor product in the reaction of ethyl benzoylacetate (**3**) with 1,1-dimethylhydrazine along with the expected product, ethyl benzoylacetate dimethylhydrazone (**4**). In addition, **1** was produced in 58% yield from the reaction of methyl *p*-toluenesulfonate with ethyl benzoylacetate dimethylhydrazone (**4**) at 55-65°. When the latter reaction was attempted at room temperature only starting materials were recovered, whereas at 80° 1,1,1-trimethylhydrazinium *p*-toluenesulfonate (**5**) was the only product observed. Compound **5** probably arose from hydrolysis of the desired quaternary salt of **4**; the dimethylhydrazone has been used as a protecting group for ketones, which may be regenerated by quaternization followed by facile hydrolysis (5).



Elemental analysis of **1** demonstrated an empirical formula of $C_{11}H_{12}N_2O$. A strong parent peak at m/e 188 in the mass spectrum established that the molecular formula is also $C_{11}H_{12}N_2O$, which corresponds to **4** minus the elements of ethanol. The nmr spectrum of **1** showed dimethylamino, vinyl and phenyl protons in the ratio 6:1:5. These data permitted the postulation of a number of isomeric structures. Compound **1**, however, reacts with methanol *at room temperature* with opening of the ring and formation of methyl benzoylacetate dimethylhydrazone (**6**). This facile reaction is an indication that a rearrangement has not occurred and therefore only formulas **1** and **2** were further considered.



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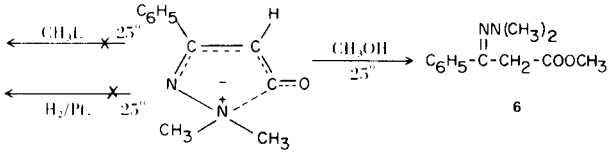
Further chemical reactions were attempted and additional spectral data obtained to distinguish between the remaining two structures represented by the hitherto unknown ring system **1** and the unsaturated β-lactam 2. There are two reports in the literature describing three azetinones (6,7). Since hydrogenation of 1,2-diphenyl-2-azetin-4-one proceeds readily in the presence of platinum (6), a similar reaction was attempted on **1** but only starting



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material was recovered (80% yield). 2-Pyrazolinium-3-oxides (**7**) were reported not to undergo hydrogenation (8). An attempted reaction of **1** with methyl iodide at room temperature for ten hours gave only a 95% recovery of the starting material.

7 a) R R' H
b) R H, R' CH_3
c) R CH_3, R' H

The infrared spectrum of **1** included strong absorption at 1710 and 1730 cm^{-1}. The three reported unsaturated β-lactams have bands at 1750 (6) and 1759-1769 cm^{-1} (7). The ultraviolet spectrum (cyclohexane) of **1**, with absorption at 236 (ε 25,000), 285 (ε 3,300) and 320 (ε 7,500) mμ, bears little resemblance to the uv spectrum (ethanol) of 1,2-diphenyl-2-azetin-4-one which has maxima at 252 (ε 11,500) and 358 (ε 530) mμ (6). The mass spectrum of **1** demonstrated a peak at 57.058 (C_3H_7N) which requires, in the absence of a rearrangement, that the dimethylamino group be joined to a third carbon and hence is compatible with **1** but not with **2**.

The chemical shift of the single proton at δ 4.76 is relatively close to that of the ring proton (δ 5.10) of 1,2-diphenyl-2-azetin-4-one, the only unsaturated β-lactam for which an nmr spectrum is reported (6). Structure **1** is supported, however, by the chemical shift for the hydrogens on the quaternary dimethylamino group (δ 3.11). This value is within the range (δ 3.05-3.30) characteristic for this grouping in the dipolar five-membered heterocyclic 2-pyrazolinium-3-oxides (**7**). Kol'stov found further that the signal for the dimethylamino protons in these dipolar compounds was intermediate between the signal for similar protons in neutral molecules (δ 2.50-2.60) and the signal observed for the positively-charged methiodides (δ 3.40-3.55) derived from **7** (9).

The dipole moment of **1**, 2.9 D, was inconclusive for distinguishing between structures **1** and **2**. Dipole moment data have not been reported for unsaturated β-lactams, but short-chain amides fall in the range 3.4-3.6 D and γ-butyrolactam has a value of 3.55 D (10). For sydnones (11a,b) and other mesoionic compounds (12a,b), dipole moment values have been found over the wide range of 1.14 to 7.36 D.

The nuclear magnetic resonance spectrum of ethyl benzoylacetate dimethylhydrazone (**4**) was of interest in that it showed that the compound exists as two forms which give rise to separate signals. Tautomerism in **4** would be analogous to that observed in β-dicarbonyl compounds (13a-c) and their monoimino derivatives (13d-f). Two tautomeric structures, the imine form **4a** and an enamine form **4b**, are shown for the dimethyl hydrazone.

4a 4b

For comparison purposes, the nmr signals for ethyl benzoylacetate were determined and these resonances agreed very well with the literature values (13b), which are recorded in Table I. Based on these assignments, the spectrum of **4** was similarly interpreted and the results are also given in Table I. The signals for the two methylene groups in **4a** overlapped so that it was not possible to determine separate integration ratios for them; however, the sum of the integration values for the methylene protons, the vinyl proton and the proton on the nitrogen was 4.0, the expected value. The peak at δ 8.80 was broad (∿ 10 Hz), a feature characteristic of signals arising from hydrogen-bonded protons. To provide further evidence for the proposed tautomeric equilibrium, the spectrum was recorded at -30° and at this temperature the peak at δ 8.80 was very sharp. This variation with temperature probably indicates that the proton which gives rise to the signal is undergoing slow exchange at room temperature, causing a broadening of the signal, while at the lower

TABLE I

Nmr Data (a) of Ethyl Benzoylacetate (**3**) and Ethyl Benzoylacetate Dimethylhydrazone (**4**)

Compound	Form	CH_3	CH_2	CH_2	$N(CH_3)_2$	=CH	OH and/ or NH
3	Keto	1.12	4.10	3.97	---		
	Enol	1.22	4.22		---	5.70	12.83
	Integration Ratios	3.0	2.0	1.7		0.15	0.15
4	Imine	1.18	4.19	4.05	2.50		
	Enamine	1.29	4.24		2.61	4.77	8.80
	Integration Ratios	3.0	3.3		6.0	0.35	0.35

(a) Chemical shifts (in deuteriochloroform) in parts per million from tetramethylsilane used as internal standard.

temperature no tautomerization is taking place (13a). From the integration values it was calculated that the imine form **4a** was present to the extent of 65% at room temperature. The nmr spectrum of methyl benzoylacetate dimethylhydrazone (**6**), formed from the reaction of **1** with methanol, also indicated the presence of tautomeric forms.

EXPERIMENTAL

Microanalyses were performed by Dr. Franz J. Kasler. Melting points and boiling points are uncorrected. The following spectrometers were used: nuclear magnetic resonance (nmr), Varian A-60 (peaks reported in parts per million downfield from tetramethylsilane as internal standard, except as noted); infrared (ir), Beckman IR-8s or Perkin-Elmer Model 337; ultraviolet (uv), Cary Model 14; and mass spectrometer, Varian Model M66. The dipole moment measurement was performed by Dr. R. L. Keiter using a transistorized heterodyne-beat apparatus. Vapor phase chromatographic analyses were performed on a Varian Aerograph A90-P3 gas chromatograph using helium pressure 40 p.s.i., flow rate 60 ml./min., filament current 150 milliamp, a 5 foot x 0.25 inch copper column, 10% SE-30 on 70-80 Anachrom ABS.

1,1-Dimethyl-3-phenylpyrazolium-5-oxide (**1**).

Method A.

A solution of 9.61 g. (0.05 mole) of freshly distilled ethyl benzoylacetate (**3**) and 6.47 g. (0.106 mole) of 1,1-dimethylhydrazine in 10 ml. of absolute methanol was heated under reflux in a system protected from moisture for 24 hours and then evaporated at 35° *in vacuo* to a bright orange oil. The oil was distilled *in vacuo* to give 8.5 g. (73%) of ethyl benzoylacetate dimethylhydrazone, b.p. 127-140° (0.70 mm.), and a higher boiling fraction, b.p. 150-160° (1.1 mm.), which crystallized upon standing at room temperature for a day.

An analytical sample of ethyl benzoylacetate dimethylhydrazone (**4**) was prepared by preparative vapor phase chromatography (injector temperature 212°, column 168°, detector 231°, collector 208°); ir, 1655 (C=N), 1730 (ester C=O) and three bands at 2775, 2820 and 2855 cm^{-1} due to the C–H stretching of the *N*-methyl groups (14); and mass spectrum where the molecular ion peak at m/e 234 (M) was the strongest peak and major fragments occurred at 178, 163, 135, 108, 96, and 70.

Anal. Calcd. for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.70; N, 11.96. Found: C, 66.90; H, 7.97; N, 12.04.

The crystalline product (**1**) from the higher boiling fraction was triturated with ether and purified by sublimation *in vacuo* (~ 80° at 1.1 mm.) to afford 0.1 g. (2.8%) of colorless needles, m.p. 135.0-135.5°, identical with **1** from Method B. Compound **1** is soluble in water, ethanol and benzene and is stable in air and light at room temperature

Method B.

A mixture of 3.2 g. (0.0136 mole) of ethyl benzoylacetate dimethylhydrazone (**4**) and 3.0 g. (0.016 mole) of methyl *p*-toluenesulfonate was stirred for 20 hours at 55-65° in a system protected from moisture. On cooling to room temperature the fine colorless crystals which formed were collected by filtration and recrystallized twice from cyclohexane to afford 1.50 g. (58%) of **1**, m.p. 135.0-135.5°; ir (potassium bromide), 3110 (m), 1730 (s) and 1710 (s) cm^{-1}; uv (cyclohexane), λ max 236, 285 and 320 (ε = 25,000, 3,300 and 7,500); nmr (deuteriochloroform) δ 3.11 (6H, s, dimethylamino protons), 4.76 (1H, s, vinyl proton) and 7.72 (5H, m, phenyl protons); mass spectrum m/e 188 (M), 173, 151, 145, 116, 102, 100, 89, 86, 77, 58, 57, 51, 43. Precise mass spectral data for four ions are: 100.060 (calcd. for $C_4H_8N_2O$, 100.065), 86.043 (calcd. for $C_3H_6N_2O$, 86.048), 58.052 (calcd. for $C_2H_6N_2O$, 58.053) and 57.058 (calcd. for C_3H_7N, 57.057).

Anal. Calcd. for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.30; H, 6.63; N, 14.75.

After the mother liquor had stood at room temperature for two days, additional solid precipitated. Recrystallization of this material from dichloromethane-methanol gave colorless crystals of 1,1,1-trimethylhydrazinium *p*-toluenesulfonate (**5**), m.p. 217-219°; ir (potassium bromide) 3270 and 3180 (N–H stretching), and 1625 cm^{-1} (N–H bending); nmr (deuterium oxide peaks reported in parts per million downfield from DSS as internal standard) δ 2.40 (3H, s, methyl protons on aromatic ring), 3.33

(9H, s, trimethylammonium protons), 7.33 (d, 2H, J = 8.5 Hz aromatic protons), and 7.73 (d, 2H, J = 8.5 Hz, aromatic protons).

Anal. Calcd. for $C_{10}H_{18}N_2O_3S$: C, 48.76; H, 7.36; N, 11.37; S, 13.02. Found: C, 48.70; H, 7.35; N, 11.35; S, 12.96.

The Reaction of 1,1-Dimethyl-3-phenylpyrazolium-5-oxide (**1**) with Methanol.

A small amount of compound **1** was dissolved in methanol and allowed to stand at room temperature for two days during which time the solution changed from colorless to light yellow. The methanol was removed at room temperature *in vacuo* to give a yellow liquid, methyl benzoylacetate dimethylhydrazone (**6**): ir, 2855, 2820 and 2775 (due to C–H stretching of *N*-methyl groups) (14), 1730 (ester C=O) and 1655 cm^{-1} (C=N); nmr (deuteriochloroform), singlets at δ 2.46 and 2.55 (5.7H, dimethylamino protons), 3.01 (0.5H, s, dimethylamino protons in unreacted **1**), singlets at 3.63 and 3.68 (3H, *O*-methyl protons), 3.97 (1.1H, s, methylene protons), 4.69 (0.4H, s, vinyl proton) and 7.39 (5H, m, phenyl protons).

Anal. Calcd. for $C_{12}H_{16}N_2O_2$: C, 65.41; H, 7.34; N, 12.72. Found: C, 65.13; H, 7.07; N, 12.47.

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