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Physicochemical Properties of Isomeric Azines of 3-Acetyl-4-hydroxy-2-methoxy-4-phenylcrotonic Acid Lactones[1)]

TAKUSHI KURIHARA,* KEIKO NASU, MASATOSHI INOUE, and TOSHIMASA ISHIDA

Osaka College of Pharmacy, 2-10-65, Kawai, Matsubara, Osaka 580, Japan

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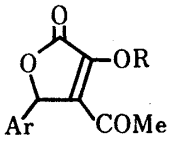
X-Ray crystallographic analyses of two isomeric azines of 3-acetyl-4-(2-chlorophenyl)-4-hydroxy-2-methoxycrotonic acid lactones (**5b** and **6b**), which were prepared by reaction of **1b** with hydrazine dihydrochloride, were carried out. The stereochemical difference between **5b** (red needles) and **6b** (yellow needles) is mainly in the =N–N= bonding mode; this group takes the completely planar conformation in **5b**, and the twisted conformation in **6b**. From the results of energy calculations, thermal analyses, and epimerization reactions, it could be concluded that the yellow crystals (**6**) are structurally more stable than the red crystals (**5**).

Keywords——isomeric azine of 3-acetyl-4-hydroxy-2-methoxy-4-phenylcrotonic acid lactone; X-ray analysis; Newman projection; thermogravimetry; differential thermal analysis

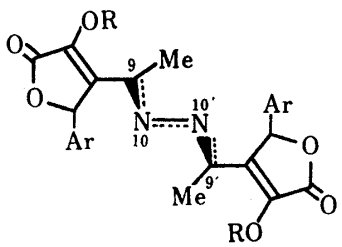
Previously, we reported[2)] that substituted benzaldehydes reacted with ethyl 2,4-dioxovalerate in the presence of piperidine to give 3-acetyl-2,4-dihydroxy-4-phenylcrotonic acid lactones (**1a**—**d**), and showed that these lactones exist as 3-benzylidene-2,4-dioxovaleric acid structures in polar solvents. It is well known[3)] that one of the major methods of pyrazole synthesis involves the reaction of a 1,3-difunctional compound, such as β-diketone, β-keto ester, or β-keto nitrile, with hydrazine or its analog. Among them, ethyl acetoacetate gives a mixture of the azine of ethyl acetoacetate and 3-methylpyrazolone when treated with hydrazine.[4)] We reported[5)] that the reaction of benzylideneacetylacetones with hydrazine dihydrochloride in acetonitrile gave 4-benzylidene-3,5-dimethyl-4*H*-pyrazoles. The present paper describes the results of the reaction of crotonic acid lactones (**1a**—**d**) with hydrazine dihydrochloride.

Synthesis

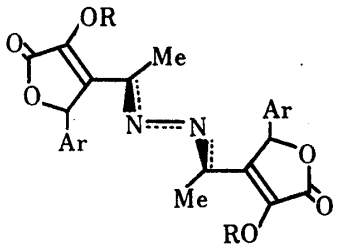
Addition of hydrazine dihydrochloride ($NH_2NH_2 \cdot 2HCl$) to an aqueous acetonitrile (70%) solution of **1a** at room temperature and further stirring of the mixture for 5 d gave a yellow



1a—d : R=H
2a—d : R=Me



3a—d : R=H
5a—d : R=Me



4b : R=H
6a—d : R=Me

a : Ar=phenyl
b : Ar=2-chlorophenyl
c : Ar=3-nitrophenyl
d : Ar=4-methylphenyl

Chart 1

Table I. Yields and Product Ratios of the Two Isomeric Azines

Starting material	Yield (%)	Product ratio of azines
1a	80.1	**3a** only
1b	94.1	**3b** : **4b** = 55 : 45
1c	74.8	**3c** only
1d	78.6	**3d** only
2a	73.8	**5a** : **6a** = 70 : 30
2b	96.3	**5b** : **6b** = 50 : 50
2c	95.2	**5c** : **6c** = 60 : 40
2d	89.7	**5d** only

Table II. Physical and Analytical Data for Azines

Compound No.	Appearance	mp (°C) (Recrystn. solv.)	Formula	Analyses (%) Cacld (Found) C	H	N
3a	Yellow	190—191 (DMF–H_2O)	$C_{24}H_{20}N_2O_6$	66.64 (66.64	4.66 4.67	4.66 6.61)
3b	Yellow	187—189 (MeOH)	$C_{24}H_{18}Cl_2N_2O_6 \cdot MeOH$	56.29 (56.30	4.15 4.09	5.25 5.43)
4b	Yellow	184—185 (MeCN)	$C_{24}H_{18}Cl_2N_2O_6$	57.49 (57.62	3.62 3.88	5.59 5.64)
3c	Yellow	165—166 (DMF)	$C_{24}H_{18}N_4O_{10} \cdot DMF$	54.45 (54.43	4.23 4.27	11.76 11.54)
3d	Yellow	179—181 (MeOH)	$C_{26}H_{24}N_2O_6 \cdot H_2O$	65.26 (65.43	5.48 5.34	5.86 5.85)
5a	Red	183—185 (AcOEt)	$C_{26}H_{24}N_2O_6$	67.81 (67.90	5.25 5.14	6.08 6.21)
6a	Yellow	187—189 (MeOH)	$C_{26}H_{24}N_2O_6$	67.81 (68.09	5.25 5.08	6.08 6.22)
5b	Red	190—192 (AcOEt)	$C_{26}H_{22}Cl_2N_2O_6$	58.99 (59.21	4.19 3.98	5.29 5.10)
6b	Yellow	187—188 (AcOEt)	$C_{26}H_{22}Cl_2N_2O_6$	58.99 (59.01	4.19 4.27	5.29 5.30)
5c	Red	187—188 (DMF–H_2O)	$C_{26}H_{22}N_2O_{10}$	56.73 (56.51	4.03 4.11	10.18 10.37)
6c	Yellow	189—190 (MeCN)	$C_{26}H_{22}N_2O_{10}$	56.73 (56.84	4.03 4.21	10.18 10.24)
5d	Red	165—166 (MeOH)	$C_{28}H_{28}N_2O_6$	68.84 (68.76	5.78 5.60	5.73 5.60)
6d	Yellow	189—191 (Benzene)	$C_{28}H_{28}N_2O_6$	68.84 (68.93	5.78 5.82	5.73 5.61)

crystalline substance $C_{24}H_{20}N_2O_6$ (**3a**) in 80.1% yield as the sole product. On the other hand, treatment of the corresponding methyl ether **2a** with $NH_2NH_2 \cdot 2HCl$ in methanol at room temperature gave rise to an orange solution which showed two components on thin layer chromatography (Al_2O_3/benzene); red needles $C_{26}H_{24}N_2O_6$ (**5a**) and yellow needles $C_{26}H_{24}N_2O_6$ (**6a**) were isolated in a ratio of 7: 3 in 73.8% yield. Reaction of **3a** with diazomethane gave **5a.** Analogously, when an aqueous acetonitrile solution of **1b** was treated with $NH_2NH_2 \cdot 2HCl$ at room temperature for 6 d, yellow crystals, which consisted of two substances in a ratio of 55: 45 as judged from the proton magnetic resonance (PMR) spectrum, were obtained in 94.1% yield. This crystalline mixture could be partially separated into **3b** and **4b** by fractional recrystallization from acetonitrile. Similarly, reaction of **2b** with $NH_2NH_2 \cdot 2HCl$ in methanol afforded a mixture of **5b** (red needles) and **6b** (yellow needles) in a ratio of 50: 50 in 96.3% yield. Compound **3b** or **4b** also reacted with diazomethane to give **5b** or **6b,** respectively.

The physical and analytical data, and also the results of the reactions of *m*-nitrophenyl and *p*-tolyl derivatives (**1c**, **1d**, **2c**, and **2d**) with $NH_2NH_2 \cdot 2HCl$ are summarized in Tables I and II.

Spectroscopic Properties

The infrared (IR) spectrum (KBr) of **5b** (or **6b**), as shown in Fig. 1, exhibited a strong carbonyl band at 1765 cm^{-1} (or 1765 cm^{-1}) and a strong band at 1650 cm^{-1} (or 1660 cm^{-1}) attributable to a C=N-group. The ultraviolet (UV) spectrum (EtOH) of **5b** [310 nm (log ε 4.31) and 330 nm (log ε 4.32)] was very similar to that [308 nm (log ε 4.40) and 330 nm (log ε 4.35)] of **6b**. In the mass spectra (MS), the molecular ions of **5b** and **6b** were observed at *m/z* 529. These data indicate that both have the azine structure. The PMR spectra in deuteriodimethylsulfoxide (DMSO-d_6) of **5b** (or **6b**) showed singlet signals at 1.77 (or 1.33), 4.12 (or 4.10) and 6.50 (or 6.50) ppm assignable to $=C-CH_3$, OCH_3, and Ar–CH protons, respectively. These observations clearly demonstrate that all the protons of both parts of the azine molecules are isochronous. The spectral data for these azines are listed in Table III.

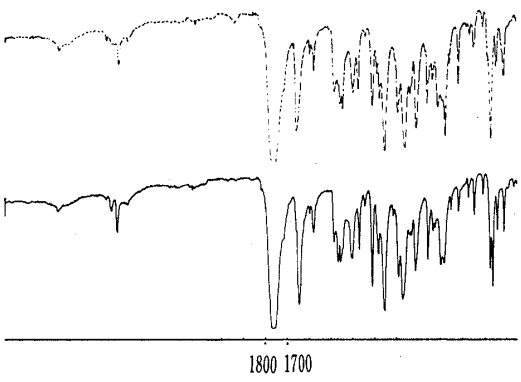


Fig. 1. Infrared Spectra (KBr) of **5b** (——) and **6b** (—·—·—)

Table III. Spectral Data for Azines

Compound No.	IR ν_{max}^{KBr} cm^{-1} C=O	IR ν_{max}^{KBr} cm^{-1} C=N	PMR (DMSO-d_6)δ $2\times CH_3$	PMR (DMSO-d_6)δ $2\times OCH_3$	PMR (DMSO-d_6)δ $2\times$ Ar–CH	MS(M^+) *m/z*
3a	1780	1600	1.95		6.25	
3b	1785	1600	1.90		6.47	
4b	1785	1600	1.78		6.51	
3c	1780	1605	1.98		6.47	
3d	1780	1605	1.97		6.20	
5a	1780	1630	1.72	4.12	6.20	460
6a	1760	1640	1.32	4.11	6.20	460
5b	1765	1650	1.77	4.12	6.50	529
6b	1765	1660	1.33	4.10	6.50	529
5c	1760	1650	1.78	4.15	6.38	550
6c	1760	1650	1.43	4.13	6.38	550
5d	1770	1650	1.72	4.12	6.18	488
6d	1770	1650	1.42	4.12	6.16	488

Theoretically, three stereostructures including configurational isomers on a lactone ring are possible for azines as shown in Chart 2. However, the above data did not provide definitive evidence for the structure of these azines, and thus X-ray crystallographic determinations of **5b** and **6b** were carried out.

Crystal Structures of 5b and 6b

A single crystal (red needles) of **5b** (dimensions $0.3\times0.4\times0.4$ mm^3) or a yellow needle of **6b** (dimensions $0.4\times0.4\times0.6$ mm^3), recrystallized from ethyl acetate, was used for the X-ray studies. The crystal data are summarized in Table IV. Unit-cell dimensions were determined on a Rigaku four-circle diffractometer using high-angle reflections (2 θ) by employing graphite-monochromated Cu K_α radiation and were refined by the least-squares method. From these

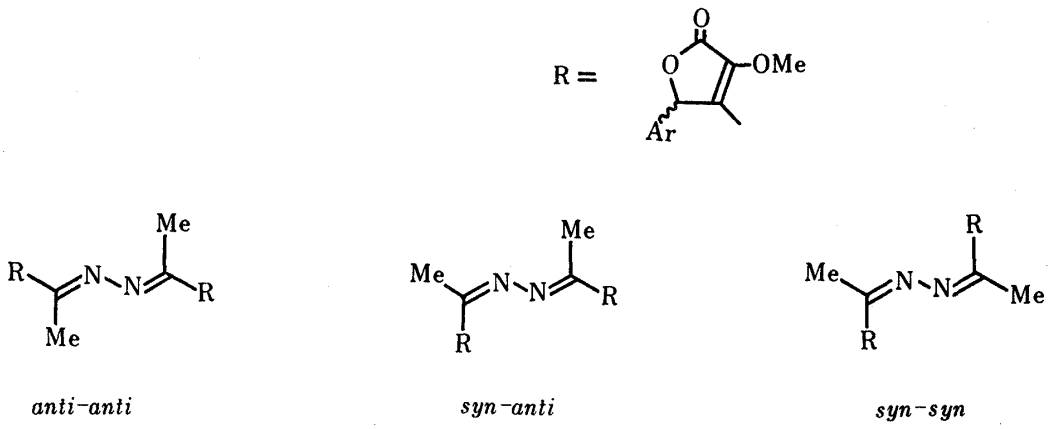


Chart 2

TABLE IV. Crystal Data for Two Isomeric Azines (**5b** and **6b**)

	5b	**6b**
Molecular formula	$C_{26}H_{22}Cl_2N_2O_6$	$C_{26}H_{22}Cl_2N_2O_6$
Mr	529.37	529.37
Crystal system	Orthorhombic	Orthorhombic
Space group	Pbcn	Pbca
Cell constant		
a	20.132(4) Å	18.911(5) Å
b	6.162(1)	17.245(3)
c	19.954(3)	15.463(4)
Volume	2475(2) Å^3	5043(2) Å^3
Z	4	8
D_m	1.414(1) g cm^{-3}	1.414(1) g cm^{-3}
D_x	1.421	1.394

data, the molecular weight of **5b** was equal to half of that determined by MS, indicating that the molecule of **5b** itself has a center of symmetry in the middle of the =N–N= bond. On the other hand, the crystal of **6b** contained one molecule per asymmetric unit. A total of 1838 (**5b**) or 4252 (**6b**) independent reflections ($2\theta_{max} \times 130°$) was measured using a ω-2θ scan mode and a scan rate of 4°/min. Both structures were solved by the direct method using the MULTAN program[7] and refined by the least-squares method to R=0.072 (**5b**) and 0.075 (**6b**). The details of these crystal structures will be published in the near future.[8] Spectroscopic views of the molecules of **5b** and **6b** are shown in Fig. 2.

The most significant difference between the isomers **5b** and **6b** is in the N(10)–N(10′) bond; the torsion angle of C(9)–N(10)–N(10′)–C(9′), ϕ, is n the *trans* region [180.0(8)°] for isomer **5b** and is in the *-anti clinal* region [−114.8(3)°] for **6b**. These results may reflect a difference of =N–N= bonding mode, as illustrated by the Newman projection (Fig. 3). Furthermore, the difference between **5b** and **6b** in crystal color may be mainly a consequence of a difference of their energy levels for HOMO (highest occupied molecular orbital)-LUMO (lowest unoccupied molecular orbital) electron transition states. For convenience, **5b** and **6b** were designated as *cis*-azine and *trans*-azine of 3-acetyl-4-(2-chlorophenyl)-4-hydroxy-2-methoxy crotonic acid lactones, respectively.

Structural Stability of the Two Isomeric Azines

In order to clarify the relation between ϕ and its bonding energy, CNDO/2 energy calculations were carried out for the $H_2C{=}N{-}N{=}CH_2$ molecule[8] as a model with various values of ϕ.

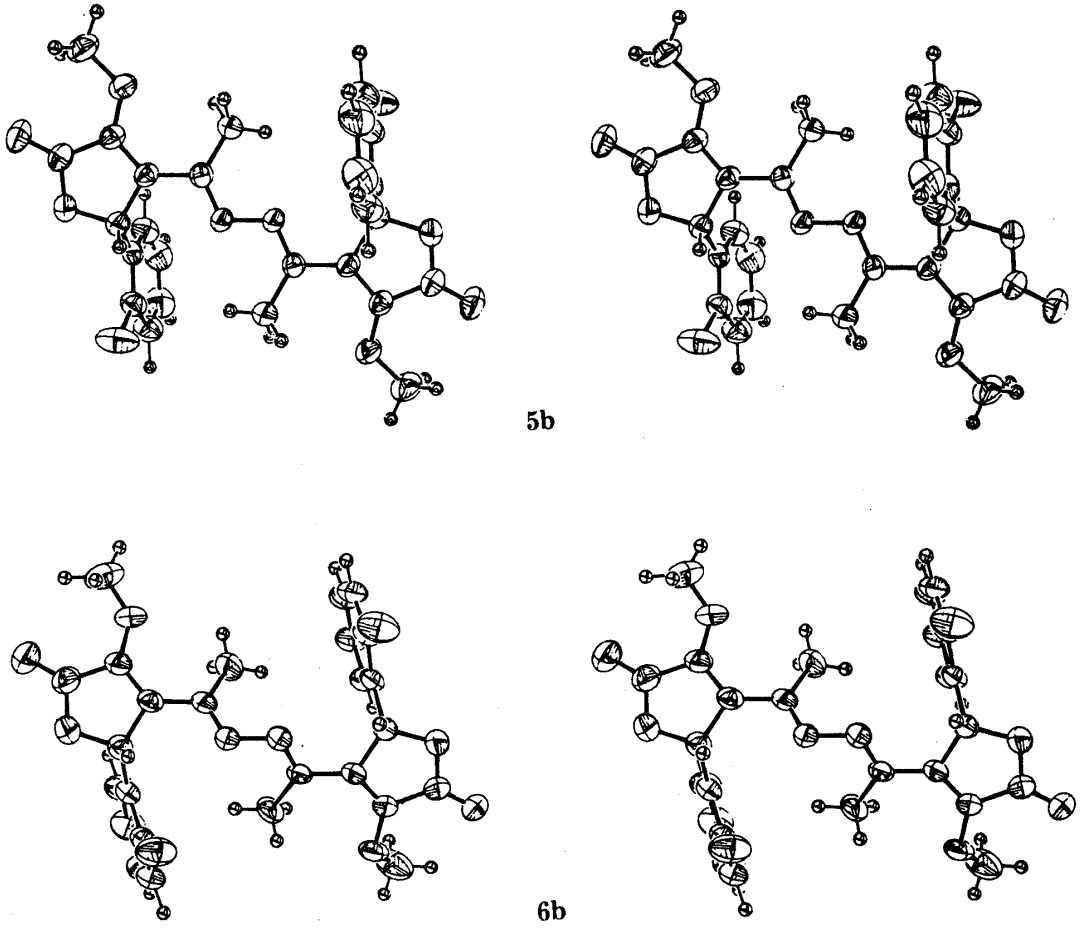


Fig. 2. Stereoscopic Views of the Molecules of **5b** and **6b**

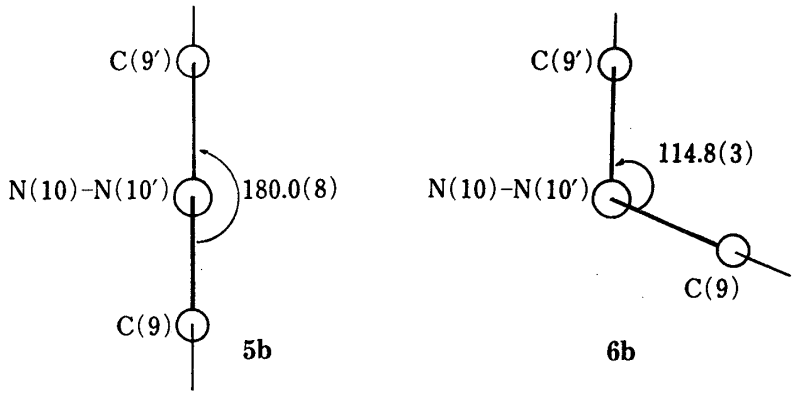


Fig. 3. Newman Projections around the N(10)–N(10′) Bond of **5b** and **6b**

The bonding parameters for **5b** and **6b** are as follows: C(9)–N(10)=1.296(5), N(10)–N(10′)=1.379(5), C(9′)–N(10′)=1.296(5)Å, C(9)–N(10)–N(10′)=114.1(3), C(9′)–N(10′)–N(10)=114.1(3)° for **5b**; C(9)–N(10)=1.282(4), N(10)–N(10′)=1.376(4), C(9′)–N(10′)=1.274(4)Å, C(9)–N(10)–N(10′)=117.0(3), C(9′)–N(10′)–N(10)=117.5(3)° for **6b**.

When ϕ is near $\pm 100°$, which nearly corresponds to that of isomer **6b**, the molecule had the most stable energy value. The difference between the energy values for $\phi = \pm 100°$ and $\phi = 180°$ was *ca.* 4.1 kcal/mol.

The thermal behaviors of **5d** and **6d** were measured with thermogravimetry (TG) and differential thermal analysis (DTA) instruments (Rigaku Denki Co., Japan) to investigate the

structural stability of the isomeric azines; SiO_2 was used as a standard compound. The heating rate was 5°C/min, and samples of 20.0 and 21.0 mg were used. The results are shown in Fig. 4. The characteristics observed for the crystals were as follows; the first degradation process of **6d** occurs in the range of 190 to 210°C, accompanying two exothermic reactions. On the other hand, **5d** has an endothermic peak at 162 to 170°C, which is presumably caused by the structural change of **5d** to another form during the melting process. This structural change is thermodynamically unstable and is followed by a degradation reaction at 170—190°C.

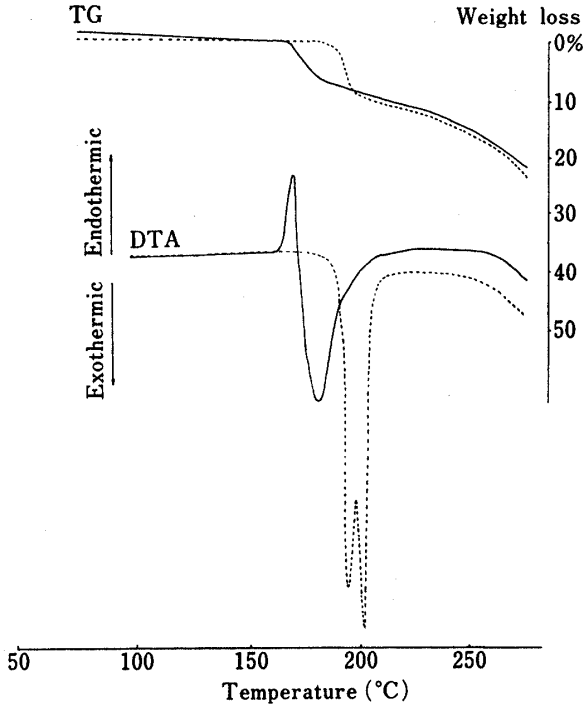
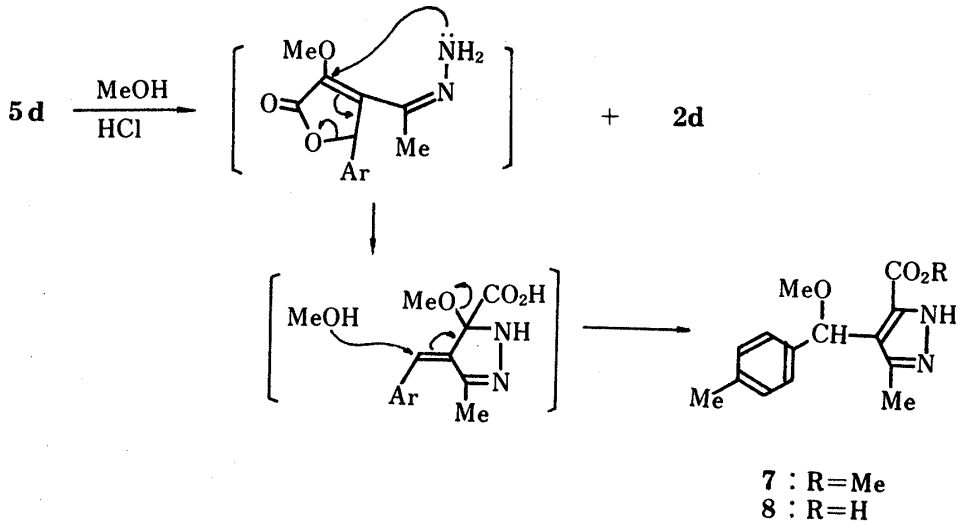


Fig. 4. TG and DTA Curves of **5d** (——) and **6d** (·····)

Finally, the stability of the azines in solution was investigated. Upon refluxing **5d** with a small amount of hydrochloric acid in methanol for 1 h, compound **5d** epimerized to **6d** in *ca.* 30% yield, while **6d** was recovered unchanged. From the results of the energy calculations, thermal analyses, and epimerization reactions, it could be concluded that the yellow crystals (**6**) are structurally more stable than the red crystals (**5**), and that the twisted conformation around the =N–N= bond is more stable than the co-planar one.

Interestingly, prolonged heating of **5d** under the above epimerization reaction conditions afforded 65.8% yield of methyl 4-(α-methoxy-4-methylbenzyl)-3-methylpyrazole-5-carboxylate (**7**) as an oil, which was analyzed as the corresponding carboxylic acid (**8**), together with 5.0% yield of **2d**.



7 : R=Me
8 : R=H

Chat 3

Experimental

All melting points were determined on a Yanagimoto micromelting point apparatus, and are uncorrected. The IR spectra were recorded on a JASCO model IRA-1 spectrophotometer and the UV spectra on a JASCO UVIDEC-505 spectrophotometer. The PMR spectra were recorded with a Hitachi R-40 spectrometer using tetramethylsilane as an internal standard and MS were obtained on a Hitachi RMU-7L spectrometer.

Azines of 3-Acetyl-2,4-dihydroxy-4-phenylcrotonic Acid Lactones (3a—d, and 4b)——A solution of a hydroxylactone (**1a**—**c**, or **1d**) (1 mmol) and $NH_2NH_2 \cdot 2HCl$ (1 mmol) in 70% aqueous acetonitrile (10 ml) was stirred at room temperature for 5—6 d. The resulting precipitate was collected by filtration and recrystallized (Tables I—III).

Azines of 3-Acetyl-4-hydroxy-2-methoxy-4-phenylcrotonic Acid Lactones (5a—d, and 6a—d)——A solution of a methoxylactone (**2a**—**c**, or **2d**) (1 mmol) and $NH_2NH_2 \cdot 2HCl$ (1 mmol) in MeOH (30 ml) was stirred at room temperature for 2 d. The resulting precipitate was collected by filtration, and recrystallized (Tables I—III).

Reaction of The Hydroxyazines (3a—d, and 4b) with Diazomethane——A hydroxyazine (**3a**—**d**, or **4b**) was added to an ethereal solution containing excess diazomethane, and the suspension was stirred for 2 h at room temperature. The resulting precipitate was collected by filtration, and recrystallized from an appropriate solvent to give the corresponding methoxyazine (**5a**—**d**, or **6b**), which was found to be identical with an authentic sample by comparison of PMR spectra.

Epimerization of 5d under a Acidic Condition——A solution of 0.2 g of **5d** containing a drop of conc. HCl in MeOH (10 ml) was refluxed for 1 h, and then evaporated to dryness. The PMR spectrum of the residue showed *ca.* 30% content of the epimerization product (**6d**).

Reaction of 5d with Hydrochloric Acid in Methanol——A solution of **5d** (1 g) and conc. HCl (1 ml) in MeOH (70 ml) was refluxed for 30 h. After removal of the solvent by evaporation, the residue was basified with satd. $NaHCO_3$ and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water and dried over Na_2SO_4. The residual oil, which was obtained by evaporation of $CHCl_3$, was subjected to silica gel column chromatography. Elution with benzene gave 25 mg (5.0%) of **2d**. Further elution with $CHCl_3$ gave 370 mg (65.8%) of methyl 4-(α-methoxy-4-methylbenzyl)-3-methylpyrazole-5-carboxylate (**7**) as a pale yellow oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1725 (CO). PMR ($CDCl_3$) δ: 2.10 (3H, s, CH_3), 2.40 (3H, s, Ar–CH_3), 3.25 (3H, s, OCH_3), 3.65 (3H, s, $COOCH_3$), 4.52 (1H, s, CH), 7.35 and 7.55 (each 2H, each d, J=8 Hz, Ar–H). MS *m/z*: 274 (M^+).

4-(α-Methoxy-4-methylbenzyl)-3-methylpyrazole-5-carboxylic Acid (8)——A solution of NaOH (48 mg, 1.2 mmol) in H_2O (5 ml) was added to a solution of **7** (274 mg, 1 mmol) in EtOH (20 ml), and the mixture was allowed to stand overnight. After removal of the solvent by evaporation, the residue was dissolved in H_2O (5 ml). The aqueous solution was acidified by the addition of conc. HCl under ice cooling. The precipitate was collected by filtration, and recrystallized from aqueous EtOH to give 78 mg (30%) of **8** as colorless needles of mp 252—254°C. IR ν_{max}^{KBr} cm^{-1}: 1710 (CO). PMR (DMSO-d_6) δ: 2.26 and 2.36 (each 3H, each s, 2×CH_3), 3.25 (3H, s, OCH_3), 4.75 (1H, s, CH), 7.25 and 7.55 (each 2H, each d, J=8 Hz, Ar–H). *Anal.* Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.69; H, 6.38; N, 10.74.

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