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A novel solid-state Michael addition between pyrazolone **1** and 4-arylidenepyrazolones **2** at ambient temperature produced Michael adducts, 4,4'-arylidenebis(3-methyl-1-phenyl-5-pyrazolones) **3**. Pyrazolones **3** formed salts **4** with Cu^{2+} in solution, indicating the enolic structure of the pyrazolone rings. The reactivity of **2** with **1** is discussed in terms of the electronic and steric effects of the substituent on the arylidene group of compounds **2**. Pyrazolone **1** also underwent the solid state Michael addition reaction with maleimide at 100° to give the adducts **7**, **8** and **9**.

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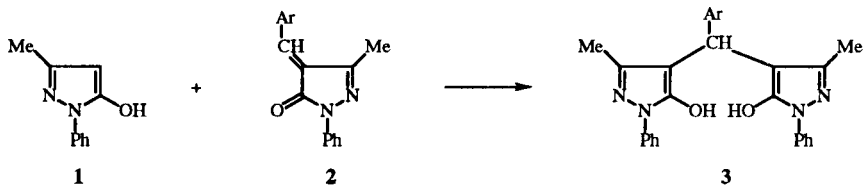
Many organic reactions occur more efficiently in the solid state than in solution [1] and in some cases even more selectively, using various types of organic reactions [2,3], including oxidation [4], reduction [5], rearangement [6], coupling reactions [7], aldol condensations [8] and the Michael reaction [9]. Enantioselective organic reactions are also achieved in an inclusion crystal prepared by complexation of a prochiral reactant and an optically active host compound [9,10,11]. In continuation of our work on solid state organic syntheses [8,12,13], we have found that the condensation reactions of the aromatic aldehydes [14] and ketones [15] with 3-methyl-1-phenyl-5-pyrazolone proceed more efficiently and selectively in the solid state than in solution.

3-Methyl-1-phenyl-5-pyrazolone **1**, like a common 1,3-dicarbonyl compound, can easily undergo various reactions as a nucleophile in solution [16], such as substitution, condensation and the Michael reaction [17]. Now we apply the solid-state reaction to the Michael addition reaction of 3-methyl-1-phenyl-5-pyrazolone (**1**) occurring more readily in the solid state than in solution.

Scheme 1



1 **2** **3**

2a:	Ar = Ph	**e:**	Ar = 4-IC_6H_4	**i:**	Ar = 4-$O_2NC_6H_4$	**m:**	Ar = 4-HOC_6H_4
b:	Ar = 4-FC_6H_4	**f:**	Ar = 4-$BzOC_6H_4$	**j:**	Ar = 3-$O_2NC_6H_4$	**n:**	Ar = 4-HO,3-$MeOC_6H_3$
c:	Ar = 4-ClC_6H_4	**g:**	Ar = 4-MeC_6H_4	**k:**	Ar = 2-$O_2NC_6H_4$		
d:	Ar = 4-BrC_6H_4	**h:**	Ar = 4-$MeOC_6H_4$	**l:**	Ar = 4-$Et_2NC_6H_4$		

Results and Discussion.

The solid-state Michael reactions of 4-arylidene-3-methyl-1-phenyl-5-pyrazolones **2a-n** and 3-methyl-1-phenyl-5-pyrazolone **1** were carried out by grinding a mixture of **2** and excess **1** and allowing it to stand at room temperature for a certain numbers of hours. The Michael adducts **3a-n**, 4,4'-arylidenebis(3-methyl-1-phenyl-5-pyrazolone) (Scheme 1), were the sole products obtained in reasonable yields. The results were compared to those obtained in chloroform solution as shown in Table 1.

The reaction proceeded more efficiently in the solid state than in the solution phase. In chloroform solution, only compounds **2** having an electron-withdrawing substituent on the *para*- or *meta*-position, **2c, 2d, 2f, 2i** and **2j**, could afford the Michael reaction adducts **3c, 3d, 3f, 3i** and **3j**, respectively. This is reflected by the determination of the equilibrium constants shown in Scheme 2. Using representative 4-substituted arylidenepyrazolones **2** the apparent equilibrium constants were determined in chloroform.

Compounds **2** and **3** have different λ_{max}, the concentration changes of **2** can be reflected by the absorbance (A) changes of **2** at λ_{max}. The K_{obs} is obtained from the initial concentration (C^2_o) and the equilibrium concentration (C^2_{eq}) of **2** (See Experimental).

The reactivity of **2** both in the solid state and in solution was affected by the electronic and steric natures of the Ar group in compound **2**. The electron-withdrawing group on the *para*-position of the arylidene group **2c, 2d, 2f, 2i** and **2j** leads to an increase in reactivity, and the electron-donating group of **2l** and **2m** makes the electron density on the methylidene carbon too high to be attacked by nucleophile **1**. If there is a substituent on the *ortho*-position, even an electron-witdrawing group such as that in **2k**, the addition reaction did not take place most probably due to the steric hindrance of the *ortho*-substituent for **1** attacking the methylidene carbon. From the above observations, it can be seen that the substituent effects observed in the case of **2c,**

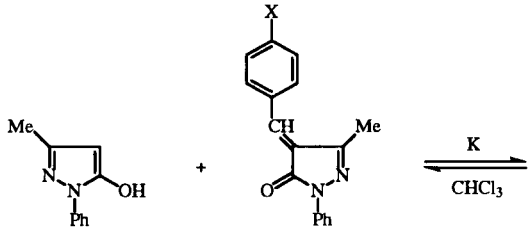
Table 1

The Michael Addition of **1** and **2a-n** in the Solid State and in Solution

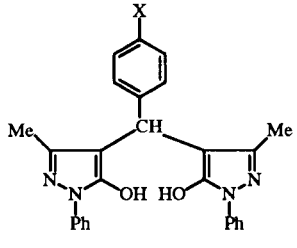
Product **3**	Physical Aspect	mp of **3** [a] (°C)	grinding time [b] minutes	reaction time [b] hours	yields of **3** in the solid state	yields of **3** in solution
3a,	white solid	150 (148)	30	15	50	no reaction
3b,	white solid	182 (183)	30	15	59	no reaction
3c,	white solid	210 (210)	30	15	72	30
3d,	white solid	215 (216)	30	15	67	32
3e,	white solid	210 (211)	40	15	47	no reaction
3f,	white solid	214 (213)	30	20	66	25
3g,	white solid	203 (204)	40	20	49	no reaction
3h,	white solid	148 (147)	40	20	43	no reaction
3i,	pale-yellow solid	229 (231)	20	10	78	45
3j,	pale-yellow solid	154 (152)	20	10	75	40
3k,		60	30	no reaction	no reaction	
3l,		60	30	no reaction	no reaction	
3m,		60	30	no reaction	no reaction	
3n,	white solid	201 (199)	30	15	65	no reaction

[a] Literature mp in parentheses [14]; [b] Accumulated time; [c] Based upon the amount of compound **2** consumed.

Scheme 2



1 **2**



3

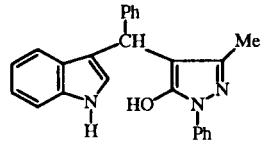
	2g	**2a**	**2c**	**2i**
X:	MeO	H	Cl	NO_2
K_{obs}	15.6	31.8	35.7	185.0

2d, 2f, 2i and **2j** (higher reactivity) and in the case of **2k** (no reactivity) showed the same tendencies both in the solid state and in solution.

Products **3** were identical with the corresponding enol products **3** obtained from the direct condensation of aromatic aldehydes and **1** in the solid state [14].

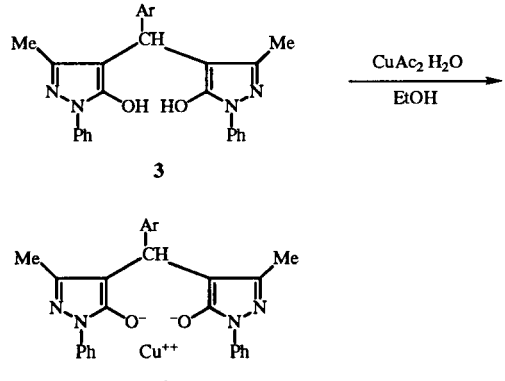
In order to obtain further information on the enolic structure of **3**, the complexation reaction of **3a-n** with Cu^{2+} was investigated. In ethanol solution, **3** and copper acetate ($Cu(OAc)_2$) rapidly formed cupric salts **4a-n** as brown precipitates (Scheme 3), but other transition metal ions [*e.g.* $Co(OAc)_2$, $Ni(OAc)_2$, $Mn(OAc)_2$, $Cr(OAc)_2$, $Zn(OAc)_2$, *etc.*] gave no precipitates of salts under similar conditions. According to the elemental analyses of **4a-n**, the ratio of Cu and **3** was 1:1.

The ir spectra of **4a-n** and **3a-n** are listed in Table 2. For compounds **3**, the broad band which appeared around 2660-2500 cm^{-1} was assigned as the strongly H-bonded enolic OH due to cooperative proton transfer [18] and the absorption around 1400 cm^{-1} as the bending vibrations of enolic =C-O-H [19] while the spectra of **4a-n** did not have these two characteristic absorption bands, indicating that the acidic H of the enolic OH no longer existed in compounds **4**. Furthermore, the ir spectrum of compound **5** (See Experimental) containing



5

Scheme 3



3

4

Table 2

The structure analyses of **4**

4 (Formula)	Yield (%)	Elemental analysis [a] C	H	N	Cu	IR of **4** (cm^{-1})				IR of **3** [14] (cm^{-1})	
a	92	65.01	4.21	11.09	12.98	3058	1598	1565	2590	1597	1406
$C_{27}H_{22}N_4O_2Cu$		65.12	4.45	11.25	12.76	1499	753	695	1289	743	
b	93	62.61	3.92	10.58	12.66	3066	1598	1565	2510	1594	1572
$C_{27}H_{21}FN_4O_2Cu$		62.85	4.10	10.86	12.31	1499	1220	695	1402	1280	745
c	92	60.72	3.89	10.22	12.13	3041	1598	1567	2515	1597	1578
$C_{27}H_{21}ClN_4O_2Cu$		60.90	3.98	10.52	11.93	1499	755	694	1406	1294	747
d	94	56.08	3.48	9.52	11.42	3066	1598	1565	2500	1590	1572
$C_{27}H_{21}BrN_4O_2Cu$		56.21	3.67	9.71	11.01	1499	752	695	1400	1291	742
e	91	51.81	3.29	8.84	10.72	3066	1598	1565	2520	1590	1572
$C_{27}H_{21}IN_4O_2Cu$		51.98	3.39	8.98	10.18	1499	752	695	1399	1289	741
f	94	67.41	4.39	8.96	11.01	3060	1599	1568	2500	1598	1504
$C_{34}H_{28}N_4O_3Cu$		67.59	4.67	9.27	10.53	1501	1226	695	1365	1247	
g	90	65.34	4.48	10.59	12.32	3050	1598	1565	2510	1590	1572
$C_{28}H_{24}N_4O_2Cu$		65.68	4.72	10.94	12.41	1499	753	695	1399	1285	745
h	91	63.51	4.43	10.49	12.50	3066	1598	1547	2660	1595	1575
$C_{28}H_{24}N_4O_3Cu$		63.69	4.58	10.61	12.03	1499	1245	695	1400	1244	750
i	94	59.40	3.49	12.58	11.98	3061	1599	1518	2540	1594	1515
$C_{27}H_{21}N_5O_4Cu$		59.72	3.90	12.90	11.70	1499	1346	696	1412	1345	1294
j	93	59.57	3.74	12.73	12.11	3065	1598	1528	2550	1598	1500
$C_{27}H_{21}N_5O_4Cu$		59.72	3.90	12.90	11.70	1499	1350	695	1410	1348	748
n	93	61.72	4.30	10.27	11.96	3350	3061	1597	3205	2560	1597
$C_{28}H_{24}N_4O_4Cu$		61.81	4.45	10.30	11.68	1315	1125	684	1415	1253	754

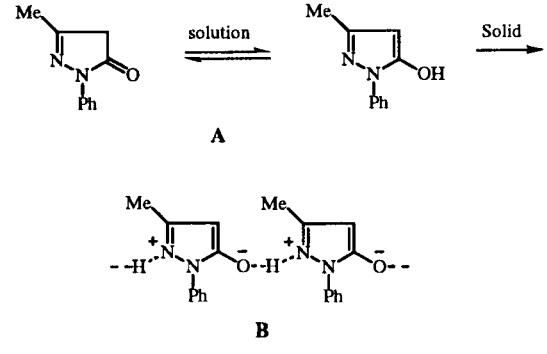
[a] Each lower line shows calculated value.

two different heterocyclic groups shows that the H-bond no longer exists, the characteristic broad absorption of H-bonded enolic OH around 2500 cm^{-1} for **2** is not found, although the pyrazolone ring is still in the enolic form; (no carbonyl absorption is evident). In **5**, it is unlikely that an intramolecular H-bond will be formed. From the above evidence it is suggested that the pyrazolonyl groups in compounds **3** exist in the enolic form.

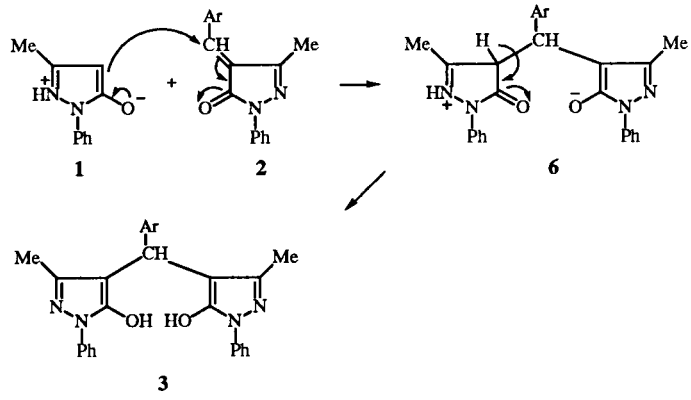
The most characteristic chemical property of **1** is the nucleophilic reactivity of the C-4 carbon atom, which is seen from its facile Michael addition reaction, and all of the reactions occurs on C-4 to give the 4-pyrazolonyl products due to the acidity of the C-4 hydrogen atom [16]. Compound **1** tautomerizes in solution as a result of hydrogen transfer; the tautomeric equilibrium is affected by the polarity of the solvent (Scheme 4, A) [18]. For example, in chloroform or dioxane **1** exists preferably in the 5-ketone form and in pyridine, the 5-hydroxyl form is dominant [20]. The X-ray crystallographic analysis of **1** has shown that **1** occurs in the enol form and the molecules of **1** are linked together by H-bonds (N...H...O) 1.66, 1.56Å) (Scheme, 4 B) [21]. The spectral data also indicate that in the solid state, **1** exists as a zwitterionic structure [20]. This zwitterionic structure plays an important role in the solid-state Michael addition reaction of **1**.

Generally speaking, the reactivity of the Michael addition of conjugated unsaturated compounds (acceptor) is influenced by the polarity of its carbon-carbon double

Scheme 4



Scheme 5



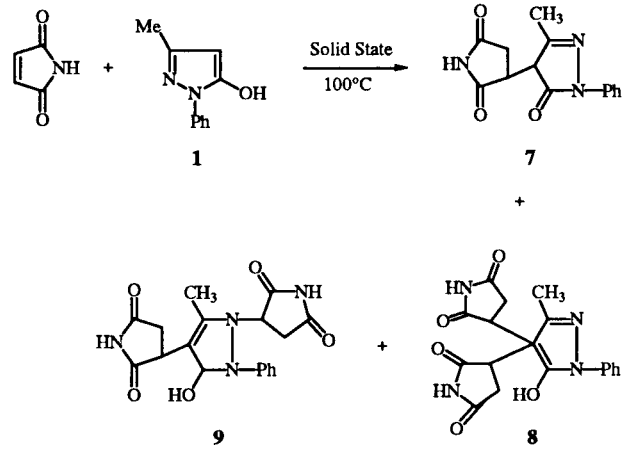
bond [22]. The arylidenepyrazolones **2**, where the α,β-unsaturated carbonyl group has a lactam character, possess a polar C=C bond and can undergo Michael-type addition reaction in solution [22]. Accordingly, the Michael reaction between **1** and **2** might proceed *via* the nucleophillic attack of the C-4 atom of **1** to the enone system of **2**.

The structure of the dipolar intermediate **6** has already been proposed for the Michael-type addition reactions of some enamines to arylidenepyrazolones [23]. With the proposed course of the reaction, the substituent effects on the reactivity of **2** are manifested.

Maleimide and pyrazolone **1** did not undergo the solid state Michael addition reaction at ambient temperature, but at a higher temperature (100°) the reaction occurred smoothly to give the Michael adducts, a 1:1 adduct **7** and 2:1 adducts **8** and **9**. Isomeric **8** and **9** were distinguished by their proton nmr spectra. Since the two maleimide groups are attatched to the same carbon atom of compound **8**, the two CH protons have the same chemical shifts (t, δ = 4.02, J = 7.1). On the other hand, the two maleimide groups in compound **9** are at different positions, one at C-4, the other at N-2. Thus the signals of the two CH_2 protons appear with different shifts, 2.65 ppm (d, J = 7.1) and 3.10 ppm (d, J = 7.1).

Maleimide, where the C=C bond conjugated with two carbonyl groups has a high electrophilicity, can similarly undergo the Michael-type reaction with pyrazolone **1** to result in the formation of the Michael adduct **7** followed by its further Michael addition to maleimide to give **8** and **9**.

Scheme 6



1 **7** **9** **8**

EXPERIMENTAL

All melting points were uncorrected; the ir spectra were measured with a NICOLET 170SX FT-ir spectrophotometer in potassium bromide. The ^1H nmr spectra were determined with a JEOLFX-90Q spectrometer in dimethyl-d_6 sulfoxide. The mass spectra were recorded on a 7070E-HE spectrometer, and the uv spectra were determined on a Schimadzu UV-240 UV-VIS spectrophotometer. Elemental analyses were performed on a YANACO CHN CORDER MT-3 analyzer.

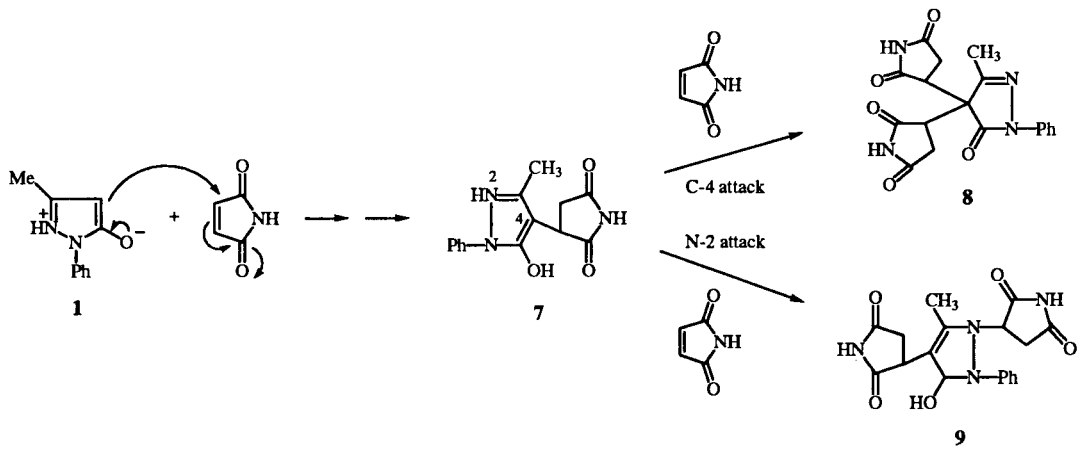
Solid-state Michael Addition Reaction of **1** and **2a-n**.

A mixture of **2** (1 mmole) and excess **1** (3 mmoles) was ground with an agate mortar and pestle and allowed to stand at room temperature for a specified number of hours. Then the mixture was washed with chloroform to remove colored materials to give a white solid which was recrystallized from methanol to give Michael adducts **3a-n**, 4,4'-arylidenebis(3-methyl-1-phenyl-5-pyrazolones). They were characterized by ir, ^1H nmr and elemental analyses and were identical with the authentic samples obtained previously [14] (Table 1).

The Michael Addition Reaction of **1** and **2** in Chloroform Solution.

A solution of **2** (2 mmoles) and **1** (6 mmoles) in chloroform (10 ml) was allowed to stand at ambient temperature for 48 hours. The crystals of the Michael adducts **3** which formed in some cases were filtered, washed with chloroform and recrystallized by methanol. The results are shown in Table 1.

Scheme 7



1 **7** **8** **9**

The Solid State Michael Addition Reaction of **1** and Maleimide.

Maleimide (0.20 g, 2 mmoles) and **1** (0.35 g, 2 mmoles) were ground thoroughly and reacted at 100° for 1 hour. Then the reaction mixture was dissolved in chloroform and separated by silica gel preparative tlc using ethyl acetate-chloroform (v/v = 2:1) as eluant. The products **7, 8** and **9** were obtained in 45%, 22% and 22% yield, respectively.

4-(2'-Maleimidyl)-3-methyl-1-phenyl-5-pyrazolone (**7**).

This compound was obtained as a colorless solid, mp 224-226°; ir: νNH 3170 (s), νCO 1778 (m), 1713 (s), 1622 (s) cm^{-1}; uv [ethanol, λ_{max}, (log ε)]: 247.1 nm (4.12), 275.0 nm (2.61); ^1H nmr (dimethyl-d_6 sulfoxide): δ 2.12 (s, 3H, CH_3), 2.80 (d, J = 7.1 Hz, 2H, CH_2), 3.76 (t, J = 7.1 Hz, 1H, CH), 4.96 (br, OH), 7.00-7.92 (m, 5H, phenyl protons), 11.2 ppm (s, 1H, NH); ms: m/z 271 (M^+), 185 (4-methylidenepyrazolone$^+$) 174 (pyrazolone **1**).

Anal. Calcd. for $C_{14}H_{13}N_3O_3$: C, 61.98; H, 4.83; N, 15.49. Found: C, 62.15; H, 4.70; N, 15.35.

4,4-Di(2-maleimidyl)-3-methyl-1-phenyl-5-pyrazolone (**8**).

This compound was obtained as a colorless solid, mp 233-235°; ir: νNH 3296 (s), νCO 1770 (m), 1721 (s) cm^{-1}; uv [ethanol, λ_{max}, (log ε)]: 242.7 nm (4.11), 273.0 nm (2.23); ^1H nmr (acetone-d_6): δ 2.21 (s, 3H, CH_3), 2.87-3.00 (m, 4H, $2CH_2$), 4.02 (t, J = 7.1Hz, 2H, 2CH), 7.38-7.85 (m, 5H, phenyl protons), 11.56 ppm (br, s, 2H, NH); ms: m/z 368 (M^+), 271 (M^+ -maleimide), 173 (pyrazolone$^+$), 97 (maleimide).

Anal. Calcd. for $C_{18}H_{16}N_4O_5$: C, 58.69; H, 4.38; N, 15.21. Found: C, 58.65; H, 4.68; N, 15.26.

2,4-Di(2-maleimidyl)-3-methyl-1-phenyl-5-pyrazolone (**9**).

This compound was obtained as a colorless solid, mp 238-240°; ir: νNH 3247 (s), νCO 1778 (s), 1713 (s) cm^{-1}; uv [ethanol, λ_{max}, (log ε)]: 243.9 nm (4.10), 279.3 nm (2.45); ^1H nmr (acetone-d_6): δ 2.22 (s, 3H, CH_3), 2.65 (d, J = 7.1 Hz, 2H, CH_2), 3.10 (d, J = 7.1Hz, 2H, CH_2), 4.02-4.18 (m, 2H, 2CH), 7.20-7.86 (m, 5H, phenyl protons), 11.48 (s, 1H, NH), 11.52 ppm (s, 1H, NH); ms: m/z 368 (M^+), 271 (M^+ -maleimidyl), 174 (pyrazolone$^+$), 97 (maleimide).

Anal. Calcd. for $C_{18}H_{16}N_4O_5$: C, 58.69; H, 4.38; N, 15.21. Found: C, 59.03; H, 4.47; N, 15.50.

The Reaction of **3a-n** and Cu^{2+}. The Formation of Copper Salts **4a-n**.

A solution of cupric acetate monohydrate (0.5 mmole) in ethanol (15 ml) was added dropwise into an ethanol solution containing **3** (1 mmole) while stirring. A brown precipitate formed immediately. After stirring for 0.5 hour, the precipitate was separated by centrifugation, washed with ethanol, 95% ethanol, water, 95% ethanol and ethanol in 30 ml portions successively, and dried. The salt **4** was obtained as a brown solid. The results including the data of ir and elemental analysis of **4a-n** are listed in Table 2. With a similar procedure other metallic salts, such as cobaltous acetate, nickelous acetate tetrahydrate, manganous acetate tetrahydrate, chromous acetate monohydrate, and zinc acetate dihydrate did not precipitate their salts.

Determination of the Equilibrium Constants Between **1**+**2** and **3**.

A series of solutions of **1** and **2** in different initial molar ratios (C^1_0:C^2_0 = 0.00:1.00, 0.25:1.00, 0.50:1.00, 0.75:1.00, 1.00:1.00, 1.50:1.00) with C^2_0 = 5.0 x 10^{-5} mol•l^{-1} were prepared and allowed to stand for 3 days at room temperature (30°) to reach equilibrium. The absorbances (A) of the solutions were determined in the uv spectrophotometer at λ_{max} (nm) of **2**. According to the equation $C^2 = A/\varepsilon$, the ε of **2** was obtained from the solution of $C^1 = 0.00$, and the equilibrium concentrations of **1, 2** and **3** (C^1_{eq}, C^2_{eq} and C^3_{eq}) in each solution were calculated from A_{eq} of the solution. The equilibrium constants K_{obs} were obtained from $K_{obs} = C^3_{eq}/C^1_{eq} \cdot C^2_{eq}$.

1-(5'-Hydroxyl-3-methyl-1-phenyl-4-pyrazyl)-1-(3'-indolyl)-phenylmethane (**5**).

A mixture of **2a** (1 mmole) and excess indole (3 mmoles) was ground with an agate motar and pestle for 30 minutes and allowed to stand at room temperature for 15 hours. The mixture was thoroughly washed with methanol to leave **5** as a colorless solid, mp 236°; ir: νOH (and NH) 3410 (s), νC=N (cyclic) 1601; ^1H nmr (acetone-d_6): δ 1.80 (s, 3H, CH_3), 5.54 (s, 1H, C-H), 6.78-7.97 (m, 15H, phenyl protons), 10.65 ppm (s, 1H, NH); ms: (FAB) m/z 380 (M+1), 263 (M-indole+1), 206 (M-pyrazolone+1).

Anal. Calcd. for $C_{25}H_{21}N_3O$: C, 79.13; H, 5.58; N, 11.07. Found: C, 78.96; H, 5.47; N, 10.92.

Acknowledgment.

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