# A $^{15}N$ Isotope Tracer Study on 3-Anilino-1-phenyl-2-pyrazolin-5-one

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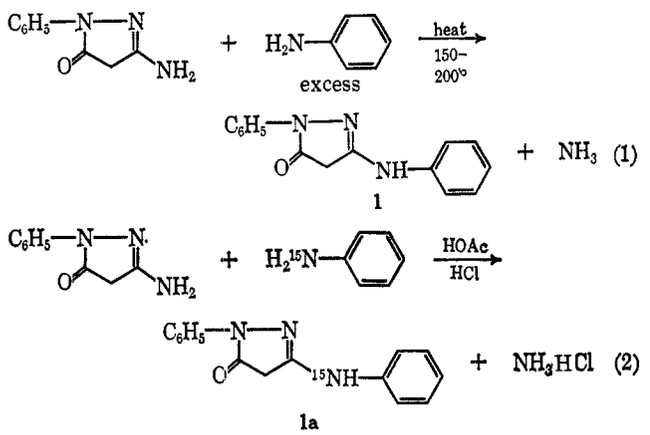
Certain pyrazolin-5-ones have found use in medicine as analgesics and antipyretics and in color photography as magenta dye formers.[2] An important addition to this last class of compounds has been the 3-anilino-1-aryl-2-pyrazolin-5-ones. The simplest example of this group, 3-anilino-1-phenyl-2-pyrazolin-5-one, was first synthesized by Weissberger[3] in the manner shown by eq 1. The purpose of the present work was to determine the tautomeric forms of **1** in solvents of different polarities and to show some relationships between the tautomers of **1** and those of other 2-pyrazolin-5-ones.

We have synthesized **1a** by an improved method (eq 2) from aniline containing more than 90% $^{15}N$ isotope. In this preparation, equivalent amounts of reactants were refluxed in acetic acid containing 10% aqueous hydrochloric acid. This method gave a clean anilinopyrazolinone in 30% yield; the ammonia formed as a by-product was isolated as ammonium chloride. Compound **1a** had the same melting point and infrared spectrum as the unlabeled material.




Mass spectrometric analysis of labeled and unlabeled compounds showed that **1a** contained more than 95% labeled material of mol wt 252, *i.e.*, 1 mass unit (mu) higher than the unlabeled sample. Moreover, a similar analysis of the recovered ammonium chloride showed no nitrogen-15 beyond its natural abundance. These results indicate that the 3-amino group in the starting pyrazolinone was displaced by the labeled aniline (eq 2). Further analysis of the fragmentation pattern of **1a** showed that the nitrogen-15 was located only at the 3-anilino position. The mass spectra of **1** and **1a** contained metastable ion peaks which indicated that the pyrazolinone ring opened in a one-step cleavage to give the fragments $C_6H_5NHC_2H_2$, 118.0655 mu (calcd, 118.0657 mu) and $C_6H_5{}^{15}NHC_2H_2$, 119.0628 mu (calcd, 119.0627 mu), respectively.[4] In the absence of any ion rearrangements these fragments probably originated from the anilino moiety and carbon atoms 3 and 4 of the pyrazolinone ring.

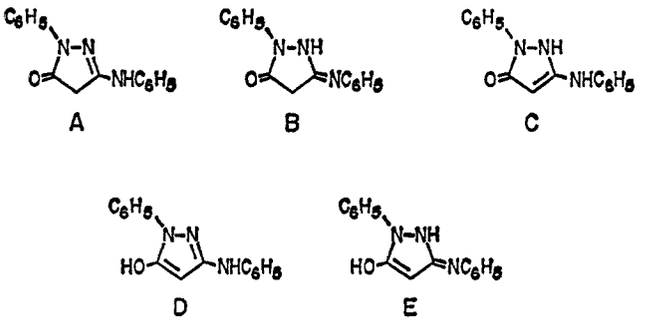



Figure 1.—Possible tautomeric forms of 3-anilino-1-phenyl-2-pyrazolin-5-one.

The relative abundance of the various tautomeric forms of pyrazolin-5-ones has been the subject of much work[5] since Knorr's synthesis[6] of the first example of this class. Some of the possible tautomeric forms (A–E) of **1** are shown in Figure 1. With the knowledge that **1a** was enriched with more than 95% nitrogen-15 at the 3-anilino site, we analyzed the nmr spectra of **1** and **1a** in the hope of determining the preferred tautomeric form(s) in solvents of different polarities, namely, deuterated chloroform, pyridine, and DMSO.

Typical nmr spectra of **1** and **1a** are shown for their DMSO-$d_6$ solutions in Figure 2. For the unlabeled compound, **1**, the methylene proton peak at 3.85 ppm and the aromatic proton peaks at 7–8 ppm are easily distinguishable. An olefinic proton, if present, would absorb upfield from the aromatic grouping. The single peak at 9.45 ppm is assigned to an N–H resonance.

Integration gave a good 1:10:2 ratio for one nitrogen-bonded proton to ten aromatic protons to two methylene protons. The methylene proton ratio plus the absence of an olefinic resonance peak shows that there is very little carbonyl enolization, even though the methylene protons rapidly exchange with deuterium oxide. Since the spectra in both chloroform and pyridine showed similar results, we must conclude that C, D, and E do not exist in detectable concentrations.

The choice between forms A and B was determined by the splitting of the $^{15}N$–H resonance into a doublet[7] in the nmr spectrum of **1a** (Figure 2). Since there is no evidence of a $^{14}N$–H resonance in this spectrum, all of the nitrogen-bonded protons must be attached to the 3-anilino nitrogen exclusively. This evidence, coupled with the lack of an olefinic resonance peak, means that form A correctly represents the only detectable species of **1** and **1a** in solution in the three solvents used.

A summary of the pertinent nmr data is given in Table I. The data for compound **1** show that the methylene peak position has remained fairly constant over the range of experimental conditions, but the position of the $^{14}N$–H peak has varied from 6.4 ppm in

(1) To whom inquiries should be sent.

(2) R. H. Wiley and P. Wiley, "Pyrazolones, Pyrazolidones, and Derivatives," A. Weissberger, Ed., John Wiley and Sons, Inc., New York, N. Y., 1964, Part 2, Chapters 1 and 2.

(3) A. Weissberger and D. Porter, *J. Amer. Chem. Soc.*, **64**, 2133 (1942).

(4) One referee commented that the $C_6H_5NHC_2H_2$ fragment could be the protonated ketenimine $C_6H_5NH{=}C{=}CH_2{}^+$.

(5) (a) A. R. Katritzky and F. W. Maine, *Tetrahedron*, **20**, 299 (1964); (b) J. Elguero, R. Jacquier, and G. Tarrago, *Bull. Soc. Chim. Fr.*, 3780 (1967).

(6) L. Knorr, *Ber.*, **16**, 2597 (1883).

(7) (a) J. D. Roberts, G. Binsch, J. B. Lambert, and B. W. Roberts, *J. Amer. Chem. Soc.*, **86**, 5564 (1964); (b) A. K. Bose and I. Kugajevsky, *Tetrahedron*, **23**, 1489 (1967); (c) G. Dudek and E. P. Dudek, *J. Amer. Chem. Soc.*, **86**, 4283 (1964).

chloroform to 9.45 ppm in DMSO and 10.3 ppm in pyridine. These shifts in the N–H resonance probably reflect the differences in hydrogen bonding of **1** with these solvents.

TABLE I

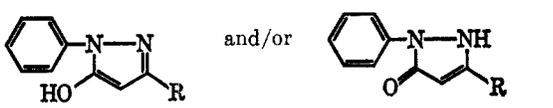
THE NMR SPECTRA[a] OF 3-ANILINO-1-PHENYL-2-PYRAZOLIN-5-ONE

| Solvent | Temp, °C | δ,[b] ppm CH₂ | δ,[b] ppm NH | Relative area[c] of NH peak | $J$ $^{15}$NH |
|---|---|---|---|---|---|
| **Unlabeled Compound (1)** | | | | | |
| $CDCl_3$[d] | 50 | 3.63 | 6.40 | ... | |
| Pyridine-$d_5$ | 38 | 3.7 | 10.3 | 0.854 | |
| Pyridine-$d_5$ | 100[e] | 3.7 ± 0.05 | 9.5 ± 0.1 | ... | |
| DMSO-$d_6$ | 38 | 3.85 | 9.45 | 1.0 | |
| **Labeled Compound (1a)** | | | | | |
| $CDCl_3$[d] | 30 | 3.61 | 6.35[f] | 1.0 | 92 ± 1 |
| $CDCl_3$[d] | 50 | 3.63 | 6.45 | ... | 91.5 ± 0.5 |
| Pyridine-$d_5$ | 38 | 3.74 | 10.3 | 0.88 | 91.5 ± 0.5 |
| Pyridine-$d_5$ | 100[e] | 3.70 ± 0.03 | 9.6 ± 0.1 | ... | 91 ± 1 |
| DMSO-$d_6$ | 38 | 3.87 | 9.43 | 0.96 | 92 ± 0.5 |

[a] Recorded on the Varian A-60 nmr spectrometer. [b] δ is parts per million downfield from internal TMS. [c] The $CH_2$ area is assigned the value 2.0. [d] Spectra in $CDCl_3$ were recorded at 100 MHz on the Varian HA-100. [e] At 100° the peaks had broadened considerably and are less exact. [f] Center of gravity positions.

TABLE II

THE PER CENT TAUTOMER CONTENT[a] OF SOME 3-SUBSTITUTED PYRAZOLIN-5-ONES IN DMSO-$d_6$




| R | Tautomer, % | δ, ppm =CH- | δ, ppm -CH₂- |
|---|---|---|---|
| $CH_3$ | 74[b] | 5.43 | 3.55 |
| $NHCCH_3$ (O) | 70 | 6.03 | 4.08 |
| $NHCC_6H_5$ (O) | 67 | 6.32 | 4.30 |
| $NHC_6H_5$ | 0 | ... | 3.85 |

[a] These values were obtained by integration of the respective olefinic proton peaks. [b] An accuracy within ±5% is expected.

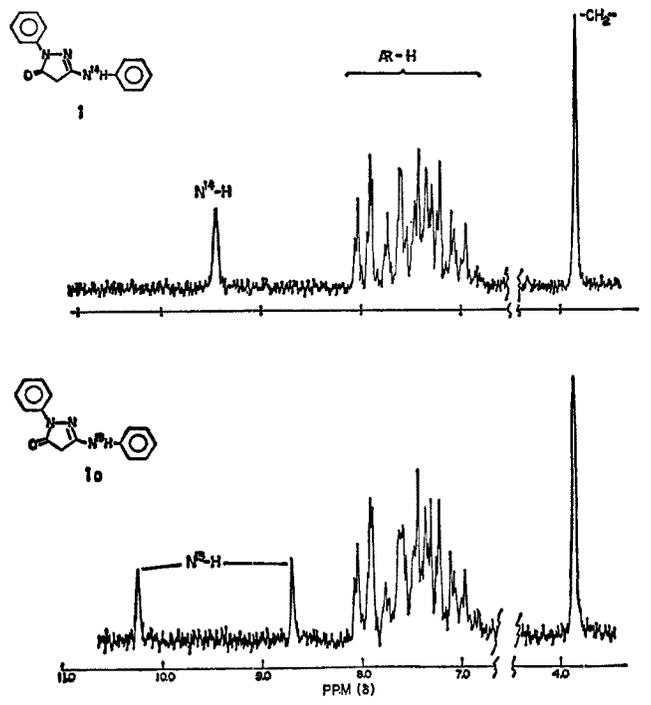



Figure 2.—Nmr spectra of **1** and **1a** in *ca.* 10% (w/v) DMSO-$d_6$ solution.

The large $^{15}$N–H coupling constant (91–92 Hz) in pyridine remained relatively unchanged when the solution was heated to 100°, although at this temperature the resonance peaks had broadened considerably. However, when this heated solution was cooled to 38°, the nmr spectrum was identical with that of a freshly prepared solution.

The lack of detectable tautomerization in DMSO-$d_6$ for compound **1** and **1a** is contrary to what we have observed for some other pyrazolinones in this solvent. As shown in Table II, some other pyrazolin-5-ones, which differ from **1** in the nature of the 3-substituent, exist substantially in another tautomeric form(s).

In summary, we have synthesized **1a** with a labeled nitrogen exclusively at the 3-anilino site and shown by mass spectrometry a decomposition path for this compound under electron impact. By means of nmr spectroscopy we have shown that **1** and **1a** exist in only one detectable tautomeric form in chloroform, pyridine, and DMSO solutions.

### Experimental Section

All melting points are uncorrected. Infrared spectra were obtained with a Beckman IR-12 grating spectrophotometer. Samples were examined as potassium bromide pressings. The solutions of **1** and **1a** were *ca.* 10% (w/v) in DMSO and pyridine and about 5% in chloroform. A 60° sector type of mass spectrometer fitted with an all-glass inlet system was operated at 230°. The exact masses were measured on a Consolidated Electrodynamics 21-110-B high-resolution mass spectrometer.

**3-$^{15}$N-Anilino-1-phenyl-2-pyrazolin-5-one (1a).**—A solution of 0.94 g (5.4 mmol) of 3-amino-1-phenyl-2-pyrazolin-5-one (EK 3841) in 10 ml of acetic acid containing 1 ml of concentrated hydrochloric acid and 0.5 g (5.3 mmol) of $^{15}$N-aniline[8] was refluxed for 1 hr. On standing, the solution deposited a white solid which, after it had been washed with water and recrystallized from acetonitrile, gave 0.4 g (30%) of **1a** as a white solid, mp 218–219°. Unlabeled **1** melted at 218–219° (lit.[3] mp 219–221°). The infrared spectrum of **1a** was identical with that of **1**.

**Isolation of Ammonium Chloride.**—The filtrate from the reaction mixture was drowned in 100 ml of water. After the resulting solids were removed, 3 ml of concentrated hydrochloric acid was added, and the solution was evaporated under reduced pressure to a gummy solid. Trituration of this material with ethanol gave 0.05 g (0.9 mmol) of a white solid, mp >320°. The infrared and mass spectrograms of the residual material were identical with those of an authentic unlabeled sample of ammonium chloride.

**Registry No.**—**1**, 7186-66-5; **1a**, 16774-23-5.

(8) Obtained from Merck Sharpe and Dohme of Canada, Ltd.

## The Synthesis of *o*-Di-*t*-butyl Heteroaromatics

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The use of 3,3,6,6-tetramethyl-1-thiacycloheptane-4,5-dione (I) as the starting compound in the synthesis of several *o*-di-*t*-butyl heteroaromatics has been reported.[1,2] A Wittig reaction with diketone I gave 5-methoxymethylene-3,3,6,6-tetramethyl-1-thiacyclo-

(1) Ae. de Groot and Hans Wynberg, *J. Org. Chem.*, **31**, 3954 (1966).
(2) Ae. de Groot, Ph.D. Thesis, Groningen, 1967.