A Study of the Spectra and Acidity of 4,5-Dihydro-1*H*-benz[*g*]indazol-7-ol and 2,3a,4,5-Tetrahydro-7-hydroxy-3a-methyl-3*H*-benz[*g*]indazol-3-one (1)

*George X. Thyvelikakath (2), Linda J. Bramlett (2), Theodore E. Snider (2), Don L. Morris (2), Donald F. Haslam (3), Wesley D. White (2), Neil Purdie (2), N. N. Durham (3), and K. Darrell Berlin (2)**

Departments of Chemistry and Microbiology, Oklahoma State University, Stillwater, Oklahoma 74074

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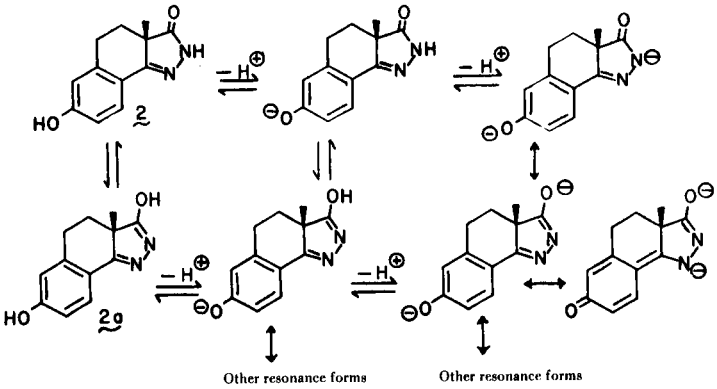
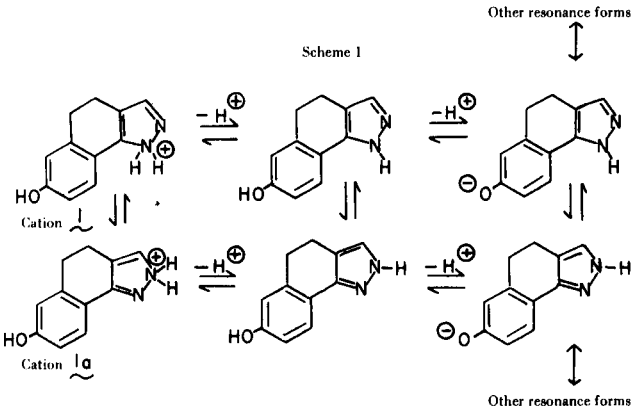
The synthesis of 2,3a,4,5-tetrahydro-7-hydroxy-3*H*-benz[*g*]indazol-3-one is recorded for the first time. Infrared, pmr, and uv spectral analysis of this pyrazolone and of 4,5-dihydro-1*H*-benz-[*g*]indazol-7-ol strongly support the presence of one tautomer in each case. Measurements of pK_a values are in agreement with the proposed tautomeric structures based upon comparisons with simpler model systems. The data are taken in aqueous solution since the compounds are soluble at 10^{-5} *M* and the results may more closely approximate that for the structure under physiological conditions.

Azasteroids and related polynuclear pyrazoles of similar structure have attracted attention for modified properties of naturally occurring steroids in chemotherapy (4-6). We recently found (7) that 4,5-dihydro-1*H*-benz[*g*]indazol-7-ol (**1**) inhibited growth of *Bacillus subtilis* W23 and *Escherichia coli*. We wish to report a spectral study of **1** and **2** (2,3a,4,5-tetrahydro-7-hydroxy-3*H*-benz[*g*]indazol-3-one), the synthesis of former being reported previously from this laboratory (8).



Scheme I

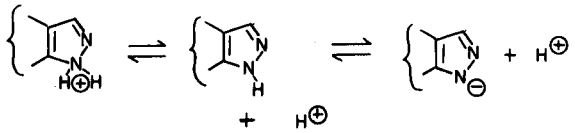


The possibility of tautomerism in both compounds exists, a situation documented in simpler systems (9). Thus, a spectral analysis of **1** was performed over a *p*H range of 3.2-9.6 in water. It was anticipated that introduction of the carbonyl group in the pyrazole ring (*i.e.* in **2**) would increase the acidity of the hydrogen on nitrogen. This is indicated by the large increase in ϵ max at 335 nm at *p*H 9.6 in the spectrum of **2**.

The absorption maxima, ϵ max, and *p*H values are given for **1** and **2** in Table I (also Figure 1). As clearly observed, the most significant observation in the spectrum of **1** is the absorption at 272.5 nm at *p*H 3.2 which disappears at *p*H 9.6 with appearance of strong absorption at 280 nm and concommitant loss of the shoulder at 294 nm. Formation of a phenoxide ion is reported to result in a bathochromic shift from 270 to 280 nm in water (10,11). Presumably, contrasting λ change at *p*H 9.6 and *p*H 3.2, the blue shift results from hydrogen bonding which lowers the energy of the n orbital. One might expect this absorption peak (at *p*H 3.2) to be found at a shorter wave length. However, nitrogen atoms present in the compound under investigation are potential chromophores which are effective in shifting the absorption towards the near visible and hence the peak's position may be justified. An additional longer wave-

length absorption (294 nm) identified (at *p*H 3.2 and *p*H 6.0) in the form of a "shoulder" may be due to n → π* transitions of the nitrogen electrons (10). Likewise, the bands at 205 and 207 nm are probably due to π → π* transitions in the benzene system (11).

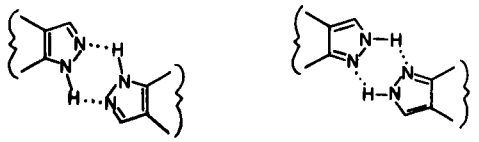
Titrations of aqueous solutions of **1** with standard, aqueous sodium hydroxide and standard aqueous hydrochloric acid revealed two inflections with pK_a values determined, to be at 9.1 and 3.7. Pyrazole has a reported pK_a of 2.5 (12) and phenol a value of 9.89 (12). Thus, a first approximation would assign the value of 3.7 to the ionization process involving the proton on nitrogen in



Cation 1 (or Cation 1a). The 9.1 value is likely due to the ionization of the phenolic proton or possibly the remaining proton on nitrogen although pyrazole is reported to have a "acidic" pK_a at about 14 (13).

Unfortunately, the uv spectrum of a suitable, structurally-related, model system could not be found for **1**. However, pmr analysis in pyridine-d_5 revealed a signal at δ 12.4 (m: N*H* and O-*H*, 2) indicating two acidic protons [other protons at δ 2.78 (broad, CH_2-CH_2, 4) and 6.78-8.12 (Ar-*H* and C=C-*H*, 4]. Thus, together these data support the structure but do not permit *unequivocal* evidence to eliminate the presence of tautomer **1a** near neutral *p*H.

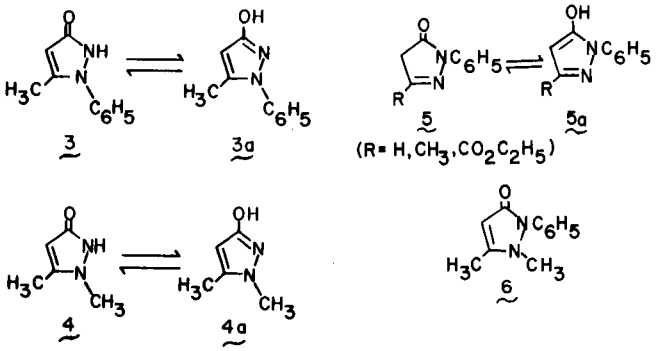
If dimer formation *via* H-bonding occurs, as was previously indicated from an infrared analysis of pyrazole (13,14), the difference in steric requirements for either dimer would probably not be great as estimated from Courtauld models. Also, pmr studies on a series of



1 1a

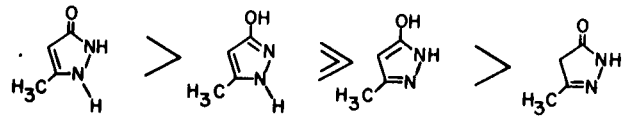
pyrazoles support dimers of pyrazole in deuteriochloroform and trichloroacetic acid (15). Intuitively, **1a** in water might expectedly be less stable than **1** since both multiple bonds in the smallest ring of **1a** are exocyclic to a six-membered ring.

As part of a study of heterosteroids and model systems, the synthesis of **2** provides a carbonyl group in the appropriate position of the smallest ring for biological activity and could promote enolization. In addition, the relationship of **2** to **1** in structure should permit identification of one tautomer since the bridgehead methyl group prevents formation of a double bond at position 3a. Although several careful studies have been made of the tautomerism in various pyrazolones (16-18), the closest model systems to **2** are **3** and **4** which are reported to exist in both enol and oxo forms in water *via* ir, uv, and pmr analysis. Acidity measurements in water gave pK_a values of 8.23 and 8.91 for **3** and **4**, respectively (17). An order of stability in water was given in a later paper

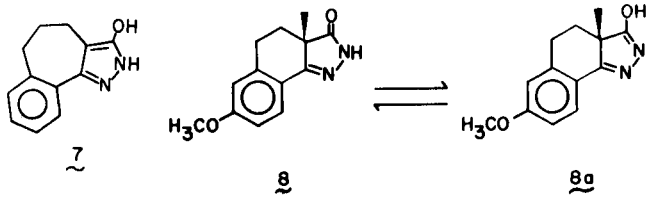


3 3a 5 5a (R= H, CH_3, $CO_2C_2H_5$) 6 4 4a

as shown below (18). ^{13}Cmr confirmed the existence of the enol **5a** rather than the oxo form **5** while nonenolizable **6** showed only a carbonyl carbon atom in DMSO as expected (19). A recent report tentatively suggests that compound **7** exists in the enol form in DMSO (pmr study),



(20). In a polar media, **7** is not expected to be a good candidate on the basis of the stability studies of pyrazalones reported early (18) although a broad two-proton signal was observed in the pmr spectrum for **7** at *ca.* δ

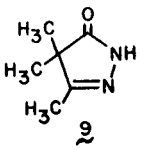


7 8 8a

10.65 (NH and OH) (pK_a = 9.69) (20).

Considering **2** and **2a** in our study, ir analysis (solid state) showed a strong peak at 1639 cm^{-1}. [This is a dramatic shift compared to the ether precursor **8** which had ν C=O = 1686 cm^{-1}.] The latter supports the oxo form **8** rather than the enol from **8a**. There is also a broad band from 2824-3125 cm^{-1}, with maxima at 2898, 3030, and 3125 cm^{-1} which support the presence of aliphatic

and aromatic C-H. For comparison compound **9** is reported (18) to have ν C=O = 1715 cm^{-1} in chloroform and a doublet in carbon tetrachloride at ν C=O 1734 and 1718 cm^{-1}. Since **2** has ν C=O = 1639



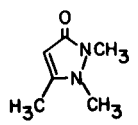
9

cm^{-1} (solid state), perhaps *H*-bonding dimers or higher order, polymeric type structures exist in the solid state as suggested for certain pyrazolones (17,18). Credence is lent to this tentative supposition by the high melting point (328°) with decomposition of **2**. Mass spectral analysis gave the correct m/e (216) for M^+ but dissociation of a dimer could have occurred in or near the ion source (250°) prior to decomposition.

Titration (in water) of **2** (or **2a**) revealed a pK_a of 8.7 which is surprisingly close to that of **7** (9.69) (19) and **3** (8.23) and **4** (8.91) (17). Recall the latter appear to exist as equilibrium mixtures, **3** ⇌ **3a** and **4** ⇌ **4a** (17). A tentative assumption is that the pK_a of 8.7 for **2** represents an average value not only for a tautomeric mixture (*H* on either of the two *N* atoms) but for including the phenolic proton too.

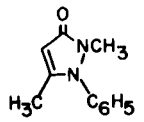
Pmr analysis of **2** in DMSO-d_6 revealed signals at δ 1.18 (CH_3, 3H), 2.52 (N-*H* and O*H*, 2H), 1.68-2.06 (CH_2, 2H), 2.84-3.12 (CH_2, 2H), and 6.68-7.52 (Ar*H*, 3H). This compares with **8** having signals (in pyridine-d_5) at δ 1.31 (CH_3, 3H), 1.62 (N*H*, 1H), 1.78-2.12 (CH_2, 2H), 2.76-3.08 (CH_2, 2H), 3.68 (OCH_3, 3H), and 6.77-7.94 (Ar-H, 3H). Deuterium oxide exchanged the protons in **2** at δ 2.52 and thus confirmed the assignment.

The ultraviolet spectrum (in tripled distilled water) of **2** gave absorption maxima of high intensity as shown in Table I. Good correlation of these intensities and maxima in the heterocyclic ring of **2** with data for known close model systems is difficult because of the additional absorption of the arene position of **2**. However, comparison of intensities for **10** (17) and **11** (17) contrasts somewhat with that for **12** (18). In aqueous media, a predominance of **12a** (~ 80%) was suggested (18).



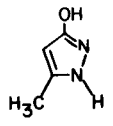
10

λ = 246.5 nm (ε, 9,570) [*p*H = 5; aq. buffer]

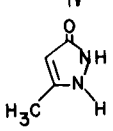


11

λ = 258.7 nm (ε, 11,750) [*p*H = 7; aq. buffer]



12



12a

λ = 238 nm (7,600) [*p*H = 5.2; aq. buffer]

TABLE I

Ultraviolet Absorption Data for **1** and **2** in Aqueous Medium at 10^{-5} *M*

	Wavelength	
1 *p*H	nm	ε max
3.20	205	5,803
	272.5	3,839
(shoulder)	294	2,366
6.0	205	6,607
	270	4,286
(shoulder)	294	1,696
9.6	207	5,803
	280	3,839
2		
3.7	202	14,664
	225	7,332
	300	13,254
7.5	202	14,946
	226	7,050
	307	12,126
9.6	206	13,254
	273	6,486
	335	18,612

In **2**, the maxima at λ = 225 nm (*p*H = 3.7) and at λ = 226 nm (*p*H = 7.5) have intensities close to that of **12a** at λ = 238 nm (*p*H = 5.2) as illustrated and are probably comparable on the reasonable assumption the maxima are due to $\pi \rightarrow \pi^*$ transitions. Since position 3a in **2** does not possess an enolizable proton, exact comparison of these tautomeric systems must be treated cautiously, however. This is reinforced by the recent work showing **5a** the preferred tautomer rather than **5**. Nevertheless, in **2** there is not a phenyl ring on nitrogen to provide any driving force to favor **2a** (as is in **5a** ⇌ **5**). Thus, taken on the whole, the evidence suggests tautomer **2** predominates over **2a** in the solid state and in aqueous solution.

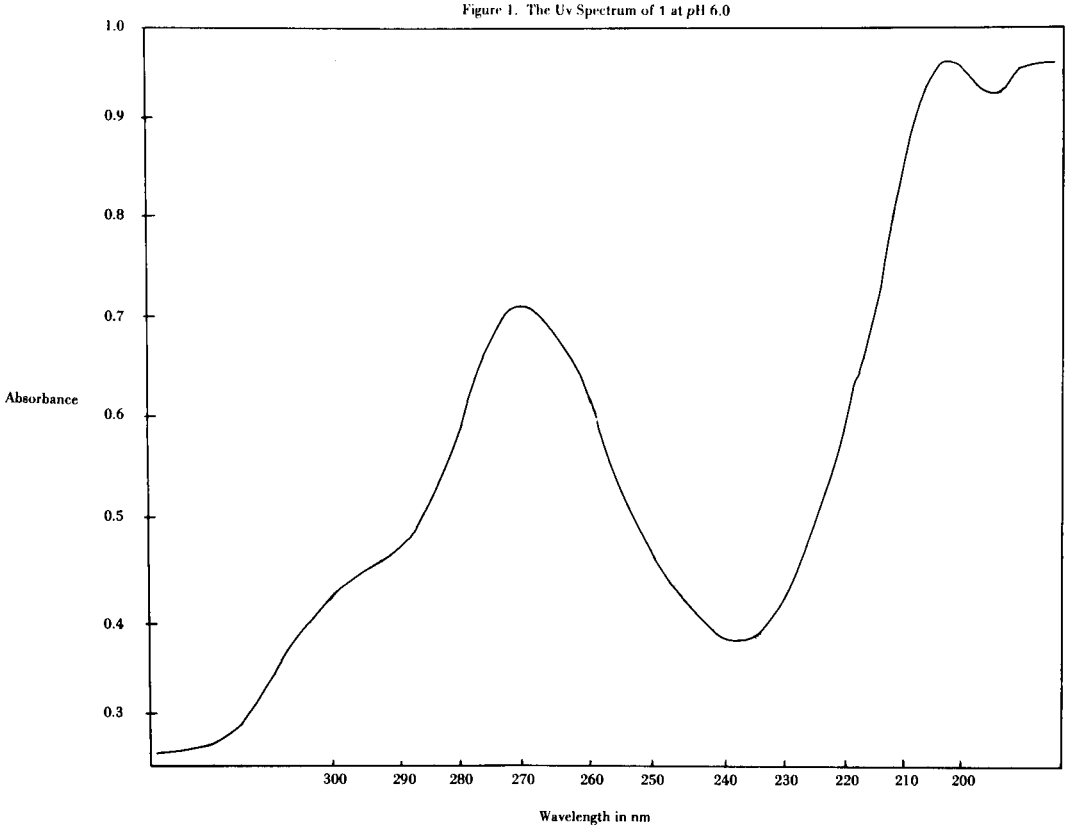
EXPERIMENTAL

Melting points were determined on a Hoover apparatus and are not corrected. Ir spectra were taken with a Beckman 5-A unit. Uv spectra were recorded on a Cary 14 spectrophotometer. Nmr spectra were obtained with a Varian Associates Model XL-100 with TMS as an internal standard.

Synthesis of **1** and **2**.

A mixture of 6-methoxytetralone (6.82 g., 0.388 mole), dimethyl carbonate (416 ml., 4.94 mole), and sodium methoxide (24.2 g., 0.448 mole) were boiled under nitrogen for 2.5 hours.

Figure 1. The Uv Spectrum of 1 at *p*H 6.0



A yellowish precipitate formed. The mixture was allowed to cool and 200 ml. of absolute methanol was added to dissolve the precipitate. A solution of methyl iodide (9.14 g., 0.644 mole) in 200 ml. of absolute methanol was added and the mixture was stirred overnight at room temperature. The mixture turned a greenish color. The mixture was then boiled for 10 minutes and neutralized with 2*N* acetic acid (*p*H ~ 6). Upon cooling, 6-methoxy-2-methyl-2-carbomethoxy-1-keto-1,2,3,4-tetrahydronaphthalene (**13**) crystallized as a yellow solid. Recrystallization from methanol gave 54 g. [82%, m.p. 91-92.5° (S.T.); recorded m.p. 91-92° (20)].

Purified **13** (14.8 g., 0.059 mole) with 95% hydrazine (19.2 g., 0.60 mole) was stirred at ambient temperature under nitrogen for 4.0 hours. As the mixture thickened, absolute methanol (*ca.* 50 ml.) and additional 95% hydrazine (*ca.* 5.0 g.) were added to keep the mixture fluid. At the end of the reaction period, distilled water (200 ml.) was added and the mixture was stirred for 45 minutes. The product was filtered and washed (3 x 100 ml. of water) to give 12.29 g. of 2,3a,4,5-tetrahydro-3a-methyl-7-methoxy-3*H*-benz[*g*]indazol-3-one (**8**) (90.5%, m.p. 217.5-218.5° . An analytical sample, purified by sublimation (178°, 0.1 mm., m.p. 218-219°), gave the following analysis.

Anal. Calcd. for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.12; N, 12.17. Found: C, 67.69; H, 6.22; N, 12.34.

Compound **8** (1.92 g., 0.0086 mole) was boiled with 48% hydrobromic acid (50 ml.) for 3.0 hours under nitrogen. Upon cooling, the solution was made strongly basic with 10% sodium hydroxide (*p*H = 9-9.5) and then filtered. The filtrate was then acidified with dilute hydrochloric acid and filtered to yield brownish crystals of 2,3a,4,5-tetrahydro-3a-methyl-7-hydroxy-3*H*-benz[*g*]indazol-3-one (**2**). These crystals were purified by successively (3-5 times) dissolving the compound in 10% sodium hydroxide and precipitating with dilute hydrochloric acid, m.p. 328° dec.

Anal. Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.66; H, 5.55; N, 12.96. Found: C, 66.29; H, 5.57; N, 12.78.

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