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Crystal and Molecular Structure of 3-Pyrazolone Derivatives. III.[1] 5-Amino-2-phenyl-4-(9*H*-thioxanthen-9-yl)-1,2-dihydro-3*H*-pyrazol-3-one

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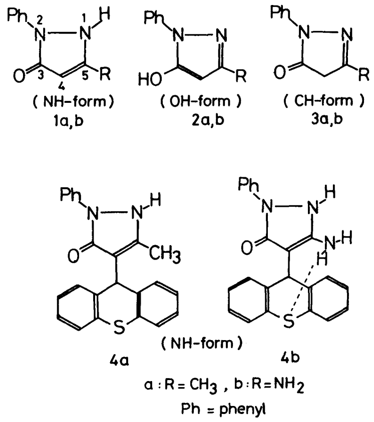
The crystal and molecular structure of 5-amino-2-phenyl-4-(9*H*-thioxanthen-9-yl)-1,2-dihydro-3*H*-pyrazol-3-one has been determined by the X-ray diffraction method to establish the predominant tautomeric form of the 3-pyrazolone ring in the solid state. The title compound, $C_{22}H_{17}N_3OS$, crystallizes in the space group $P2_1/c$ with lattice parameters: a=18.179(4), b=8.333(1), c=11.961(7) Å, β=95.88(3)°, and Z=4. The 5-amino group is intramolecularly hydrogen-bonded to the sulfur atom of the thioxanthene ring (N–H···S=3.284 Å). In the packing structure, molecules are linked to each other through hydrogen bonds between the NH of amino and C=O groups [2.849 Å] and the NH moiety and C=O group [2.939 Å] of the 3-pyrazolone ring.

3-Pyrazolone derivatives have important uses in medicine as analgesics and antipyretics and in color photography as magenta dye-formers.[2] The tautomerism in 2,5-disubstituted 3-pyrazolone[3–6] has been the subject of much work since Konn's synthesis[7] appeared as the first example of this class. In the course of studying the reactivity of 5-methyl- and 5-amino-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one, which has three possible tautomeric forms (designated as the NH-, OH-, and CH-forms (**1a,b**, **2a,b**, and **3a,b** in Scheme 1)), according to the position of the labile proton), it has been reported that these 3-pyrazolone derivatives undergo dehydration at the 4-position of the active methylene of the 3-pyrazolone ring with the OH group of 9*H*-xanthen-9-ol or 9*H*-thioxanthen-9-ol to form the condensed products (**4a,b**).[8] Generally, 3-pyrazolone derivatives[3,5] exist predominantly as the CH-form in nonpolar solvents, while the other tautomers, the OH- and NH-form, are formed as the polar character of the solvent is increased. On the other hand, in the crystalline state, additional tautomeric forms are expected to emerge due to the strong hydrogen bonding or other intermolecular forces. X-ray diffraction studies have elucidated that the preferred tautomeric form in the solid state of 5-methyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one is a 1:1 mixture of the NH- and OH-form(**1a** and **2a**),[9] its condensed product 5-methyl-2-phenyl-4-(9*H*-thioxanthen-9-yl)-1,2-dihydro-3*H*-pyrazol-3-one (**4a**),[8] the NH-form, and 5-amino-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one, the CH-form (**3b**).[1]

The purpose of the present work is to establish the three-dimensional structure and the preferred tautomeric form of 5-amino-2-phenyl-4-(9*H*-thioxanthen-9-yl)-1,2-dihydro-3*H*-pyrazol-3-one in the crystal, and to compare them with those of 5-amino-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one(**3b**) In the packing structure of **3b**, the molecules are linked to each other by two kinds of hydrogen bonds between the NH_2 and CO groups (2.995 and 3.170 Å) to form a two-dimensional hydrogen bond network parallel to the ac-plane, while the different hydrogen bonds could be expected from the NH_2 and CO groups of the title compound (**4b**). One of the main goals of this work was to examine the possibility of the presence of strong intramolecular hydrogen bonds between the NH_2 group and other intramolecular hydrogen bond acceptors in **4b**, because there are three hydrogen bond donors (NH_2 and NH of the 3-pyrazolone ring) in contrast to one acceptor of the C=O group requiring two hydrogen donors.



Scheme 1.

Experimental

The title compound (**4b**) was prepared by the method described previously,[8] and it was recrystallized by the slow evaporation of an EtOH–CH_3Cl solution at room temperature. The crystal used for the X-ray measurement was a cleaved piece with approximate dimensions of 0.20×0.25×0.30 mm. A preliminary examination of the crystal, carried out on a Rigaku automated, four-circle diffractometer, showed it to be monoclinic with the space group $P2_1/c$. The unit cell parameters at room temperature were refined by the least-squares fit using the Bragg angles of 24 reflections ($30° < 2\theta < 40°$).

Crystal Data: $C_{22}H_{17}N_3OS$, M 371.45, monoclinic, space group $P2_1/c$, a=18.179(4), b=8.333(1), c=11.961(7) Å, β=95.88(3)°, V=1802.3 Å^3, D_c=1.37 g cm^{-3} for Z=4, μ=16.8 cm^{-1}.

The intensity data were collected at room temperature on a diffractometer utilizing nickel-filtered Cu $K\alpha$ radiation (λ=1.54178 Å). The θ—2θ scan mode was employed. The scan rate was 6° $\min^{-1}$ in 2θ, and the scan range in θ was varied by 1.2°+0.15° $\tan\theta$. Backgrounds were counted for 5 s at both ends of the scan with an offset of 50% of the scan range from the calculated position of the $K\alpha$ peak. The intensities of the three standard reflections measured after every 57 reflections, showed a drop of 1% over the period of data collection, but no correction was made. A total of 2634 unique reflections was measured ($2\theta<125°$), of which 2342 were observed. The standard deviations in the structure amplitudes, $\sigma(F_o)$, were derived from the counting statistics. Lorentz and polarization corrections were applied, but no absorption correction was made.

Solution and Refinement of the Structure

The structure was solved by the direct method (MULTAN),[10] determining the phases of the 200 reflections with $|E_o|>1.84$. The E-map computed from the phases with the largest combined figure of merit (2.65) revealed all the non-hydrogen atoms. The structure was refined by the block-diagonal least-squares method. The function minimized was $\sum w(|F_o|-|F_c|)^2$, where $w=1$ for $0<|F_o|\leq 20$ and $w=(20/|F_o|)^{-2}$ for $|F_o|>20$. An initial refinement using individual isotropic temperature factors for the non-hydrogen atoms led to a conventional $R=(\sum||F_o|-|F_c||)/\sum|F_o|$ of 0.117. After successive refinement with anisotropic temperature factors for the non-hydrogen atoms, all the hydrogen atoms were readily located in the difference Fourier map; these atoms were then included in the further refinement with isotropic temperature factors. The efinement was completed after 6 cycles. The final values of R and $R_w=(\sum w|F_o|-|F_c|)^2/\sum w|F_o|^2)^{1/2}$ were 0.048 and 0.050 respectively. At the final cycle, the largest shift of any parameters of the non-hydrogen atoms was less than 10% of the standard deviations, while that of the hydrogen atoms was 13%. The largest peak in the final difference map, 0.2e Å^{-3}, was located near the sulfur atoms. The final atomic positional and thermal parameters* are given in Table 1. The atomic scattering factors for the S, O, and C atoms were taken from "International Tables for X-Ray Crystallography," (1974)[11a] while the factors for H were those of Stewart, Davidson and Simpson.[12] Computations were performed using the crystallographic program system *UNICS*.[13]

Table 1. Final Atomic Parameters of Non-Hydrogen Atoms, with Estimated Standard Deviations in Parentheses

$$B_{eq}=\frac{1}{3}(U_{11}+U_{22}+U_{33})$$

Atoms	x	y	z	B_{eq}/Å^2
N 1	0.1360(2)	−0.1918(4)	0.5894(3)	4.3
N 2	0.1238(2)	−0.2372(4)	0.4751(3)	3.8
C 3	0.1747(2)	−0.1568(4)	0.4161(3)	3.4
C 4	0.2251(2)	−0.0761(4)	0.4960(3)	3.2
C 5	0.2017(2)	−0.1070(5)	0.5995(3)	3.8
O 6	0.1731(2)	−0.1624(3)	0.3117(2)	4.2
N 7	0.2304(2)	−0.0660(5)	0.7047(3)	6.0
C 8	0.2915(2)	0.0146(4)	0.4618(3)	3.3
C 9	0.3628(2)	−0.0811(4)	0.4857(3)	3.5
C 10	0.3812(2)	−0.1957(5)	0.4078(3)	4.5
C 11	0.4441(3)	−0.2905(5)	0.4286(4)	5.5
C 12	0.4901(2)	−0.2714(5)	0.5271(4)	5.6
C 13	0.4738(2)	−0.1568(5)	0.6047(3)	4.9
C 14	0.4109(2)	−0.0615(4)	0.5834(3)	3.8
S 15	0.3957(1)	0.0841(2)	0.6860(1)	4.2
C 16	0.3410(2)	0.2258(4)	0.6065(3)	3.7
C 17	0.3424(3)	0.3824(5)	0.6480(3)	5.0
C 18	0.3010(3)	0.5002(5)	0.5904(4)	6.4
C 19	0.2593(3)	0.4621(5)	0.4903(4)	6.4
C 20	0.2575(2)	0.3056(5)	0.4491(3)	4.9
C 21	0.2977(2)	0.1838(4)	0.5076(3)	3.6
C 22	0.0504(2)	−0.2805(4)	0.4321(3)	4.0
C 23	−0.0094(2)	−0.2192(5)	0.4791(4)	6.0
C 24	−0.0805(3)	−0.2615(6)	0.4334(5)	8.1
C 25	−0.0901(3)	−0.3658(6)	0.3432(4)	7.5
C 26	−0.0300(3)	−0.4277(7)	0.2985(4)	7.3
C 27	0.0410(2)	−0.3866(5)	0.3430(3)	5.6

Results and Discussion

The molecular structure and the atom labeling of **4b** are presented by the *ORTEP*[20] drawing in Fig. 1. The bond distances and angles are given in Table 2. The present study has shown that the predominant tautomeric form of the title compound in the solid state adopts the NH-form (**4b**). The structure of the benzene rings in the peripheral of the 3-pyrazolone and in the thioxanthene rings has normal values [C–C$_{(av)}$=1.381 and 1.392 Å, and C–C–C$_{(av)}$=120.0°]. In Fig. 2, the geometry of the 3-pyrazolone ring observed in **4b** is compared with those of **1a**, **2a**, **3b**, and **4a**.[1,8,9] As may be seen in Fig. 2, the C–C and C–N bond distances in the 3-pyrazolone ring reflect

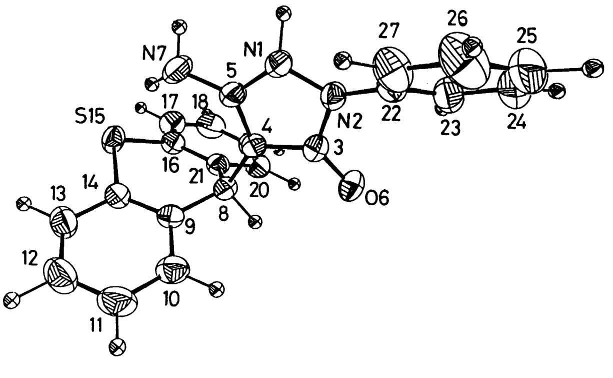


Fig. 1. Molecular structure (*ORTEP* drawing)[20] of the title compound (**4b**). Non-hydrogen atoms are drawn as thermal ellipsoids with 50 % probability level and hydrogen atoms as spheres of arbitrary radius.

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* Tables of the anisotropic thermal parameters, the coordinates of the hydrogen atoms, the observed and calculated structure factors and the bond distances involving hydrogen atoms are deposited at the Chemical Society of Japan, Document No. 8606.

Table 2. Bond Distances (l/Å) and Angles (ϕ/°) in **4b**, with Estimated Standard Deviations in Parentheses

(a) Bond lengths for non-hydrogen atoms

N 1-N 2	1.414(4)	N 1-C 6	1.382(4)	N 2-C 3	1.392(4)
N 2-C22	1.426(4)	C 3-O 6	1.247(4)	C 3-C 4	1.424(4)
C 4-C 5	1.375(4)	C 4-C 8	1.517(4)	C 5-N 7	1.356(4)
C 8-C 9	1.523(4)	C 8-C21	1.513(4)	C 9-C10	1.399(5)
C 9-C14	1.396(4)	C10-C11	1.391(5)	C11-C12	1.384(5)
C12-C13	1.385(5)	C13-C14	1.396(5)	C14-S15	1.767(3)
S15-C16	1.759(3)	C16-C17	1.396(5)	C16-C21	1.397(4)
C17-C18	1.378(5)	C18-C19	1.387(6)	C19-C20	1.394(5)
C20-C21	1.397(5)	C22-C23	1.374(5)	C22-C27	1.382(5)
C23-C24	1.395(5)	C24-C25	1.382(7)	C25-C26	1.365(6)
C26-C27	1.389(6)				

(b) Bond angles

C 5-N 1-N 2	105.7(2)	C22-N 2-C 3	125.8(3)
C22-N 2-N 1	117.7(2)	C 3-N 2-N 1	108.4(2)
C 4-C 3-O 6	129.6(3)	C 4-C 3-N 2	107.6(2)
O 6-C 3-N 2	122.8(3)	C 8-C 4-C 5	131.7(3)
C 8-C 4-C 3	122.0(2)	C 5-C 4-C 3	106.2(3)
N 7-C 5-C 4	131.6(3)	N 7-C 5-N 1	117.2(3)
C 4-C 5-N 1	111.2(3)	C21-C 8-C 9	112.9(2)
C21-C 8-C 4	113.4(2)	C 9-C 8-C 4	112.0(2)
C14-C 9-C10	117.8(3)	C14-C 9-C 8	122.9(3)
C10-C 9-C 8	119.3(3)	C11-C10-C 9	121.1(3)
C12-C11-C10	120.2(3)	C13-C12-C11	119.8(3)
C14-C13-C12	119.9(3)	S15-C14-C13	116.6(2)
S15-C14-C 9	122.2(2)	C13-C14-C 9	121.2(3)
C16-S15-C14	101.9(1)	C21-C16-C17	121.6(3)
C21-C16-S15	121.9(2)	C17-C16-S15	116.5(2)
C18-C17-C16	119.9(3)	C19-C18-C17	119.4(4)
C20-C19-C18	120.7(4)	C21-C20-C19	120.7(3)
C20-C21-C16	117.6(3)	C20-C21-C 8	118.7(3)
C16-C21-C 8	123.7(3)	C27-C22-C23	120.8(3)
C27-C22-N 2	118.6(3)	C23-C22-N 2	120.6(3)
C24-C23-C22	119.1(4)	C25-C24-C23	120.2(4)
C26-C25-C24	120.1(4)	C27-C26-C25	120.3(4)
C26-C27-C22	119.5(3)		

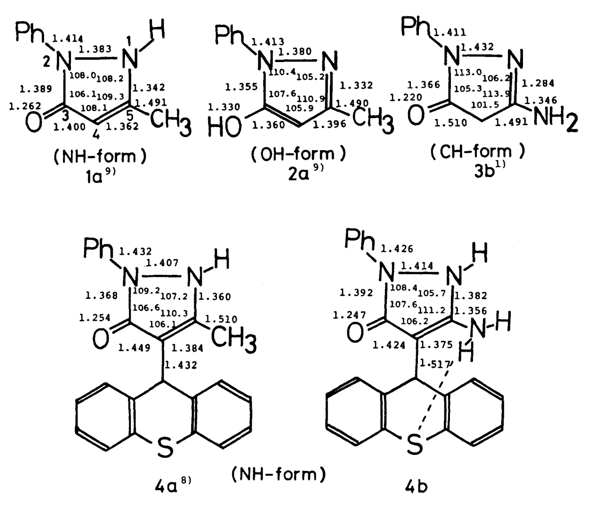


Fig. 2. The selected bond distances and angles of the 3-pyrazolone ring of **1a**, **2a**, **3b**, and **4a,b**. The stadard deviations are described in Table 2.

their predominant tautomeric forms, which are slightly shorter or longer than the normal value (1.44—1.53 and 1.35—1.36 Å respectively).[11b)] The N1-C5, C4-C5, and C3-C4 bond distances are significantly different from each other in the NH-, OH-, and CH-forms (**1a**, **4a,b**, **2a**, and **3b**), showing the differences in the degree of the delocalization of the π electrons in the 3-pyrazolone ring. The C4-C5 bond distances are shorter in the NH-form (1.362, 1.384(6), and 1.375(4) Å for **1a**, **4a**, and **4b** respectively) than in the OH-form (1.396 Å for **2a**) and the CH-form (1.491(5) Å for **3b**), indicating the double-bond character of the C4-C5 in the NH-form. On the other hand, the short C3-C4 distances in the NH-form (1.400, 1.449(6), and 1.424(4) Å for **1a**, **4a**, and **4b** respectively), compared with the value of the single bond (1.510(5) Å) in the CH-form, appears to be caused by the conjugation with the C4-C5 double bond. The N1-C5 bond distances in the OH- and

CH-forms (1.332 and 1.284(5) Å for **2a**, and **3b** respectively) are shorter than the corresponding values of the NH-form (1.342, 1.360(6), and 1.382(4) Å for **1a**, **4a**, and **4b** respectively), reflecting their double-bond character. The N1–N2, N2–C3 (in the NH- and CH-form), and C3–OH bonds (in the OH-form) have typical single bond distances in the ranges of 1.383(5)—1.432(5), 1.355(5)—1.392(4), and 1.330(5) Å respectively. The C=O distances in the NH-form (**1a** and **4a,b**), 1.262, 1.254(6), and 1.247(4) Å respectively, are slightly longer than that (1.220(5) Å) in the CH-form(**3b**). These facts show the electron delocalization of the (O=C–C=C–) conjugation system in the NH-form.

Regarding the hydrogen bond, 5-methyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one exists in two crystallographycally independent molecules in the crystal, one in the NH-form (**1a**) and the other in the OH-form (**2a**), which are characterized by the hydrogen bonds of O–H···O (2.48 Å) and N–H···N (2.80 Å)[9] respectively. The **4a** molecules are packed with hydrogen bonds between the NH and CO groups (2.799(6) Å) to form endless chains along the c-axis in the crystal.[8] In the case of 5-amino-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (**3b**), however, the molecules are linked together by two kinds of hydrogen bonds between the NH_2 and CO groups (2.955(5) and 3.170(5) Å) to form a network of hydrogen bonds parallel to the ac-plane.[1] It is shown that one NH of the amino group in **4b** is intramolecularly hydrogen bonded to the sulfur atom of thioxanthene (N–H···S= 3.284(3) Å). Another NH of the amino group forms an intermolecular hydrogen bond with the CO group of the neighbouring molecule (2.849(4) Å), which is also linked to the NH group of the 3-pyrazolone ring (2.939(3) Å) to form a sheet parallel to the ac-plane, as is shown in Fig. 3.

Scheme 2 shows the four chemical species (three neutral tautomers-**1a,b**, **2a,b**, and **3a,b**, and one cation-**5a,b**) in the equilibrium state in an acid solution. The structure of the 5-substituted 3-pyrazolone corresponding to **5a,b** has been established by IR, UV, and NMR spectroscopy,[14] which has shown that all three tautomeric form (OH-, NH-, and CH-forms) possess a common cation (**5a,b**). The complete equations for these equilibria have been given by a simple equation, because the CH-form is much less basic than the OH- and NH-forms.[15] As the molecular structures of **1a**, **2a**, **3b**, and **4a,b** have been established by the X-ray diffraction method, a plausible mechanism by which the tautomers are trapped in the crystal is as follows. Each NH- or OH-form is trapped in crystals by shifting the equilibrium from the common cation (**5a,b**) by electron transfer, as is shown in Scheme 2. The thioxanthene-bearing forms (**4a,b**) exist as the NH-form is a result of the removal of a proton from the protonated carbonyl group, as is shown in Scheme 2. The CH-form of **4a,b** can not participate in hydrogen bondings in crystals like the **1a** and **2a** types because of the low basicity of the pyridine-like nitrogen atom in the 3-pyrazolone ring.

The best least-squares planes, together with the displacement of atoms from the best planes and the dihedral angles between these planes were calculated. It is well known that the dihedral angle (butterfly angle) of the related thioxanthene nucleus is quite sensitive to alterations in the electronegativity of its substituents,[16] as may be seen in the change in the dihedral angle on going from phenothiazine (158.5°) to thioxanthen-9-ol (132.4°). The value (148.6°) of **4b** is in good agreement with the 143.4° value of **4a**

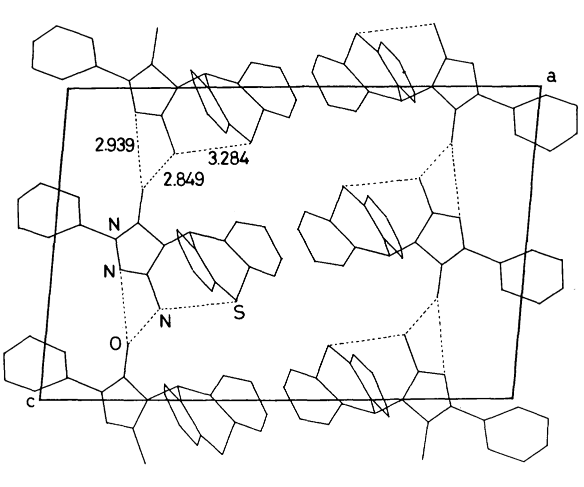
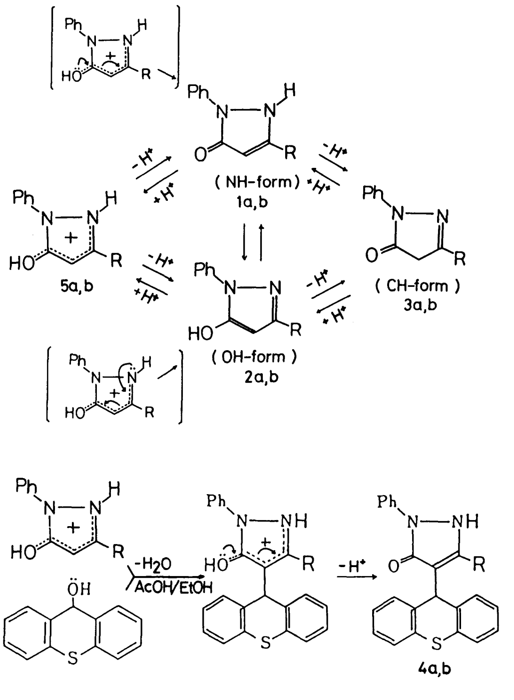


Fig. 3. Crystal structure projected along the b axis. Hydrogen bonds between molecules are shown by broken lines.



Scheme 2.

within the limits of experimental error. A final point of particular interest concernes the dihedral angles between the planes of 3-pyrazolone and phenyl rings; 47.0° for **4b**, which are to be compared with the values 47.8°, 23°, 38°, and 1.7° for **4a**, **1a**, **2a**, and **3b** respectively. These values show that the dihedral angles are different in spite of having the same tautomeric form, and that of the CH-form is significantly different. The conformation of the phenyl group in the present compounds may be mainly affected by the packing of molecules in the crystal.

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