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Studies on Prototropic Tautomerism in Nitrogen Heterocyclic Compounds. II.[1] A Ring-Chain Tautomerism in 3-Hydroxy-6-(2-oxocycloalkyl)-methyl-2(1H)-pyridone and 3-Hydroxy-6-(3-oxoalkyl)-2(1H)-pyridone Derivatives

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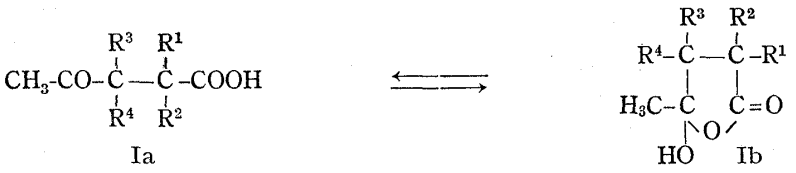
A ring–chain tautomerism between 3-hydroxy-6-(3′-oxoalkyl)-2(1H)-pyridone (VIII) and the alternative ring–form, 3,6-dihydroxy-1,2-dihydro-2-alkylindolizin-5(3H)-one (IX), was studied by means of infrared (IR) and nuclear magnetic resonance (NMR) spectroscopy. The IR spectra of VIII show the presence of a lactam–NH at 3100—3150 cm^{-1}, a lactam–CO at 1620—1650 cm^{-1} and a ketone at 1700—1750 cm^{-1}. However, the IR spectra of the ring–form (IX) lack a lactam–NH band and show only a lactam–CO band at 1620—1650 cm^{-1}.

The structures obtained from their IR spectra were also supported by their NMR spectra, in which the signal at *ca.* 1.45τ, due to a lactam–NH, indicates the predominance of a chain–form and also the signals at 3—4τ, due to two aliphatic OH (*cis* and *trans*), do the predominance of a ring–form.

From these results, the following conclusions were made. (1) When R^3=H, a ring–form is the prefered, and, when R^3= an alkyl, a chain–form is the prefered. However, when R^2 becomes bigger than *n*-C_5, some steric hinderance appears to keep a chain–form. (2) When R^2,R^3=$-(CH_2)_n-$, *i.e.* cyclic ketone, a chain–form is the prefered except in the case of n=4. (3) These results indicate that the ring–chain tautomerism of this type is an intramolecular, nucleophilic addition reaction of a lactam–NH to a carbonyl function.

Many examples[3] of a ring–chain tautomerism involving ketone and carboxyl function in a molecule (ketocarboxylic acid⇄lactol) have been known. For example, 2,2-dimethyllevulinic acid (Ia: R^1, R^2=CH_3, R^3, R^4=H) and 3,3-dimethyllevulinic acid (Ia: R^1, R^2=H, R^3, R^4=CH_3) exist as an equilibrium mixture of the chain–form (Ia) and the alternative ring—form (Ib) on the basis of their nuclear magnetic resonance (NMR) spectra.

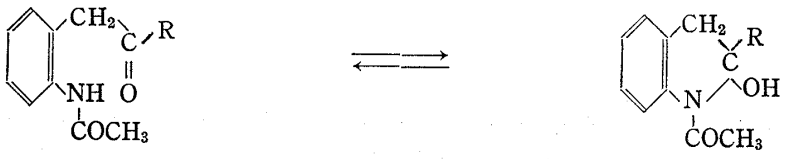


Ia Ib

On the other hand, there are a few reports on a ring–chain tautomerism including a lactam-NH and a carbonyl group. Recently, Buchardt, *et al.*[4] have reported that the compound having the general formula (IIa) exists in equilibrium with the ring–form (IIb). In this case, when R=H, the ring–form (IIb) is the prefered and, when R=CH_3, the chain–form is the prefered.

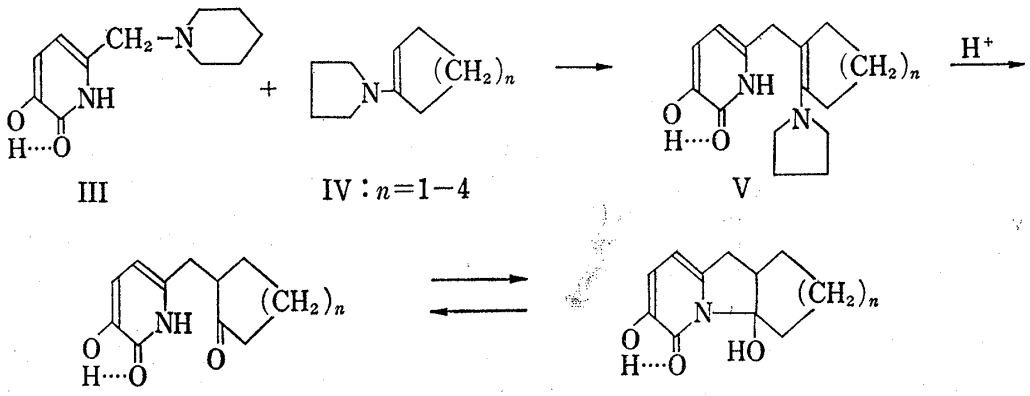
In our previous paper,[1] it has been reported that the compound obtained by the reaction of 3-hydroxy-6-piperidinomethyl-2(1H)-pyridone (III) with cyclohexanone enamine (IV:

1) Part I: A. Nakamura and S. Kamiya, *Chem. Pharm. Bull.* (Tokyo), **16**, 1466 (1968).
2) Location: *Tamagawayoga, Setagaya, Tokyo.*
3) P.R. Jones, *Chem. Rev.*, **63**, 461 (1963); C. Pascual, D. Wegmann, U. Graf, R. Scheffold, P.F. Sommer, and W. Simon *Helv. Chim. Acta*, **47**, 213 (1964); J. Finkelstein, T. Williams, V. Toome, and S. Traiman, *J. Org. Chem.*, **32**, 3229 (1967); J. Kagan, *ibid.*, **32**, 4060 (1967).
4) O. Buchardt, J. Becher and C. Lohse, *Acta Chem. Scand.*, **20**, 2467 (1966).



IIa IIb

n=2) does not exist as the chain–form (**2a**) in solid,[5] but as the alternative ring–form (**2b**).



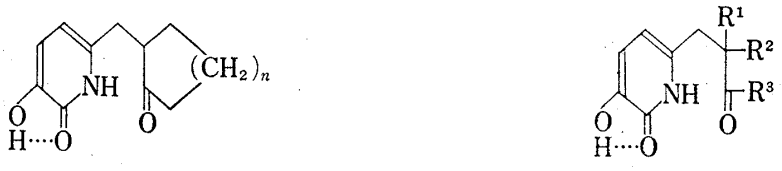
III IV : n=1–4 V

1a	n=1	**1b**
2a	n=2	**2b**
3a	n=3	**3b**
4a	n=4	**4b**

(——: prefered from)

Chart 1

As an extension of this series, the synthesis of many compounds possessing the moieties of 3-hydroxy-6-(2′-oxocycloalkyl)methyl-2(1H)-pyridone (VI) and 3-hydroxy-6-('3-oxoalkyl)-2(1H)-pyridone (VII) was carried out in order to gain a better understanding with regard to the ring–chain tautomerism in these systems.



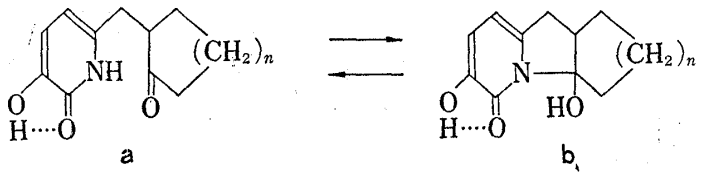
VI VII

The condensation products noted in Table I, were all synthesized by the similar method as reported in our previous paper.[1] In most cases the reaction was successful and the products were easily isolated after decomposing resulted enamines, V and XI.

As shown in Chart 1, treatment of III with the pyrrolidine enamines of cyclopentanone (IV: n=1), cyclohexanone (IV: n=2), cycloheptanone (IV: n=3) and cyclooctanone (IV: n=4) at the boiling temperature in a dioxane medium followed by hydrolysis yielded the corresponding condensation products, analytical data and yields of which were tabulated in Table I.

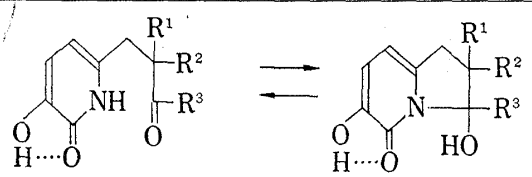
5) In this paper the infrared (IR) spectra were measured in a nujol mull and the NMR spectra in a hexadeuterodimethyl sulfoxide (DMSO-d_6) solution. "A structure in solid," therefore, means that in a nujol mull, and "a structure in solution" does that in a DMSO-d_6 solution.

TABLE I



a b

n	Prefered form In solid	Prefered form In soln.	Reaction time (hr)	Yield (%)	mp (decomp.) (°C)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
1	**1a**	**1a**	7	60	219—221	$C_{11}H_{13}O_3N$	63.75	6.32	6.76	63.69	6.35	7.08
2	**2b**	**2a+2b**	20	82	236—237	$C_{12}H_{15}O_3N$	65.15	6.83	6.33	64.98	7.08	6.31
3	**3a**	**3a**	20	62	239—241	$C_{13}H_{17}O_3N$	66.36	7.28	5.95	66.23	7.35	6.16
4	**4a**	**4a**	4	61	251—252	$C_{14}H_{19}O_3N$	67.44	7.68	5.62	67.97	7.67	5.80



a b

R^1	R^2	R^3	Prefered form In solid	Prefered form In soln.	Reaction time (hr)	Yield (%)	mp (decomp.) (°C)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
H	C_2H_5	CH_3	**5a**	**5a**	8	23	192—196	$C_{11}H_{15}O_3N$	63.14	7.23	6.69	63.39	7.37	6.84
H	CH_3	C_2H_5	**6a**	**6a**	15	17	190—191[a]	$C_{11}H_{15}O_3N$	63.14	7.23	6.69	63.61	7.51	6.71
CH_3	CH_3	H	**7b**	**7b**	8	45	260—262	$C_{10}H_{13}O_3N$	61.52	6.71	7.18	61.96	6.72	7.54
H	CH_3	H	**8b**	**8b**	7	7	213—215	$C_9H_{11}O_3N$	59.66	6.12	7.73	59.71	6.20	7.80
H	C_2H_5	H	**9b**	**9b**	8	19	208—210	$C_{10}H_{13}O_3N$	61.52	6.71	7.18	61.07	6.81	7.32
H	n-C_3H_7	H	**10b**	**10b**	10	32	194—195	$C_{11}H_{15}O_3N$	63.14	7.23	6.69	63.08	7.43	6.79
H	i-C_3H_7	H	**11b**	**11b**	7.5	53	192—194	$C_{11}H_{15}O_3N$	63.14	7.23	6.69	62.70	7.18	6.20
H	n-C_4H_9	H	**12b**	**12b**	5	28	177—179	$C_{12}H_{17}O_3N$	64.55	7.68	6.27	64.57	7.70	6.52
H	n-C_5H_{11}	H	**13b**	**13a**	7	11	172—173	$C_{13}H_{19}O_3N$	65.80	8.07	5.90	65.97	7.85	5.74
H	n-C_6H_{13}	H	**14b**	**14a**	12	55	168—170	$C_{14}H_{21}O_3N$	66.90	8.42	5.57	66.86	8.37	5.81

a) mp

Among these compounds the IR spectra of the products arising from cyclopentanone enamine (IV: n=1), cycloheptanone enamine (IV: n=3) and cyclooctanone enamine (IV: n=4) show the presence of a lactam-NH at the 3100—3150 cm^{-1} region and a typical cyclic ketone carbonyl (n=1:1745 cm^{-1}, n=3:1703 cm^{-1}, n=4:1700 cm^{-1}). The IR spectrum of **4a** was shown in Fig. 1-a as an example. These facts indicate that their structures in solid are the chain-forms, **1a**, **3a** and **4a**.

The structures of **1a**, **3a** and **4a** as a chain-form were also supported by their NMR spectra which exhibited a broad low field proton, characteristic to a lactam-NH, and a pair of doublet (AB-pattern), due to the two aromatic ring protons. For instance, the NMR spectrum of **4a** (Fig. 1-b) indicates a chelating phenolic OH at $-1.57\ \tau$, a lactam-NH at 1.43τ and a pair of doublet centered at 3.18τ and 4.00τ (J=7.5 cps). The doublet (3.18τ) is reasonable to assign as H^4-proton and that (4.00τ) as H^5-proton.

In contrast, the 100 Mc NMR spectrum (Fig. 2, at 25°) of the compound arising from cyclohexanone enamine (IV: n=2), of which structure in solid[1] was already established to

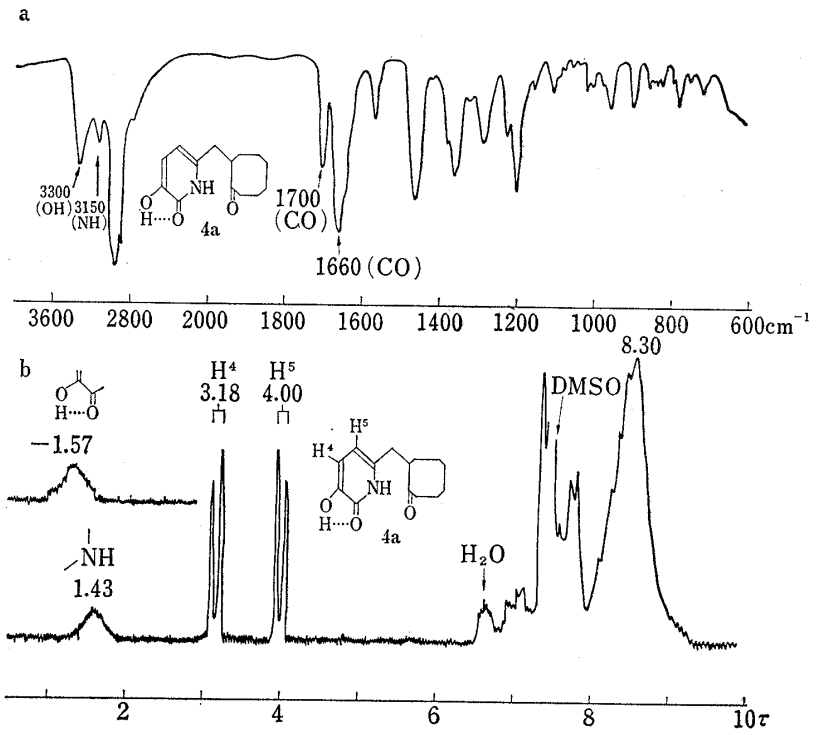


Fig. 1. IR (Nujol) and NMR(60 Mc/s, DMSO-d_6) Spectra of 3-Hydroxy-6-(2′-oxocyclooctyl)methyl-2(1H)-pyridone

be a tricyclic ring–form (**2b**), shows a chelating OH at −1.37τ (singlet, 1H), a lactam–NH at 1.45τ (broad, 0.2H), and two isomeric aliphatic tertiary OH at 3.58τ (broad singlet, 0.4H) and 3.80τ (singlet, 0.4H). These low filed protons vanished on addition of deuterium oxide. Also, the signals for H^4– and H^5–protons exhibit a somewhat comlicated pattern.

These facts indicate that, in solution, it exists as an equilibrium mixture of the chain–form (**2a**) and the ring–form (**2b**) in a coexisting ratio of 1:4 from the relative intensity of signals of the NH and tertiary OH. In addition to the ring–chain tautomers, the relative intensity of two signals for the tertiary OH proton suggests that the ring–form consists of the *cis* and *trans* isomers in approximately equal amounts.

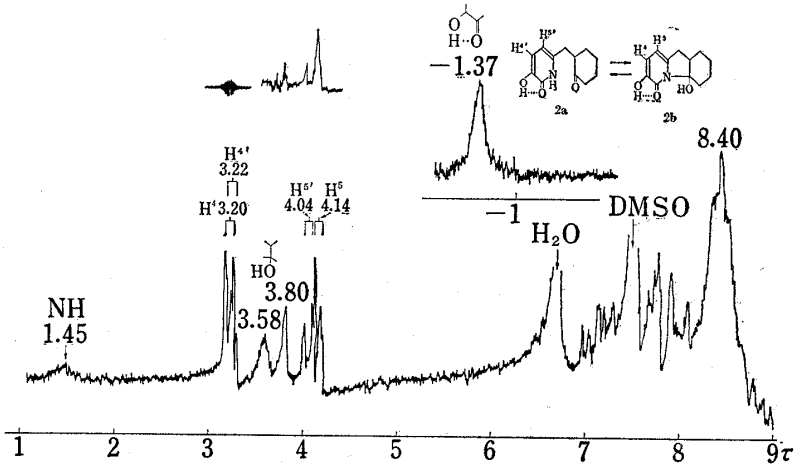
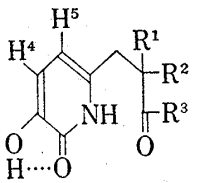


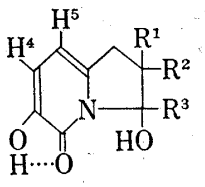
Fig. 2. NMR Spectrum (100 Mc/s) of 3-Hydroxy-6-(2-oxocyclohexyl)methyl-2(1H)-pyridone in DMSO-d_6

As mentioned in this work, the NMR spectra of chain compounds having a general form (VIII) show the signals for H^4– and H^5–protons at 3.18—3.22τ and 3.99—4.05τ, respectively. The signals for H^4– and H^5–protons of ring compounds having a general form (IX) also appear at 3.18—3.23τ and 4.10—4.16 τ, respectively.



VIII

H^4:3.18—3.22τ
H^5:3.99—4.05τ



IX

H^4:3.18—3.23τ
H^5:4.10—4.16τ

From these data, the doublets at 3.20 τ (J=7.5 cps) and 4.14 τ (J=7.5 cps) can be assigned to H^4- and H^5-protons of the ring-form (**b**), and the weak doublets at 3.22 τ (J=7.5 cps) and 4.04 τ (J=7.5 cps) to H^4- and H^5-protons of the chain-form (**2a**), respectively.

By spin decoupling at H^4 (Fig. 2), the doublets at 4.04 τ and 4.14 τ changed to the singlets with a relative ratio of 1:3. This ratio of the chain and ring tautomers agrees with that obtained from the relative intensity of the NH and tertiary OH.

As shown in Fig. 3, when its NMR spectrum was measured by charging temperature in the presence of deuterium oxide, the signals for the ring protons varied remarkably. Namely, as the temperature rises, the ratio of **2a** in this tautomerism (**2a**⇄**2b**) increases.

The products derived from such a chain ketone enamine as diethyl ketone enamine (X: R^1=CH_3, R^2=C_2H_5) or

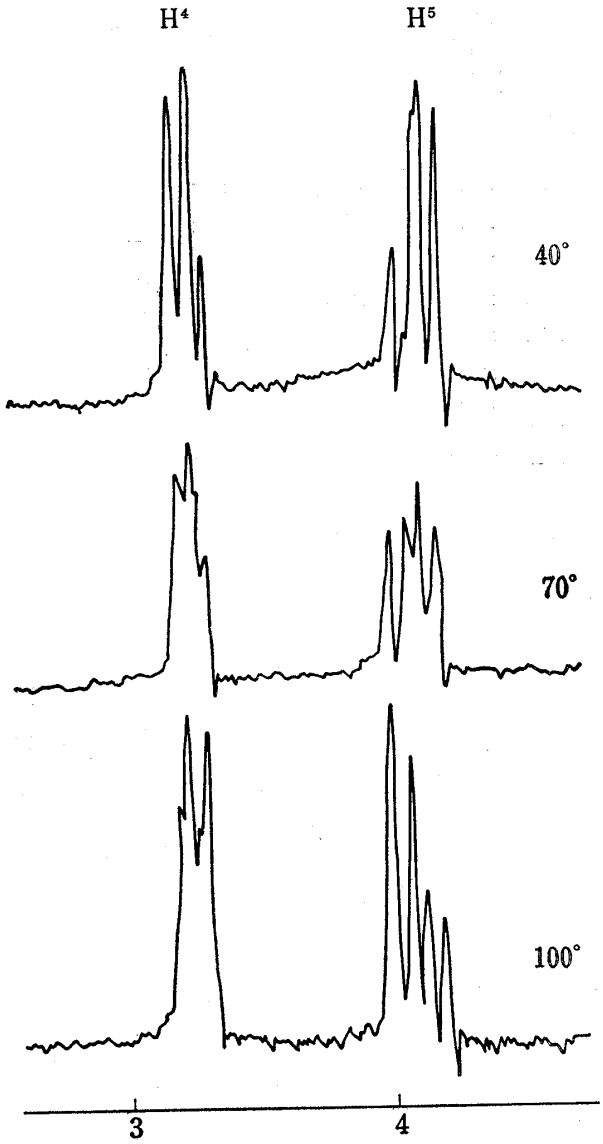
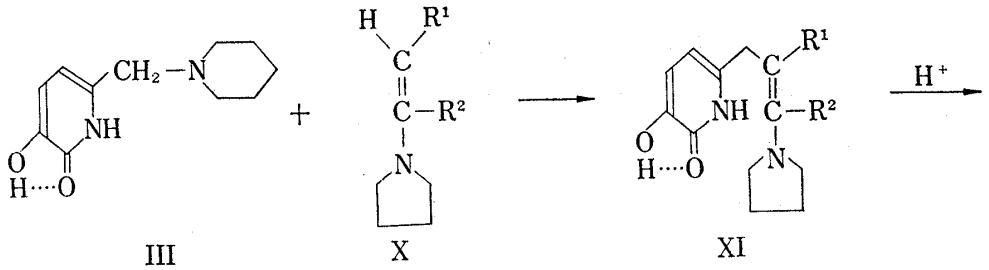
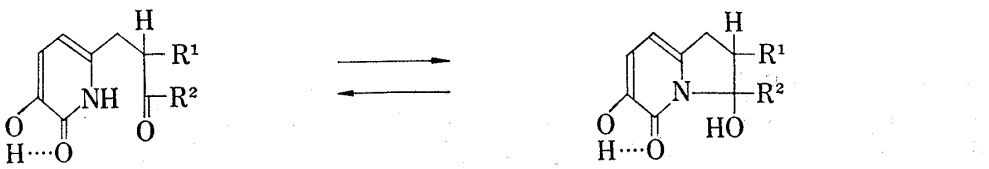


Fig. 3. NMR Spectrum (100 Mc/s, 3—5 τ Region) of 3-Hydroxy-6-(2′-oxocyclohexyl) methyl-2(1H)-pyridone measured at Different Temperatures



III X XI

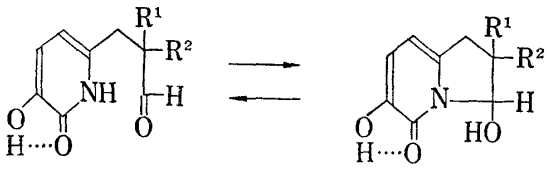


5a R^1=CH_3, R^2=C_2H_5
6a R^1=C_2H_5, R^2=CH_3

5b
6b

(——: prefered form)

Chart 2



7a	: $R^1, R^2=CH_3$	:	**7b**
8a	: $R^1=H, R^2=CH_3$	:	**8b**
9a	: $R^1=H, R^2=C_2H_5$	:	**9b**
10a	: $R^1=H, R^2=n\text{-}C_3H_7$	:	**10b**
11a	: $R^1=H, R^2=i\text{-}C_3H_7$	:	**11b**
12a	: $R^1=H, R^2=n\text{-}C_4H_9$	:	**12b**
13a	: $R^1=H, R^2=n\text{-}C_5H_{11}$	:	**13b**
14a	: $R^1=H, R^2=n\text{-}C_6H_{13}$	:	**14b**

(——: prefered form)

Chart 3

methyl propyl ketone enamine (X: $R^1=C_2H_5$, $R^2=CH_3$) exist as the chain-forms, **5a** and **6a**, in solid on the basis of their IR spectra (Fig. 4-a) which show the presence of a lactam-NH (**5a**: 3140 cm^{-1}, **6a**: 3120 cm^{-1}) and a ketone carbonyl (**5a**, **6a**: 1710 cm^{-1}). In solution, they also exist as the chain-forms, **5a** and **6a**, on the basis of their NMR spectra which indicate the presence of a lactam-NH at 1.29 τ (broad, 1H) and a clear AB-pattern for the ring protons, as shown in Fig. 4-b and 4-c.

Then, the ring-chain tautomerism in the products (Chart 3) derived from various aldehyde enamines was examined. The IR spectra of these compounds (for instance,

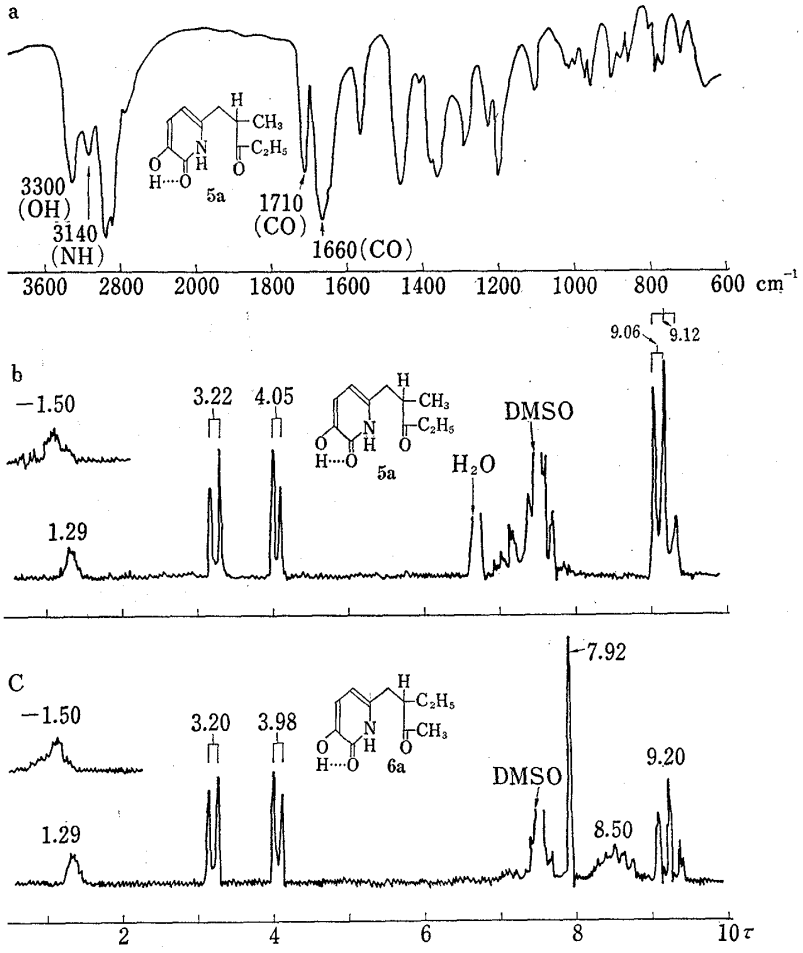


Fig. 4

Fig. 5-a), in which the carbon number of R^2 is from C_1 to C_4, show a strong absorption at 1620—1660 cm^{-1}, due to a lactam-CO, and no peak in aldehyde-CO and lactam-NH regions. These facts are evidence for the ring compounds, 3,6-dihydroxy-1,2-dihydro-2-alkylindolizin-5(3*H*)-one (**7b**, **8b**, **9b**, **10b**, **11b**, **12b**).

However, when the carbon number of R^2 becomes bigger than n-C_5, the chain-forms, **13a** and **14a**, are the prefered. Namely, as shown in Fig. 5-b and 5-c, the aldehyde absorp-

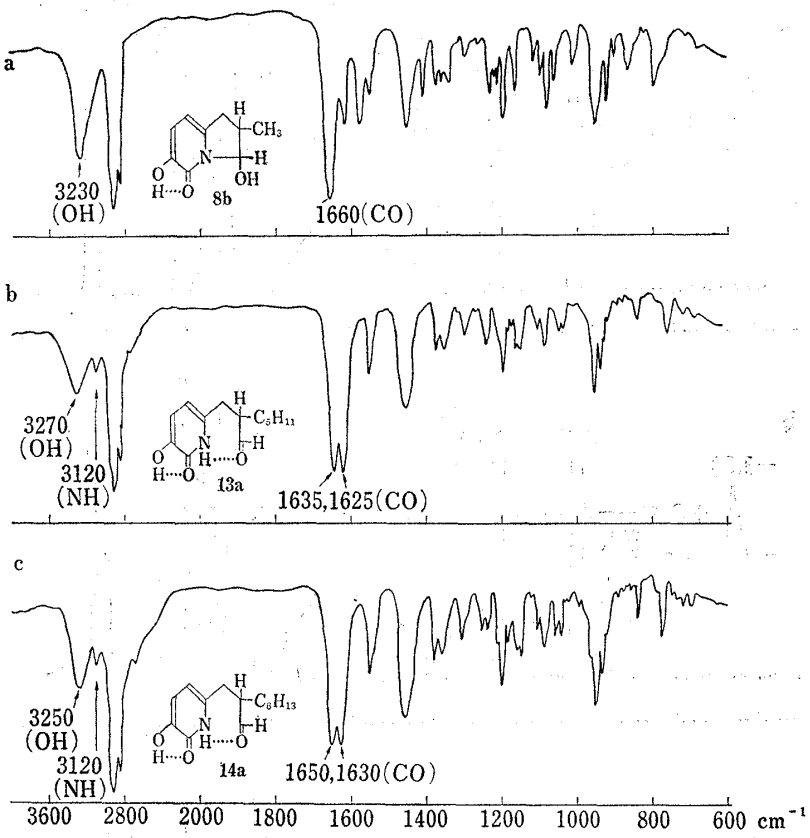


Fig. 5

tions are present at 1635 cm^{-1} and 1650 cm^{-1} which considerably shifted by an intramolecular hydrogen bonding, and are in contrast with the IR spectra of **5a** and **6a**, showing a ketone carbonyl at the normal region. The NH absorptions of **13a** and **14a** as an additional evidence for a chain-form are also observable at both 3120 cm^{-1}.

The NMR spectra of **7b**, **8b**, **9b**, **10b**, **11b** and **12b** show the absence of the low filed signals, due to aldehyde-H and lactam-NH. This fact reveals that they are also present as a ring-form in solution. Among these NMR spectra, that of **7b** (Fig. 6-a) exhibits a doublet centered at 2.96 τ, due to the secondary OH, and a doublet centered at 5.08 τ, due to the >C<u>H</u>-OH. Reasonably, the former vanished and the latter changed to a singlet on addition of deuterium oxide.

The NMR spectrum of **8b** (Fig. 6-b) is, however, somewhat complicated, showing a triplet centered at 2.96 τ, due to the *cis* and *trans* OH, and the two signals at 4.73 τ and 4.99 τ, due to the >C<u>H</u>-OH. On treatment with deuterium oxide the former vanished, but the latters changed to the two doublets, coupling constants of which are $J=1.7$ cps and 4.4 cps, respectively. From the magnitude of the coupling constants, the two signals at 4.73 τ and 4.99 τ are reasonably assigned as the *trans*-H and the *cis*-H of the >C<u>H</u>-OH, respectively. In the higher filed, the two doublets centered at 9.04 τ and 9.14 τ are observed. A possible interpretation for these two signals involves the *cis* and *trans* isomers of the methyl group in the ring-form, and also the relative intensity reveals that the *cis* and *trans* isomers in these ring compounds are present in approximately equal amounts. The NMR spectra of other aldehyde derivatives indicate the similar pattern to be a ring-form in solution. However, it is of interest that **13** and **14**, which exist as a chain-form in solid, prefer the ring structures, **13b** and **14b**, in solution (Fig. 6-c).

Several attempts to convert the ring compounds to the corresponding chain-forms by recrystallization or heating, were unsuccessful except **7b**. When an ethanol solution of **7b** was evaporated to dryness on a water bath, a new absorption at 3150 cm^{-1}, due to a lactam-

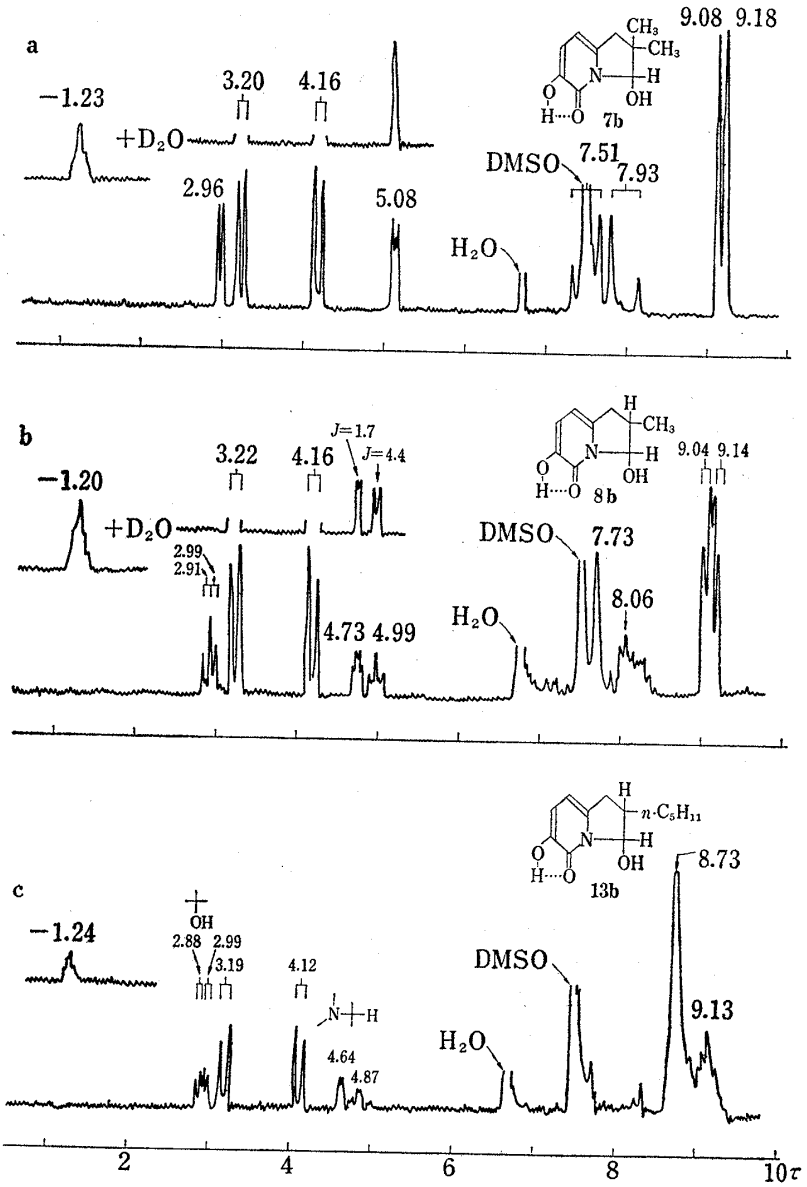


Fig. 6

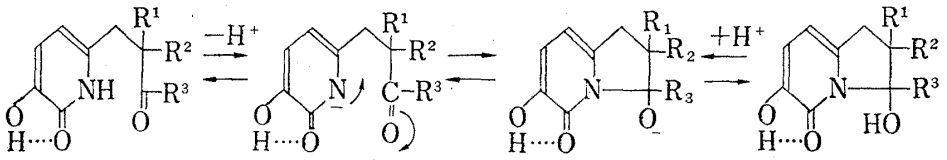
NH, appeared as a shoulder. Whereas, when this new compound was recrystallized from ethanol again, the new absorption vanished. This phenomenon could be explained that a part of 7b changed to the chain–form rather than due to polymorphism.

From the present experimental results, the following conclusions were made. (1) When R^3=H, a ring–form is the prefered, and, when R^3= an alkyl, a chain–form is the prefered. However, when R^2 becomes bigger than n-C_5, some steric hindrance[6] appears to keep a chain–

6) The polar effect of R^2 toward the carbonyl function is able to express as Taft's σ^* parameter.[7] Since positive charge on the carbon atom of the carbonyl function increases as the magnitude of σ^* does and also the sum of σ^* values of the two methyl groups in **7b** (ring–form), which could convert to a chain–form in part by heating, is −0.200, the compounds having larger values than −0.200 are expected to be predominant of a ring–form. However, though the magnitudes of σ^* of the compounds, **13** (−0.160) and **14**(−0.175), are larger than −0.200, they are present as a chain–form (**13a**, **14a**) in solid and as a ring–form (**13b**, **14b**) in solution. As a matter of fact, the relative intensities of the *cis* and *trans* >CH–OH in the 100 Mc/s NMR spectrum of **14** indicate the predominance of the trans compound in a ratio of 3:4, as shown in Fig. 6–c. These facts indicate that the carbonyl group must be sterically hindered by an n-pentyl or n-hexyl group in this intramolecular addition reaction.

7) R.W. Taft, Jr., "Steric Effects in Organic Chemistry," ed. by M.S. Newman, John Wiley & Sons, New York, 1956, Chapter 13.

form. (2) When $R^2,R^3=-(CH_2)_n-$, *i.e.* cyclic ketone, a chain-form is the prefered except in the case of $n=4$. (3) These results indicate that the ring-chain tautomerism of this type is an intramolecular, nucleophilic addition reaction of a lactam-NH to a carbonyl function and should proceed through the following mechanism.



Experimental[8]

3-Hydroxy-6-(2′-oxocyclopentyl)methyl-2(1H)-pyridone (1a)——A typical experiment for the reaction of 3-hydroxy-6-piperidinomethyl-2(1H)-pyridone (III)[1] with various cyclic and chain ketone pyrrolidine enamines is described with 3-hydroxy-6-(2′-oxocyclopentyl)methyl-2(1H)-pyridone. A mixture of 3.70 g (0.044 mole) of cyclopentanone, 3.20 g (0.044 mole) of pyrrolidine and 50 ml of dehyd. benzene was refluxed in a flask attached to a Dean-Stork water separator for 2 hr, during which time about 0.5 ml of water was collected. The reaction mixture was evaporated to dryness under reduced pressure. To the residue was added 4.16 g (0.020 mole) of III and 50 ml of dehyd. dioxane, the mixture was refluxed for 7 hr, and the reaction mixture was evaporated to dryness under reduced pressure. The residue was heated with 50 ml of water at the boiling temperature for 2 hr, and the reaction mixture was evaporated to dryness under reduced pressure. The residue was treated with a small amount of ethanol, and the separated crystals were filtered. Yield, 2.50 g (60%), mp 210—213° (decomp.). This product was recrystallized from ethanol three times to give colorless granules, mp 219—221° (decomp.).

The analytical data for these compounds are tabulated in Table I.

3,6-Dihydroxy-1,2-dihydro-2-ethylindolizin-5(3H)-one (9b)——A typical experiment for the reaction of III with various aldehyde piperidine enamines is described with 3,6-dihydoxy-1,2-dihydro-2-ethylindolizin-5(3H)-one. To an ice-cooled mixture of 3.60 g (0.05 mole) of *n*-butylaldehyde and 3.0 g of anhyd. potassium carbonate, was added dropwise 8.50 g (0.10 mole) of piperidine. The reaction mixture was allowed to stand at room temperature overnight and filtered. By distillation of the filtrate under reduced pressure, 2.80 g (40%) of 1-N-piperidino-*n*-1-butene, bp 90° (30 mmHg), was obtained.

Other aldehyde piperidine enamines were similarly prepared.[9] 1-N-Piperidino-1-propene: bp 40—47° (7 mmHg). 1-N-Piperidino-*n*-1-pentene: bp 73—75° (7 mmHg). 1-N-Piperidino-3-methyl-1-butene: bp 73—75° (7 mmHg). 1-N-Piperidino-*n*-1-hexene: bp 115—116° (20 mmHg). 1-N-Piperidino-*n*-1-heptene: bp 107—108° (7 mmHg). 1-N-Piperidino-*n*-1-octene: bp 108—109° (4 mmHg). 1-N-Pyrrolidinoisobutene[10] was directly used without distillation.

The distilled enamine reacted similarly with 3-hydroxy-6-piperidinomethyl-2(1H)-pyridone (III) in dehyd. dioxane, and the reaction mixture was treated by the same method described for **1a**. Yield, 0.75 g (19%). Colorless needles, mp 208—210° (decomp.).

The analytical data for these compounds are tabulated in Table I.

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8) All melting and boiling points are uncorrected. IR spectra were measured on a JASCO Model IR-S infrared spectrophotometer. NMR spectra were determined on a Japan Electron Optics JNM C-60H or JNM 4H-100 spectrophotometer and tetramethylsilane was used as an internal standard.

9) C. Mannich and H. Davidsen, *Chem. Ber.*, **69**, 2106 (1936).

10) J. Szmuszkovicz, "Advances in Organic Chemistry—Methods and Results," Vol. 4, ed. by R.A. Raphael, E.C. Taylor and H. Wynberg, Interscience Publishers, New York, 1963, p. 99.