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Metalation of Alkylpyridazines. II.[1] Acylation of Metalated Methylpyridazines and Isomeric Character of Acylmethylpyridazines

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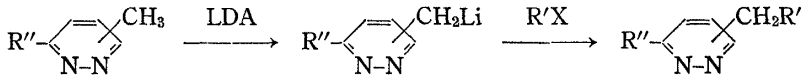
Hitherto unaccessible acylmethylpyridazines have been prepared by means of acylation of pyridazinylmethyllithiums prepared from methylpyridazines and lithium diisopropylamide. Their tautomeric characters were examined by means of nuclear magnetic resonance, ultraviolet and infrared spectra. The tautomerisms between keto and isomeric forms were observed and the structure of the isomeric form was proposed to be the hydrogen-bonded keto-enamine (*i.e.*, NH-methide) structure.

Keywords——metalation of alkylpyridazines; phenacylpyridazines; acetonylpyridazines; tautomerism of acylmethylpyridazines; heteroaromatics; pyridazines; acylation

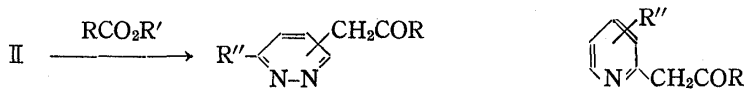
In a previous paper,[1] we reported the metalation of alkylpyridazines (I) by the use of lithium diisopropylamide (LDA) and the alkylation of the pyridazinylmethyllithiums (II) with alkyl halides, which is a brief synthetic method of pyridazine derivatives.



I II

Chart 1

Now, the syntheses of acylmethylpyridazines (pyridazinylethanones: III) are of interest in relation to the keto-enol tautomerism of the analogues in pyridine series (IV)[3] and in connection with anti-bacterial activities of IV.[4]



	R	R″
IIIa-1	3-CH_3COCH_2	H
IIIc-1	3-CH_3COCH_2	CH_3
IIIa-2	3-$PhCH_2COCH_2$	H
IIIc-2	3-$PhCH_2COCH_2$	CH_3
IIIa-3	3-$PhCOCH_2$	H
IIIc-3	3-$PhCOCH_2$	CH_3
IIIb-3	4-$PhCOCH_2$	H
Vc-1	CH_3COCH_2	CH_3COCH_2
Vc-3	$PhCOCH_2$	$PhCOCH_2$

IV

Chart 2

1) Part I: A. Ohsawa, T. Uezu, and H. Igeta, *Chem. Pharm. Bull.* (Tokyo), **26**, 2428 (1978).
2) Location: *Hatanodai, Shinagawa-ku, Tokyo 142, Japan.*
3) J. Elguero, C. Marzin, A.R. Katritzky, and P. Linda, "The Tautomerism of Heterocycles," Academic Press, 1976, p. 186, and references cited therein.
4) A.H. Beckett, K.A. Kerridge, P.M. Clark, and W.G. Smith, *J. Pharm. and Pharmacol.*, **7**, 717 (1955); R.F. Branch, *Nature* (London), **177**, 671 (1956), **179**, 42 (1957).

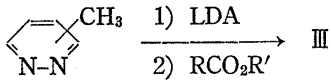
This paper describes the acylation of the lithiated methylpyridazines (II) to give III and the tautomeric behaviour of the products.

Synthesis of Acylmethylpyridazines (III)

A solution of an ester in tetrahydrofuran (THF) was added to a fresh THF solution of II which was prepared as described in our previous paper.[1] The reaction was accomplished on standing the mixture at room temperature under nitrogen atmosphere. The yields, melting points and the elemental analyses data of the products are listed in Table I.

Table I. Acylation of Methylpyridazines

Ia: 3-Me
Ib: 4-Me
Ic: 3,6-diMe



Runs	I	RCO_2R'	III	Yields (%)	mp (°C)	Formula	Anal. (%) Calcd. (Found) C	H	N
1	a	$MeCO_2Et$	IIIa-1	21	Oil[a]	$C_7H_8N_2O$[a]	61.76 (61.20	5.88 5.60	20.59 21.08)
2	a	$PhCH_2CO_2Me$	IIIa-2	15	96— 98	$C_{13}H_{12}N_2O$	73.58 (73.62	5.66 5.88	13.21 13.00)
3	a	$PhCO_2Me$	IIIa-3	29	97— 97.5	$C_{12}H_{10}N_2O$	72.71 (72.51	5.09 5.12	14.13 14.01)
4	b	$PhCO_2Me$	IIIb-3	39	142—143	$C_{12}H_{10}N_2O$	72.71 (72.60	5.09 4.71	14.13 14.05)
5	c	$MeCO_2Et$	IIIc-1	26	69— 70	$C_8H_{10}N_2O$	64.00 (63.87	6.67 7.00	18.66 18.60)
			Vc-1	1	68— 68.5	$C_{10}H_{12}N_2O_2$	62.48 (62.73	6.29 6.33	14.58 14.68)
6	c	$PhCH_2CO_2Me$	IIIc-2	19	83— 84	$C_{14}H_{14}N_2O$	74.34 (74.44	6.19 6.41	12.39 12.50)
7	c	$PhCO_2Me$	IIIc-3	30	104—104.5	$C_{13}H_{12}N_2O$	73.58 (73.90	5.66 6.00	13.21 13.39)
			Vc-3	5	184—184.5	$C_{20}H_{16}N_2O_2$	75.93 (76.04	5.10 5.13	8.86 8.97)

a) The attempts to convert IIIa-1 into a simple crystalline derivative have been unsuccessful. Although the elemental analyses of this compound have not presented the satisfactory values, VPC, NMR and MS showed that the obtained material was essentially pure.

The reaction between methylpyridazines (I) and the esters afforded the corresponding III in 15—39% yields. The acylation of 3,6-dimethylpyridazine (Ic) with ethyl acetate and methyl benzoate afforded bis-(acylmethyl)pyridazines (Vc-1 and Vc-3) and mono-(acylmethyl)-pyridazines (IIIc-1 and IIIc-3), respectively.[5]

Unlike the alkylation of II with alkyl halides,[1] the geminally substituted products (eq. 1) were not isolated and the products of the subsequent addition of II to III (eq. 2) were also not isolable (Chart 3).

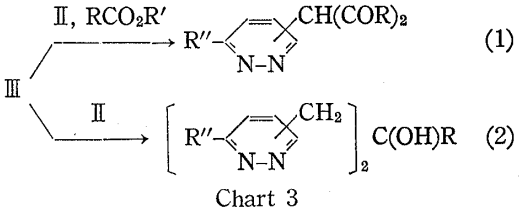


Chart 3

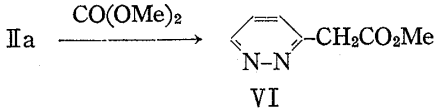


Chart 4

5) All attempts to isolate Vc-2 have been failed (run 6).

Additionally, methyl 3-pyridazinylacetate (VI) was obtained (26%) by the acylation of IIa with methyl carbonate (Chart 4).

Tautomerism of 3-Acylmethylpyridazines

The feature of the nuclear magnetic resonance (NMR) spectrum of 3-phenacylpyridazine (IIIa-3) in $CDCl_3$ is illustrated in Fig. 1 and is not assigned to the structure of the simple form of IIIa-3. Thus, it showed a broad signal around δ 15.4 ($0.4\times1H$) which is assignable to a strongly hydrogen-bonded proton, and signals due to the pyridazine ring protons and the phenyl protons are widely distributed in a range δ 9.15—7.20. The integrated intensity of a signal at δ 5.90 (s) corresponds to $0.4\times1H$, and that of a signal at δ 4.73 (s) to $0.6\times2H$. These features are characteristic of existence of tautomerism as shown in Chart 5.

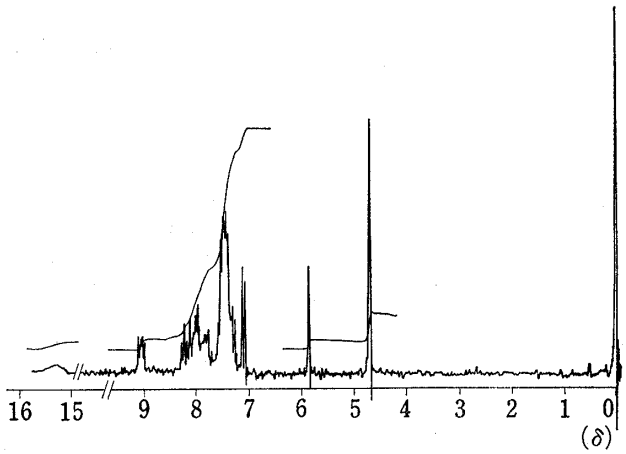


Fig. 1. NMR of IIIa-3

In this aspect, the signal at δ 15.4 is assignable to the hydrogen-bonded proton of the isomeric form (VII), δ 5.90 to the olefinic proton of VII, δ 4.73 to the methylene protons of the keto form (III), and the multiplets in region δ 9.15—7.20 are also assigned to the protons of the keto form and those of the

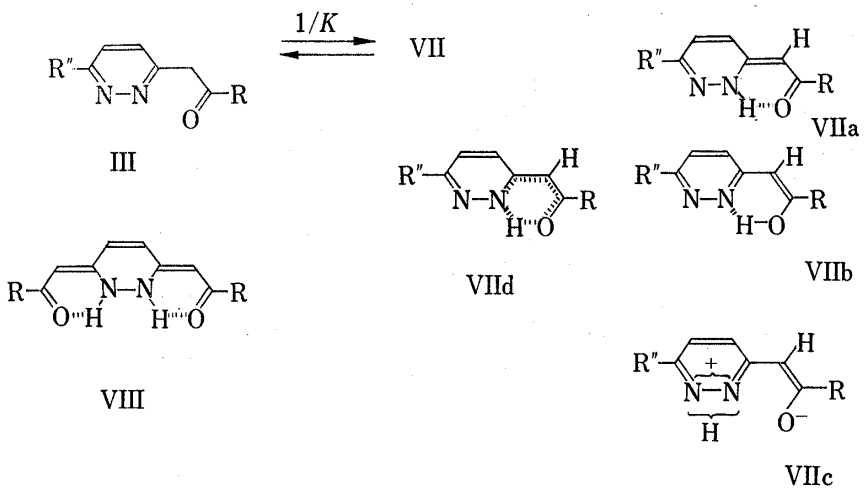


Chart 5

isomeric form. The signals due to the olefinic protons, the methylene protons, and the pyridazine ring protons of the other compounds in this series are also assigned as shown in Table II.

In the cases of Vc-1 and Vc-3, all the signals were rationally assigned to the mixture of bis-keto and mono-keto type species whereas the bis-isomeric form (*e.g.*, VIII) was not necessary to be considered.

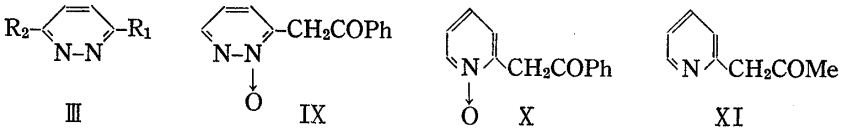
The values K (isomeric form/keto form), *i.e.*, the equilibrium constants in solutions at room temperature, have been obtained from the integrated intensities of those signals as shown in Table III, and some data obtained for other referential compounds are also listed therein.

TABLE II. NMR of Acylmethylpyridazines (δ)[a]

Compounds	Solvents	Forms	3-H	4- and /or 5-H	6-H	$COCH_2$ prd.	-CH=	Other signals
IIIa-1	$CDCl_3$	Keto		7.45(d, 3.5)[b]	9.12(t, 3.5)	4.15(s)		2.33(s) CH_3CO
		Isomer		7.00(d, 2.0) 7.08(d, 4.0)	8.30(dd, 2.0, 4.0)		5.12(s)	2.10(s) CH_3CO
	10% TFA[c]	Keto		8.28(br. s)	9.38(br. s)	4.40(br. s)		2.30(s) CH_3CO
IIIc-1	$CDCl_3$	Keto		7.33(s)		4.12(s)		2.30(s) CH_3CO 2.70(s) 6-CH_3
		Isomer		6.97(br. s)			5.12(s)	2.11(s) CH_3CO 2.44(s) 6-CH_3
	10% TFA	Keto		8.17(s)		4.31(br. s)		2.34(s) CH_3CO 2.88(s) 6-CH_3
Vc-1	$CDCl_3$	Keto[d]		7.38(s)		4.12(s)		2.30(s) CH_3CO
		Isomer[e]		6.93(d, 8.7) 7.07(d, 8.7)		3.85(s)	5.16(s)	2.09(s), 2.27(s) CH_3CO
	10% TFA	Keto[d]		8.08(br. s)		4.35(br. s)		2.35(s) CH_3CO
IIIa-2	$CDCl_3$	Keto		7.39(d, 3.5)	9.09(t, 3.5)	4.13(s)		3.88(s) $PhCH_2CO$ 7.3(m) Phenyl
		Isomer		6.96(d, 2.0) 7.00(d, 4.0)	8.16(dd, 2.0, 4.0)		5.06(s)	3.64(s) $PhCH_2CO$ 7.3(m) Phenyl
	10% TFA	Keto		8.28(br. s)	9.30(br. s)	4.40(br. s)		3.90(s) $PhCH_2CO$ 7.3(m) Phenyl
IIIc-2	$CDCl_3$	Keto		*ca.* 7.3		4.10(s)		3.86(s) $PhCH_2CO$ 7.3(m) Phenyl 2.64(s) 6-CH_3
		Isomer		6.91(s)			5.07(s)	3.61(s) $PhCH_2CO$ 7.3(m) Phenyl 2.35(s) 6-CH_3
	10% TFA	Keto		8.08(s)		4.30(br. s)		3.90(s) $PhCH_2CO$ 7.3(m) Phenyl 2.79(s) 6-CH_3
IIIa-3	$CDCl_3$	Keto		8.25—7.20(m)	9.15(dd, 3.0, 4.0)	4.73(s)		8.25—7.20(m) Phenyl
		Isomer		7.15(d, 3.0)	8.32(t, 3.0)		5.90(s)	8.25—7.20(m) Phenyl
	10% TFA	Keto		8.55(d, 4.0)	9.60(t, 4.0)	4.90(s)		8.20—7.50(m) Phenyl
IIIc-3	$CDCl_3$	Keto		8.2—7.2(m)		4.68(s)		8.2 —7.2 (m) Phenyl 2.70(s) 6-CH_3
		Isomer		8.2—7.2(m)			5.86(s)	8.2 —7.2 (m) Phenyl 2.50(s) 6-CH_3
	10% TFA	Keto		*ca.* 8.4		4.90(s)		8.4 —7.2 (m) Phenyl 2.89(s) 6-CH_3
Vc-3	$CDCl_3$	Keto[d]		8.2—7.3(m)		4.70(s)		8.2 —7.3 (m) Phenyl
		Isomer[e]		8.2—7.3(m)		4.49(s)	5.91(s)	8.2 —7.3 (m) Phenyl
	10% TFA	Keto[d]		8.55(br. s)		5.14(s)		8.3 —7.3 (m) Phenyl
IIIb-3	$CDCl_3$	Keto	9.10(s)	8.2—7.3(m)	9.18(m)	4.35(s)		8.2 —7.3 (m) Phenyl

a) The signals due to the hydrogen-bonded protons of the isomeric form of these compounds appeared around δ 15 although the chemical shift values are omitted in this table.
b) *J* in Hz.
c) In $CDCl_3$ with 10% CF_3CO_2H.
d) Bis-keto form.
e) Mono-keto form.

TABLE III. K (isomeric form/keto form) of Acylmethylpyridazines and Related Compounds



III IX X XI

Compounds No.	R_1	R_2	Solvents			
			CCl_4	$CDCl_3$	d_6-DMSO	10% TFA-$CDCl_3$
IIIa-1	CH_3COCH_2	H	0.25	0.25	0.11	0
IIIc-1	CH_3COCH_2	CH_3	0.33	0.18	0.11	0
Vc-1	CH_3COCH_2	CH_3COCH_2		0.33	0.11	0
IIIa-2	$PhCH_2COCH_2$	H	1.3	0.52	0.33	0
IIIc-2	$PhCH_2COCH_2$	CH_3	1.0	0.43	0.33	0
IIIa-3	$PhCOCH_2$	H	2.5	0.66	1.0	0
IIIc-3	$PhCOCH_2$	CH_3	2.0	0.66	0.66	0
Vc-3	$PhCOCH_2$	$PhCOCH_2$		1.3	1.0	0
IIIb-3	4-$PhCOCH_2$	H	0	0	0	0
IX	—	—	0	0	0	0
X	—	—		0	0	0
XI[a]	—	—	0.27	0.15	0.17	

a) K.R. Wurthorn and E.H. Sund, *J. Heterocycl. Chem.*, **9**, 25 (1972).

In 3-acylmethylpyridazine series, each IIIa and IIIc (and Vc) exists in two tautomeric forms in neutral solvents, and decreases of the K values in the order phenacyl-(IIIa-3, IIIc-3 and Vc-3)>phenylacetonyl-(IIIa-2 and IIIc-2)>acetonyl-(IIIa-1, IIIc-1 and Vc-1) pyridazines are recognizable in those solvents. This tendency can be explained in terms of the steric effect since a bulky group attached to the keto group might reduce the preference of the keto form by means of the inhibition of the free rotation.

TABLE IV. UV Spectra of Acylmethylpyridazines

Compounds	Solvents A: EtOH B: cyclo-C_6H_{12}	Absorptions λ_{max} (nm, ε)			
IIIa-1	A	256 (3700)		320 (2600)	
	B[a]	283 (4800)		323 (4800)	335 (4100)
IIIc-1	A	256 (4100)		320 (2000)	
	B[a]	262 (4000)	283 (sh, 2300)	323 (2000)	333 (1900)
IIIa-2[b]	A	254 (1700)		323 (3100)	
IIIc-2	A	268 (sh, 2500)		322 (5000)	
	B	283 (5600)		325 (7500)	337 (6700)
IIIa-3	A	243 (9500)		343 (5800)	
	B	238 (5600)		342 (8400)	
IIIc-3	A	238 (9600)		341 (6600)	
	B	238 (9700)		340 (13000)	
Vc-3[b]	A	244 (19000)		346 (9300)	
IIIb-3[b]	A	245 (19000)	281 (2000)		
4-Me-pyridazine	A	248 (2000)	300 (*ca.* 200)		

a) Addition of ether (5%) was necessary for IIIa-1 and IIIc-1 because these compounds are insoluble in neat cyclohexane.
b) Data are absent for IIIa-2, Vc-3, and IIIb-3 in cyclohexane as these compounds are essentially insoluble in cyclohexane.

Additionally, a solvent effect is recognizable, as the polar solvents have a tendency to decrease the K values.[6,7] On the other hand, 4-phenacylpyridazine (IIIb-3) exists only in the keto form in any examined solvent, and also, the addition of trifluoroacetic acid (TFA) lead the tautomerism of 3-acylmethylpyridazines to be inclined to the keto form nearly quantitatively.

These observations support the necessity of the presence of the free nitrogen atom which is able to form a six-membered ring by a hydrogen-bond, for the existence of the isomeric form in this series. This can be also supported by the fact that 6-phenacylpyridazine 1-oxide (IX)[8] and 2-phenacylpyridine 1-oxide (X)[8] are present only in the keto form in any solvent.

Next, the ultraviolet (UV) spectra of acylmethylpyridazines in ethanol and in cyclohexane have been examined (Table IV).

The absorptions in the shorter wave length (238—283 nm) might be due to the keto form and those in the longer wave length (320—346 nm) might be assigned to the conjugated system in the isomeric form.[9] The polar effect of the solvents was again recognizable, since ethanol seems to depress the absorptions in the longer wave length to some extent as compared with cyclohexane, although this tendency was not remarkable.

Further, the infrared (IR) spectra of those compounds have been examined and the absorptions in the stretching frequency region are listed in Table V.

Table V. IR Spectra of Acylmethylpyridazines and Related Compounds

Compounds	States	Absorptions (cm^{-1})	
IIIa-1	Neat	1720	(1635 very weak sh.)
	$CHCl_3$ sol.	1712	1625
IIIc-1	KBr disk	1720	Absent
	$CHCl_3$ sol.	1712	1626 sh.
Vc-1	KBr disk	1720	(1635 weak)
	$CHCl_3$ sol.	1730	1640
IIIa-2	KBr disk	1730	Absent
	$CHCl_3$ sol.	1710	1620
IIIc-2	KBr disk	(1730 very weak sh.)	1635
	$CHCl_3$ sol.	1715	1625
IIIa-3	KBr disk	Absent	1625
	$CHCl_3$ sol.	1682	1621
IIIa-3·HCl	KBr disk	1680	Absent
IIIc-3	KBr disk	Absent	1640
	$CHCl_3$ sol.	1683	1629
Vc-3	KBr disk	1680	1632
	$CHCl_3$ sol.	1680	1628
IIIb-3	KBr disk	1675	Absent
	$CHCl_3$ sol.	1685	Absent
IX	KBr disk	1680	Absent
	$CHCl_3$ sol.	1682	Absent
X	KBr disk	1690	Absent
	$CHCl_3$ sol.	1690	Absent
XI[a]	Neat	1710	1645

a) K.R. Wursthorn and E.H. Sund, *J. Heterocycl. Chem.*, **9**, 25 (1972).

6) IIIa-3 is only exception in 3-acylmethylpyridazine series, for which the K in DMSO increased as compared with that in $CDCl_3$.
7) Almost quantitative deuterium exchanges of the hydroxy, olefinic and the methylene protons were observed, on standing IIIa-3 in CD_3OD at room temperature for 120 min.
8) These compounds were obtained from similar acylations of the corresponding N-oxides using LDA and methyl benzoate.
9) R.F. Branch, A.H. Beckett, and D.B. Cowell, *Tetrahedron*, **19**, 401 (1963).

The strong absorptions in the region 1730—1680 cm^{-1} might be due to the carbonyl stretchings of the keto form and those of medium strength in 1650—1620 cm^{-1} might be due to the C=C stretchings[9] or the C=O stretchings (see later) of the isomeric form. All the 3-acylmethylpyridazines showed the absorptions in the both regions, in $CHCl_3$ solutions. 4-Phenacylpyridazine (IIIb-1) and the N-oxides (IX and X), however, exhibited the IR absorptions only in the former region even in the solution as well as in the solid state. These observations well consist with the information in the NMR spectra of these compounds. On the other hand, in solid state, IIIa-2 showed only the absorption of the stretching at 1730 cm^{-1}, while IIIc-2 showed an absorption of medium strength at 1635 cm^{-1} besides a very weak C=O band at 1730 cm^{-1}. Thus, no remarkable tendency of the keto and isomer precedence was observed among 3-acylmethylpyridazines in solid state.

All the discussions described above have been exempt from the discrimination of the tautomeric isomers' structures among the keto-enamine (VIIa), enol (VIIb), zwitterion (VIIc) and the delocalized (VIId) structures. This distinction is not fulfilled with the IR data; the broad (occasionally very weak) absorptions at 3400—3200 cm^{-1} due to the isomeric III are difficult to be assigned to the hydrogen-bonded OH groups or the hydrogen-bonded NH groups.[3]

From the following discussion, VIIa, rather than VIIb or VIIc,[10] is proposed to be the predominantly participating structure in an isomeric acylmethylpyridazine at least in the non-polar solvents. 1) In the NMR spectra of III, the signals due to the protons on the pyridazine rings[11] of the isomeric forms appeared in abnormally high field for the structure VIIc, which has a positively charged nitrogen atom. Additionally, the more the solvent is polar, the more dominancy of the contribution of the charge separated structure, such as VIIc, is expected in the solution. The NMR and UV spectra showed rather opposite tendency. 2) In the NMR spectra of 3-isobutenylpyridazine (XII) and 3-(β-methylstyryl)pyridazine (XIIIb), obvious allyl couplings between their methyl protons and olefinic protons were observed.[12] However, the allyl couplings, which are expected for the $CH{=}C{-}CH_2X$ (X=H or Ph) moieties of the structure VIIb, were not observed in the corresponding signals due to the isomeric forms of all the acetonylpyridazines. 3) All the NMR signals due to the protons in the 6-positions[11] of XII and styrylpyridazines (XIII) appeared in the range δ 9.05—9.00. Those of VI and the keto forms of IIIa-1, IIIa-2, and IIIa-3 also appeared around δ 9. These resonance positions agree with those of the corresponding protons of usual 3-alkyl- or 3-alkenylpyridazines. However, the corresponding signals due to the isomeric forms of III in CCl_4 or $CDCl_3$ appeared in a higher field away from the former region.[11,13,14] These facts suggest that the normal six-π aromaticity of the pyridazine rings are destroyed in the isomeric forms of those solutions. 4) The UV absorptions which have been assigned to the isomeric forms of III, appeared at considerably longer wave lengths than those of common 3-substituted pyridazines,[15] and suggest that extended π-electron systems exist in the isomeric III.

It might be worthy to mention that the UV spectra of III in cyclohexane appreciably resemble those of 2*H*-[1,2,4]oxadiazolo[2,3-*b*]pyridazin-2-one (XIVa),[16] 2*H*-[1,2,4]oxadiazolo-

10) The structure VIId might be that of the intermediate or of the transition state molecule in the interconversion between VIIa and VIIb, if it is present in the equilibrium.

11) Especially, the signals of the protons in the 6-positions of III are notable. The signals of the protons in the 4- and 5-positions of IIIa-2 and IIIa-3 were occasionally difficult to be assigned as these signals were superimposed on those of the phenyl protons, in some solutions (see Table II).

12) XII: $J(CH)/(CH_3)_A = J(CH)/(CH_3)_B = 1.2$ Hz, XIIIb: $J(CH)/(CH_3) = 1.2$ Hz.

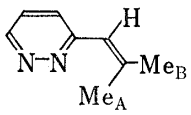
13) The simple estimation of the differences of δ, *i.e.*, δ (6-H)$_{isomer} - \delta$(6-H)$_{keto}$ of IIIa-1, IIIa-2, and IIIa-3 are 0.82, 0.93, and 0.83, respectively ($CDCl_3$).

14) The resonance positions of the pyridazine ring protons of these compounds are close to those of 1*H*-pyridazin-1-ones rather than to those of common 3-substituted pyridazines.

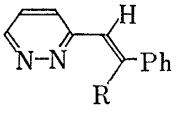
15) UV $\lambda_{max}^{cyclohexane}$; XIIIa: 290 nm (16100), XIIIb: 279 nm (5500).

16) T. Itai and T. Nakashima, *Chem. Pharm. Bull.* (Tokyo), **10**, 936 (1962).

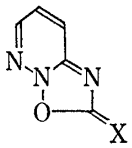
[2,3-*b*]pyridazine-2-thione (XIVb)[17] or 2*H*-3-(3-pyridazinyl)[1,3,5]triazino[1,2-*b*]pyridazine-2,-4-dione (XV).[17] 5) From such point of view, the IR absorptions near 1630 cm^{-1} in $CHCl_3$ are reasonably assigned to the hydrogen-bonded C=O stretchings in the structure VIIa.



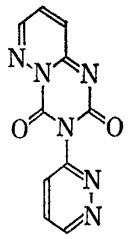
XII



XIIIa : R=H, XIIIb : R=Me



XIVa : X=O, XIVb : X=S



XV

Chart 6

Finally, the isomerizing tendency of III well explains the difficulty of the further reactions on III (Chart 3), because the stabilization due to the isomerization in the strongly basic media might retard both the reactions of eq. 1 and eq. 2.

Experimental

NMR spectra were recorded on Hitachi R-20 (60 MHz) and R-22 (90 MHz) instruments (the probe temperature was 34°). The data in Tables II and III (and Fig. 1) were obtained with 5—10% solutions of the samples. The integrations were run 2 hours after the dissolutions of the materials.

IR spectra were recorded on JASCO IRA-1 and IRA-2 instruments. The spectra in $CHCl_3$ were run at *ca.* 5% density. A Hitachi ESP-3T instrument was used for all UV spectral analyses. The IR in $CHCl_3$ and UV spectra were recorded 2 hours after the preparations of the sample solutions.

Preparation of Acylmethylpyridazines (III)——All melting points are uncorrected. The general procedure is as follows.[1] A methylpyridazine (I, 1 g) in THF (10 ml) was added to a stirred solution of LDA (1.2 molar eq.) in THF with cooling on a dry-ice acetone bath under N_2 atmosphere. The mixture was then allowed to stand at room temperature for 1 hr and again cooled on a dry-ice acetone bath. A solution of an ester (1 molar eq.) in THF was added to the mixture with stirring. The mixture was kept at room temperature for 3 hr with stirring and quenched by H_2O (3 ml). After filtration and drying ($MgSO_4$), the solution was evaporated *in vacuo* to dryness. The resulting material was subjected to the isolation procedure as described next.

Acylation of IIIa with Ethyl Acetate (Run 1)——The residue obtained from the preceding procedure, was submitted to an aluminum oxide column chromatography using CH_2Cl_2 to give an oil (crude IIIa-1) besides the starting material (Ia, 0.3 g). Crude IIIa-1 was purified with an aluminum oxide thick layer chromatography (1 : 1 ether–CH_2Cl_2, Rf=0.55) to give essentially pure IIIa-1 (pale yellow oil, 0.30 g, 21%).[18] MS of IIIa-1 showed the ion peaks at *m/e* 136 (M^+, 100%), 135 (60%), 121 (M^+-CH_3, 10%) and 93 (M^+-COCH_3, 40%) besides other fragment peaks.

Acylation of IIIa with Methyl Benzoate (Run 3)——The reaction mixture was chromatographed on aluminum oxide using ether. IIIa-3 (0.6 g, 29%) was obtained besides Ia (0.2 g). IIIa-3: orange prisms from hexane–CH_2Cl_2, mp 97—97.5°.

Acylation of IIIc with Methyl Benzoate (Run 7)——The residue was recrystallized from $CHCl_3$. Vc-3 (150 mg, 5%) was obtained as yellow needles, mp 184—184.5°. The mother liquor was chromatographed on aluminum oxide using $CHCl_3$. IIIc-3 (595 mg, 30%) was obtained besides Vc-3 (trace) and Ic (0.1 g). IIIc-3: yellow needles from CCl_4, mp 104—104.5°.

Acylation of IIIa with Methyl Carbonate——The mixture was chromatographed on silica gel using CH_2Cl_2. The essentially pure material (VI, 420 mg, 26%) was further purified by a distillation using a Büchi GKR-50 instrument to give a colorless oil of bp 143° (bath temperature)/1 mmHg. *Anal.* Calcd. for $C_7H_8N_2O_2$: C, 55.25; H, 5.30; N, 18.41. Found: C, 54.81; H, 5.45; N, 17.92. NMR (δ); 9.08 (1H, dd, J=4.5 and 2.5 Hz), 7.63 —7.32 (2H, m), 4.01 (2H, s, CH_2) and 3.71 (3H, s, OCH_3). IR (film, cm^{-1}): 1735. VI was converted into its carbamide with refluxing in conc. NH_4OH. Colorless plates from EtOH, mp 150—151°. *Anal.* Calcd. for $C_6H_7N_3O$: C, 52.54; H, 5.15; N, 30.64. Found: C, 52.90; H, 5.25; N, 30.97. IR (KBr disk, cm^{-1}): 3270, 3120, 1650, and 1620.

17) UV λ_{max}^{EtOH}; XIVb: 310 (24000), XV: 247 (*ca.* 13000), 320 (*ca.* 4000), 341 (sh) nm.
18) See the footnote in Table I.