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Studies on Pyrimidinylpyrazoles. III.[1] Tautomerism of 1- and 2-Pyrimidinylpyrazolines[2]

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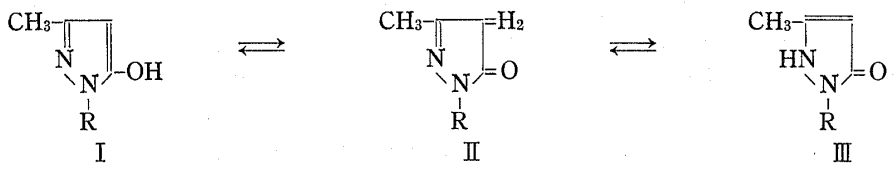
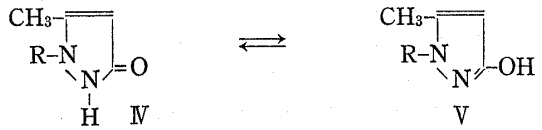
The tautomerism of 1- and 2-pyrimidinylpyrazolin-5-ones was investigated by using the combination of spectral methods, IR, NMR, and UV. 1-Pyrimidinylpyrazolin-5-ones exist in NH and OH forms in nonpolar media such as chloroform and carbon tetrachloride, while NH form increases in aqueous solution. In nonpolar media 2-pyrimidinylpyrazolin-5-ones exist predominantly in the OH form, although in aqueous solution, they are mostly in NH form.

The assigment of a structure for N-substituted pyrazolin-5-one derivatives with unsymmetrical pyrazole is a problem for which no general solution about the location of the N-substituent is available. In addition, N-substituted pyrazolin-5-one derivatives give various types of tautomeric form according to their substituents and states, and it is difficult to determine the tautomeric structure. With respect to tautomerism of pyrazolin-5-one derivatives, a number of reports have been presented, but their results appear to be contradictory, according to difference in the investigation methods used. In 1964, the investigation of the tautomerism of N-alkyl- and N-phenyl-pyrazolinones by Katritzky and Maine[4,5] reached a definite conclusion by making detailed references to previous works. The pyrazolin-5-one in which the 1- or 2-position is substituted by the heterocyclic group such as pyrimidinyl group, might be expected to show a characteristic tautomerism by the influence of a strong electronic effect different from that of N-alkyl or N-phenyl derivatives. The present paper deals with the investigation on the tautomerism of the pyrazolin-5-ones carrying several types of pyrimidinyl group, by the comparison of spectroscopic data of the compounds of which a tautomeric proton is fixed by methyl group.

1-pyrimidinylpyrazolin-5-one series



2-pyrimidinylpyrazolin-5-one series



R=pyrimidinyl groups

Chart 1

1) Part II: R. Dohmori, Y. Nakai, R. Yoshimura and T. Naito, *Chem. Pharm. Bull.* (Tokyo), **17**, 1479 (1969).
2) This work was presented at the 88th Annual Meeting of Pharmaceutical Society of Japan, Tokyo, April 1968.
3) Location: *Minamifunabori-cho, Edogawa-ku, Tokyo.*
4) A.R. Katritzky and F.W. Maine, *Tetrahedron*, **20**, 299 (1964).
5) A.R. Katritzky and F.W. Maine, *Tetrahedron*, **20**, 315 (1964).

1-Pyrimidinylpyrazolin-5-ones can exist in three tautomeric forms, I, II, and III, which were denoted as OH, CH, and NH forms by Katritzky, and 2-pyrimidinylpyrazolin-5-ones can exist either as IV or V, which were also denoted as NH or OH form for the sake of brevity.

Experimental

Materials——The 1- and 2-pyrimidinylpyrazolin-5-ones and 1- and 2-pyrimidinylpyrazole derivatives synthesized in the previous paper[1,6] were used.

1-(4-Methoxy-6-methyl-2-pyrimidinyl)-3,4,4-trimethyl-2-pyrazolin-5-one was prepared from 2-hydrazino-4-methoxy-6-methylpyrimidine[6] and ethyl 2,2-dimethyl-3-oxobutyrate in EtOH under refluxing for 14 hr. Purification of the product was effected by column chromatography through the neutral Al_2O_3 and $CHCl_3$ as solvent. The resulting product had mp 94—94.5° (from petroleum ether) and satisfactory analytical figures.

Measurement of Spectra

IR-Spectra——The Hitachi model EPI-2, EPI-S2, and EPI-G_2 infrared spectrophotometer were used. Sample in 10% solution were measured in 0.025 mm pass fixed-cell, and KBr disc method was applied to solid state measurement. The position of peaks were corrected by polystyrene.

NMR-Spectra——The Jeolco Model JNM 4H-100 high resolution NMR spectrometer was used. Samples were measured at room temperature in 10% solution of $CDCl_3$ with TMS as internal standard. Chemical shifts were directly read out on the standard chart.

UV-Spectra——The ultraviolet spectra were obtained with the Hitachi model EPS-2U spectrophotometer at 20°.

Results and Discussion

IR Spectra

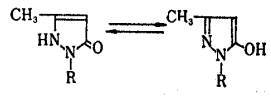
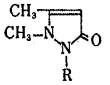
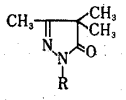
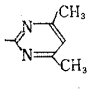
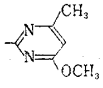
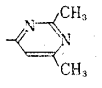
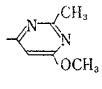
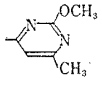
i) 1-Pyrimidinyl-3-methylpyrazolin-5-ones

Table I shows the carbonyl stretching vibration of 1-pyrimidinylpyrazolin-5-ones and the corresponding fixed-type compounds whose tautomeric protons were substituted by a methyl group. The fixed NH type compounds, 1-pyrimidinyl-2,3-dimethyl-3-pyrazolin-5-ones, give a very strong band of the carbonyl in the 1670—1675 cm^{-1} region in chloroform and in the 1659—1685 cm^{-1} region in the solid state. Only one derivative was available as the fixed CH type, and this was 1-(4-methoxy-6-methyl-2-pyrimidinyl)-3,4,4-trimethyl-2-pyrazolin-5-one, whose C=O stretching vibration was observed at 1720 cm^{-1} in chloroform solution and which was recognized as a comparable value with that of 1-phenyl-3,4,4-trimethyl-2-pyrazolin-5-one (1705 cm^{-1}). As a matter of course, there is no absorption band in the fixed OH type compounds, 1-pyrimidinyl-3-methyl-5-methoxypyrazoles, in the C=O stretching vibration region (1600—1800 cm^{-1}), in both the liquid state in chloroform and the solid state in KBr disc.

The spectra of the tautomeric compounds, 1-pyrimidinyl-3-methylpyrazolin-5-ones, show the C=O stretching vibration in the 1631—1633 cm^{-1} region in chloroform solution, and in the 1631—1638 cm^{-1} region in the solid state. This absorption suggests that these tautomeric compounds exist partially in the NH form when compared with the spectra of the fixed type compounds. As seen in Table I, however, the carbonyl band of the tautomeric derivatives exhibits a bathochromic shift from that of the corresponding fixed NH type compounds. Such a shift was observed in carbon tetrachloride solution without marked difference from that in chloroform solution. This result doesn't provide the evidence of interaction with solvent but of intermolecular hydrogen bond. In addition, since a 100 fold dilution of the tautomeric compounds was still accompanied by a 5 cm^{-1} bathochromic shift, the strong intermolecular interaction was considered. Similar shifts for the pyrazolin-5-ones were also reported by Katritzky, *et al.*[4]

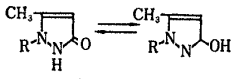
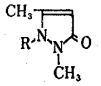
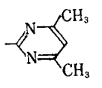
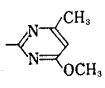
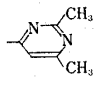
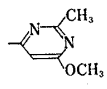
6) T. Naito, T. Yoshikawa, S. Kitahara and N. Aoki, *Chem. Pharm. Bull.* (Tokyo), **17**, 1467 (1969).

Table I. IR Data for Comparison of Tautomeric Compounds with Fixed NH and CH Type Compounds in 1-Pyrimidinylpyrazolin-5-one

R	 C=O (cm^{-1}) in $CHCl_3$ in KBr disc	 C=O (cm^{-1}) in $CHCl_3$ in KBr disc	 C=O (cm^{-1}) in $CHCl_3$ in KBr disc	$\Delta\nu$ C=O in $CHCl_3$ in KBr disc
	1633 (s)	1674 (vs)		41
	1631 (1658) (m)	1659 (vs)		28
	1632 (s)	1675 (vs)	1720 (vs)	43
	1632 (1660) (m)	1663 (vs)		31
	1633 (1670) (m)	1674 (vs)		41
	1633 (vs)	1663 (vs)		30
	1631 (m)	1620 (vs)		39
	1638 (vs)	1672 (vs)		34
	1631 (1668) (m)	1672 (vs)		41
	1638 (vs)	1685 (vs)		47

The CH form is easily eliminated from probable tautomeric forms by the absence of a carbonyl band in the region of 1720 cm^{-1} but estimation of the presence of the OH form by the IR spectrum is less simple. However, it is hardly expected that OH form coexists partially because of a rather weak C=O stretching vibration, and the correctness of this assumption will be provided by UV and NMR spectral evidence.

Table II. IR Data for Comparison of Tautomeric Compounds with Fixed NH Type Compounds in 2-Pyrimidinylpyrazolin-5-one

R	 C=O (cm^{-1}) in $CHCl_3$ in KBr disc	 C=O (cm^{-1}) in $CHCl_3$ in KBr disc	$\Delta\nu$ C=O in $CHCl_3$ in KBr disc
	—	1654 (vs)	—
	—	1667 (vs)	—
	—	1657 (vs)	—
	—	1668 (vs)	—
	—	1662 (vs)	—
	—	1662 (vs)	—
	—	1662 (vs)	—
	—	1650 (vs)	—

The NH form may be expected in the solid state but a rather strong intermolecular interaction blurs the distinction between these two forms. The influence of the difference between 2-pyrimidinyl and 4-pyrimidinyl groups upon tautomerism is scarcely observed.

ii) 2-Pyrimidinyl-3-methylpyrazolin-5-ones

The C=O stretching frequencies of the tautomeric compounds and the corresponding fixed type compounds in this series are presented in Table II. The IR spectra of the fixed NH type derivatives, 2-pyrimidinyl-1,3-dimethyl-3-pyrazolin-5-ones, in chloroform solution and in solid state show a very strong C=O stretching vibration at 1654—1662 cm^{-1} and at 1650—1668 cm^{-1}, respectively, and those of the fixed OH type compounds, 2-pyrimidinyl-3-methyl-5-methoxypyrazoles, do not show a normal carbonyl band. The spectra of the tautomeric compounds closely resemble those of the corresponding fixed OH type derivatives, and not those of the fixed NH type analog. These facts indicate that this series compounds predominantly exist in the 5-hydroxy form. In the 3000 cm^{-1} region, very broad absorption bands with several peaks exist both in chloroform solution and in solid state, indicating the presence of an intermolecular hydrogen bond. This behaviour of the 2-pyrimidinyl series resemble that of 2-alkyl and 2-phenyl series reported by Katritzky[4] and Refn.[7]

NMR Spectra

i) 1-Pyrimidinyl-3-methylpyrazolin-5-ones

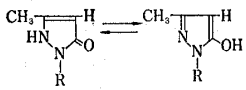
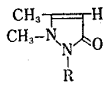
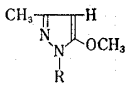
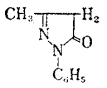
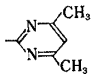
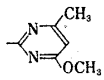
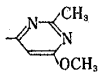
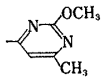
The chemical shifts of the protons of the tautomeric compounds and those of the corresponding two fixed derivatives are summarized in Table III. The resonance of the 4-proton of the tautomeric compounds is located in the position between the corresponding signals of the fixed NH type and the fixed OH type. If the 4-proton of the tautomer exists at an average position weighted by the population of each tautomer,[8] the 5-hydroxy form will be the more prefered. Additionally, the single bond between carbons 3 and 4 means that the hydroxy form is dominant, because of the undetectable long-range coupling between a proton and methyl protons at 4- and 3-positions, respectively. However, from the fact that the difference of the chemical shifts in the fixed derivatives is small and that a fine structural evidence of NMR spectrum is supported by the negative observation, it is difficult to draw a definite conclusion. It is reasonable to exclude the possibility of the CH form because of the large displacement of the aliphatic hydrogen at 4-position to a higher field. In fact, Silverstein[9] and Katritzky[4] reported that the compound assigned as N-phenyl-3-methylpyrazolin-5-one showed 2H singlet peak at 3.40 ppm.

ii) 2-Pyrimidinyl-3-methylpyrazolin-5-ones

The results are recorded in Table IV for the case of 2-pyrimidinylpyrazolin-5-one series. Although the difference in the chemical shifts between the fixed NH type and the fixed OH type compounds is scarcely recognized, location of the proton at 4-position of the tautomeric compounds is extremely close to that of the fixed OH type derivatives and indicates that the OH form will have the highest degree of probability. The lower field at which the OH peak absorbs is an indication of strong hydrogen bonding, and the sharp character of the peak is better explained by OH rather than NH form. The proton at 4-position of the 2-pyrimidinyl derivatives shows slightly broader signal than that of 1-pyrimidinyl derivatives does, and the irradiation of the methyl group at 3-position of 2-pyrimidinyl compounds brought a sharper signal of the proton at 4-position and revealed a long-range coupling ($J<1$ cps). In general, a larger long-range coupling is observed between protons which are separated by four or more bonds containing π-bond character, whereas a smaller coupling is observed in

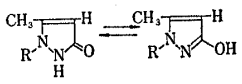
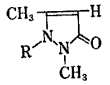
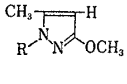
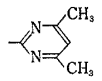
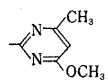
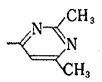
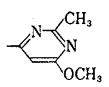
7) S. Refn, *Spectrochim. Acta*, **17**, 40 (1961).
8) J.K. Williams, *J. Org. Chem.*, **29**, 1377 (1964).
9) R.M. Silverstein and J.N. Shoolery, *J. Org. Chem.*, **25**, 1355 (1960).

Table III. NMR Data for Comparison of Tautomeric Compounds with Fixed Type Compounds in 1-Pyrimidinylpyrazolin-5-one

R	 (ppm) δ 4-H	δ 3-CH_3	 (ppm) δ 4-H	δ 3-CH_3	 (ppm) δ 4-H	δ 3-CH_3	 (ppm) δ4-H
	5.43	2.28	5.32	2.22	5.50	2.30	3.40 (2 protons)
	5.47	2.36	5.43	2.23	5.50	2.30	
	5.37	2.21	5.34	2.27	5.51	2.29	
	5.37	2.21	5.46	2.26	5.51	2.30	
	5.40	2.22	5.32	2.25	5.49	2.25	

NMR spectra were measured in 10% solution in $CDCl_3$ at room temperature at 100 MHz. Chemical shift is showed in ppm from TMS as internal standard.

Table IV. NMR Data for Comparison of Tautomeric Compounds with Fixed Type Compounds in 2-Pyrimidinylpyrazolin-5-one

R	 (ppm) δ 4-H	δ 3-CH_3	 (ppm) δ 4-H	δ 3-CH_3	 (ppm) δ 4-H	δ 3-CH_3
	5.65	2.65	5.24	2.44	5.68	2.49
	5.63	2.66	5.59	2.48	5.69	2.49
	5.70	2.09	5.48	2.39	5.69	2.50
	5.68	2.66	5.47	2.35	5.67	2.56

NMR spectra were measured in 10% solution in $CDCl_3$ at room temperature at 100 MHz. Chemical shift is showed in ppm from TMS as internal standard.

the case of a σ-bond character.[10] Thus, this is also further evidence for the results obtained in the 1-pyrimidinyl series as mentioned above.

10) J.D. Albright and L. Goldman, *J. Org. Chem.*, **31**, 273 (1966).

UV Spectra

UV spectra were recorded in cyclohexane, chloroform, methanol, and water (pH 7.0). The spectra obtained in cyclohexane and in chloroform are practically superimposable with each other and intermediate spectra between these in chloroform and in water are obtained in methanol. Chloroform was used as the nonpolar solvent and pH 7.0 buffer as the polar solvent. The following investigations were carried out with typical compounds, and the obtained result was essentially identical with that of other tautomeric compounds in the corresponding series.

i) 1-Pyrimidinyl-3-methylpyrazolin-5-ones

The spectrum of especially typical compound in this series, 1-(4-methoxy-6-methyl-2-pyrimidinyl)-3-methylpyrazolin-5-one, is shown in Fig. 1 and 2. As shown in Fig. 1, although the spectrum of the tautomeric compound in chloroform solution as a whole shows a strong resemblance to that of the fixed OH type compound, the spectral tail is raised from the base line in the region of 290 mμ. This result probably suggests that the tautomeric compound exists mainly in OH form with some NH form.

In aqueous buffer, the spectrum is intermediate between those of the fixed OH and NH derivatives. Thus, the swelling in the region of 290 mμ increases in intensity while the peak at 250 mμ decreases. This observation means that a considerable proportion is in NH form in aqueous solution and that the ratio of the two tautomeric forms is roughly 1:1. It is less easy to assess the presence of CH form by UV absorption spectra.

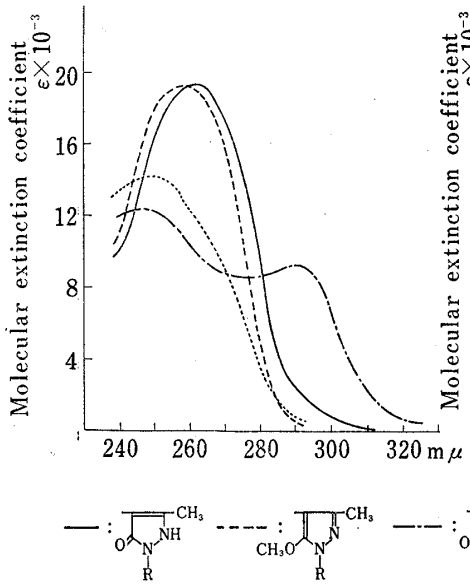


Fig. 1. UV-Spectra of the Typical 1-Pyrimidinylpyazoline Derivatives in $CHCl_3$

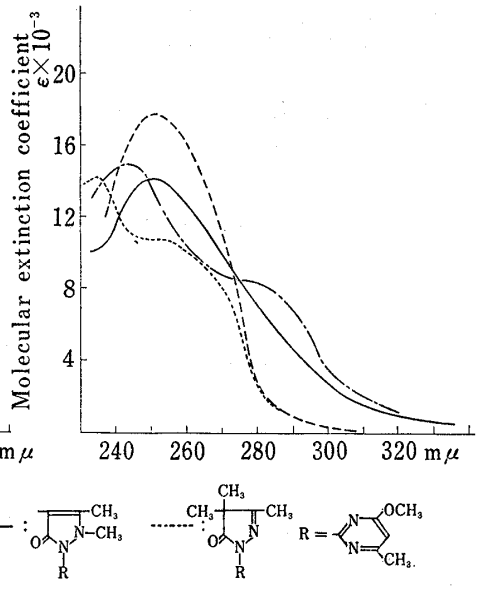


Fig. 2. UV-Spectra of the Typical 1-Pyrimidinylpyrazoline Derivatives in Aqueous Solution(pH 7.0)

ii) 2-Pyrimidinyl-3-methylpyrazolin-5-ones

As in the case of 1-pyrimidinyl series, the spectra of typical 2-(4-methoxy-6-methyl-2-pyrimidinyl)-3-methylpyrazolin-5-one and the corresponding fixed type compounds were examined and are summarized in Fig. 3 and 4. As shown in Fig. 3, the spectrum of tautomeric compound in chloroform is identical with that of OH type compound and it no doubt exist in the OH form. In aqueous solution, the spectra of fixed OH and NH type compound are similar, and one cannot say with precision but the tautomeric compound might well exist in the NH form.

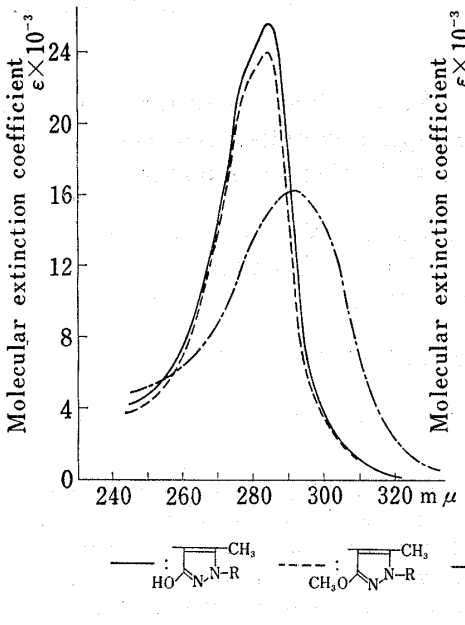


Fig. 3. UV-Spectra of the Typical 2-Pyrimidinylpyrazoline Derivatives in $CHCl_3$

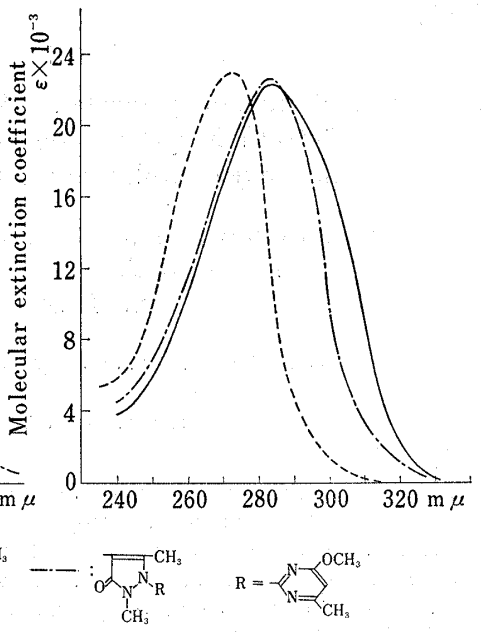


Fig. 4. UV-Spectra of the Typical 2-Pyrimidinylpyrazoline Derivatives in Aqueous Solution (pH 7.0)

Conclusion

The results of the tautomerism of pyrimidinylpyrazolin-5-ones are summarized in Table V. There is a good agreement among the results obtained by different methods and the whole forms a logical pattern. 1-Pyrimidinyl-3-methylpyrazolin-5-ones exist in OH and NH forms in nonpolar media and NH form increases in aqueous solution. 2-Pyrimidinyl-3-methylpyrazolin-5-ones exist predominantly in the OH form in nonpolar solvent and NH form in aqueous solution. That these tautomeric compounds exist in NH form will be due to their being more polar and polarizable than in the OH form, and that NH form will be favoured in media of high dielectric constant and hydrogen bonding ability. This conclusion about the form in nonpolar solvent is much different from the result of Katritzky's found with 1-phenyl and 1-alkyl derivatives.

Table V. Tautomeric Composition of Pyrimidinylpyrazolin-5-ones

Compounds	IR		NMR	UV	
	$CHCl_3$	Solid	$CDCl_3$	$CHCl_3$	Aq. (pH 7.0)
1-Pyrimidinyl series	OH+NH	mainly OH/NH	OH+NH	OH+NH	OH+NH
2-Pyrimidinyl series	OH	OH	OH	OH	NH

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