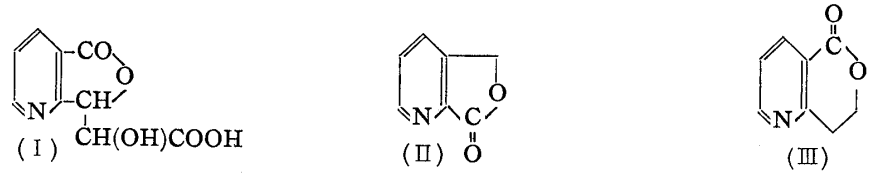
UDC 547.826.1[547.834.2].07

74. Yoshinobu Sato, Tadahiro Iwashige, and Tetsuo Miyadera: Syntheses of 2-Hydroxymethylnicotinic Acid Lactone, 2-Hydroxymethylpyridine-3-acetic Acid Lactone, and Some of their Derivatives.

(*Takamine Research Laboratory, Sankyo Co., Ltd.*[*1])

Compounds of pyridine with a lactone ring formed in the 2—3 position are not known widely and only a few examples are found in literature. For example, Rosenheim and Ochiai[1] obtained 3-(3-carboxy-2-pyridyl)glycerinic acid γ-lactone (I) by calcium chloride oxidation of 6-hydroxyquinoline, as intermediate for synthesis of 1,6-naphthyridine derivative, Zinke and others[2] obtained 3-hydroxymethylpicolinic acid lactone (II) from 3-dichloroacetylpicolinic acid, and Ikekawa[3] prepared 2-(2-hydroxyethyl)nicotinic acid lactone (III) from ethyl 2-methylnicotinate (VI).



(I) (II) (III)

Possibility of synthesizing new types of lactone from ethyl 2-methylnicotinate (VI) was considered and attempts were made to prepare 2-hydroxymethylnicotinic acid lactone (IV) and 2-hydroxymethylpyridine-3-acetic acid lactone (V).

First, 2-hydroxymethylnicotinic acid lactone (IV) was synthesized by the route shown in Chart 1.

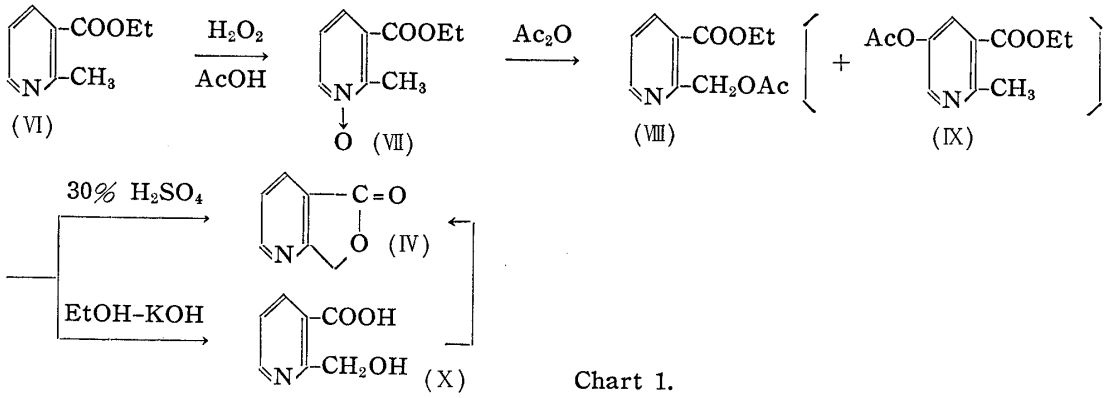


Chart 1.

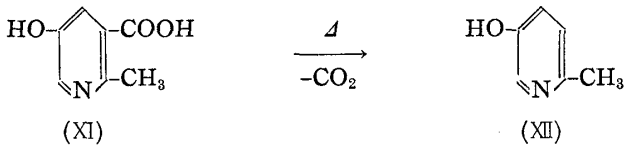
Following the usual procedure, (VI) was warmed with hydrogen peroxide in glacial acetic acid to form its 1-oxide (VII), b.p$_4$ 152°, which was submitted to rearrangement reaction in acetic anhydride, forming an oily substance which was considered to be ethyl 2-acetoxymethylnicotinate (VIII), b.p$_3$ 133~136°. Its saponification with 30% sulfuric acid and detailed examination of its reaction product revealed the presence of the lactone (IV) of m.p. 141~142° as the major product, accompanied by some crystals of m.p. 305~307° (decomp.) (XI). The latter was positive to the ferric chloride reaction and its ultraviolet spectrum in ethanol exhibited maximum absorption at 296 mμ, besides that at 263~265 mμ

*1 Nishi-Shinagawa, Shinagawa-ku, Tokyo (佐藤義信, 岩重忠博, 宮寺哲男).

1) O. Rosenheim, J. Tafel: Ber., **26**, 1501(1893); E. Ochiai, K. Miyaki, S. Sato: *Ibid.*, **70**, 2018 (1937).
2) Th. Zinke, E. Winzheimer: Ann., **290**, 353(1896).
3) N. Ikekawa: This Bulletin, **6**, 263(1958).

usually observed in 2,3-disubstituted pyridines. The former absorption showed a bathochromic shift to 311 mμ in ethanol-0.1*N* sodium hydroxide (1:1). Analytical values of this compound agreed with the formula of $C_7H_7O_3N$ and its infrared spectrum exhibited absorption of carboxyl at 1660 cm^{-1}, no absorption for phenolic hydroxyl, and a broad absorption in the region of 1700~2800 cm^{-1}. The ester of (XI), however, showed absorption at 1730 cm^{-1} considered to be due to an ester group, and two broad absorption bands thought to be characteristic to 3-hydroxypyridine at 1800 and 2500 cm^{-1}.[4]

Decarboxylation of (XI) by heating to 310~320° at atmospheric pressure afforded 2-methyl-5-hydroxypyridine[5] (XII), m.p. 168~168.5°. From these facts, it is concluded that



(XI) (XII)

this copound (XI) is 2-methyl-5-hydroxynicotinic acid. This compound must have been formed by saponification of a minor product, ethyl 2-methyl-5-acetoxynicotinate (IX), hardly separable by distillation from the main product (VIII) of rearrangement reaction of (VII). This agrees with the fact that 3-hydroxy compound as well as 2-hydroxymethyl compound is obtained from rearrangement reaction of 2-picoline 1-oxide.[5]

When the saponification of (VIII) to the lactone (IV) was carried out with ethanolic potassium hydroxide, followed by treatment of the reaction product at pH 3~4, needle crystals of m.p. 153~154° were obtained. The infrared spectrum of this product exhibited absorption bands of hydroxyl at 3240 and 1053 cm^{-1}, and absorptions characteristic to pyridinecarboxylic acid at 2450, 1950, and 1690 cm^{-1}.[6] The ultraviolet spectrum of this product showed maximum absorption (in EtOH) at 265 mμ, considered to be characteristic to 2,3-disubstituted pyridine. It was concluded from the foregoing facts and from analytical values that this compound is 2-hydroxymethylnicotinic acid (X). This compound undergoes decomposition with effervescence at its melting point and transits to the above-mentioned lactone (IV), m.p. 141~142°.

Next, 2-hydroxymethylpyridine-3-acetic acid lactone (V) was prepared by the route shown in Chart 2.

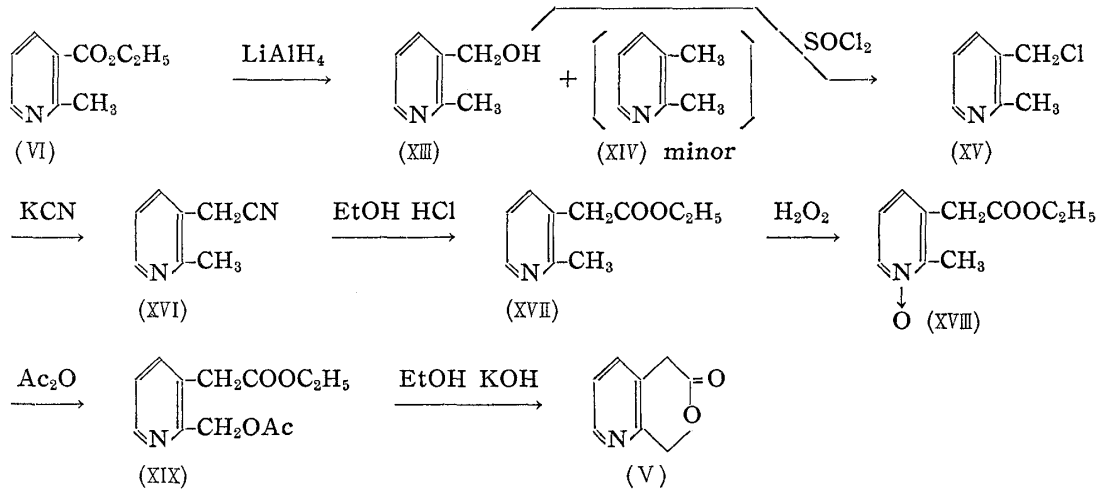
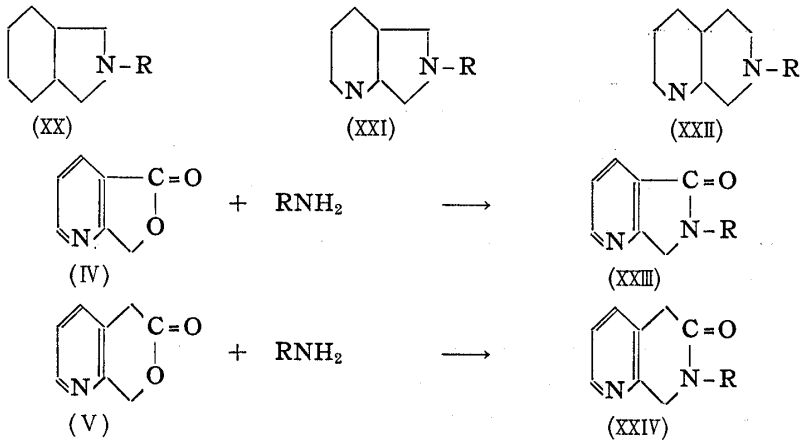


Chart 2.

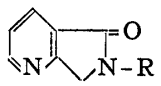
4) H. Shindo: "Infrared Absorption Spectra," Suppl. No. 28, Kagaku-no-Ryoiki, 190(1958).
5) S. Okuda: This Bulletin, **3**, 316(1955).
6) H. Shindo: "Infrared Absorption Spectra," Suppl. No. 28, Kagaku-no-Ryoiki, 191(1958).

Following the usual procedure, (VI) was reduced with lithium aluminium hydride in ether and 2-methyl-3-hydroxymethylpyridine (XIII), b.p_4 139~140°, was obtained besides a small amount of a lower-boiling fraction which formed a picrate of m.p. 187~188°. The analytical values and melting point of the latter agreed with constants given in the literature[7] for 2,3-lutidine. It was thereby assumed that a part of the main reduction product (XIII) had been reduced to 2,3-lutidine in the presence of excess of lithium aluminium hydride and prolongation of reaction time. Following the reaction route shown in Chart 2, 2-hydroxymethylpyridine-3-acetic acid lactone (V), m.p. 118~119°, was finally obtained and its infrared spectrum showed absorption at 1730 cm^{-1}, considered to be due to a carbonyl in six-membered lactone ring.

Rice and others[8] synthesized various derivatives of 2-azabicyclo[4.3.0]nonane (XX) and reported that some of them showed fairly strong hypotensive action. In order to prepare analogous derivatives (XXI and XXII) from the lactones (IV and V) newly synthesized as described above, attempts were made to obtain the lactams of (XXIII) and (XXIV).



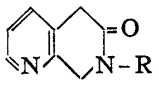
In any of the cases, the lactone and twice the calculated amount of the amine were heated at around 200°, either in a sealed tube or at atmospheric pressure, and lactam derivatives (XXIII and XXIV) were obtained in 70~90% yield, as listed in Tables I and II. Infrared spectra of (XXIII) and (XXIV) indicated the absorption of a five-membered lactam ring at 1690 cm^{-1} and of six-membered lactam ring at 1650 cm^{-1}, but not the absorption

Table I. 

Compd. (XXIII)	R	m.p. (°C) or b.p. (°C/mm.Hg)	Yield (%)	Mol. formula	Analysis (%) C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
a	C_6H_5-	m 180.5~181.5	74	$C_{13}H_{10}ON_2$	74.27	74.16	4.79	4.64	13.33	13.01
b	$C_6H_5CH_2$-	m 140~141	58.7	$C_{14}H_{12}ON_2$	74.99	75.09	5.38	5.52	12.50	12.31
c	$-(CH_2)_2N(CH_3)_2$	m 72~73	93.3	$C_{11}H_{15}ON_3$	64.36	64.42	7.37	7.37	20.49	20.39
d	$-(CH_2)_2N(C_2H_5)_2$	b 123~126/0.03	92.8	$C_{13}H_{19}ON_3$	66.92	67.12	8.21	8.09	18.01	18.29
e	$-(CH_2)_2N(iso\text{-}C_3H_7)_2$	b 142~143/0.04	55	$C_{15}H_{23}ON_3$	72.82	72.63	10.19	10.37	16.99	17.25
f	$-(CH_2)_2$N	m 95.5~97	93	$C_{13}H_{17}ON_3$	67.50	67.76	7.41	7.38	18.17	18.04
g	$-(CH_2)_3N(CH_3)_2$	b 151~154/0.28	85	$C_{12}H_{17}ON_3$	54.70	54.72	5.22	5.21	20.29	19.68
h	$-(CH_2)_3$N	b 175~177/0.01	81.8	$C_{14}H_{19}ON_3$	68.54	68.31	7.81	7.79	17.13	16.97

7) K. Tsuda, *et al.*: This Bulletin, **1**, 142(1953).
8) L. M. Rice, *et al.*: J. Am. Chem. Soc., **75**, 4911(1953), **77**, 616(1955); J. Org. Chem., **23**, 844(1958).

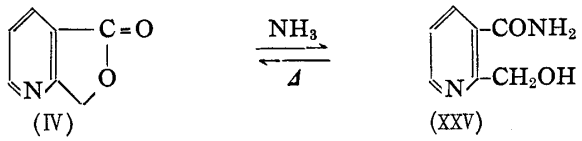
Table II.



Compd. (XXIV)	R	m.p. (°C) or b.p$_{0.01\sim0.02}$ (°C) (bath temp.)	Yield (%)	Mol. formula	Analysis (%) C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
a	C_6H_5-	m 131~132	53	$C_{14}H_{12}ON_2$	75.00	74.81	5.36	5.64	12.50	12.40
b	$C_6H_5CH_2$-	m 117~118	61	$O_{15}H_{14}ON_2$	75.60	75.55	5.87	6.08	11.76	11.84
c	-$(CH_2)_2N(CH_3)_2$	b 140~150	68	$C_{12}H_{17}ON_3$	65.80	65.75	7.76	8.02	19.20	18.95
d	-$(CH_2)_2N(C_2H_5)_2$	b 145~155	62	$C_{14}H_{21}ON_3$	68.00	67.72	8.50	8.71	17.00	17.20
e	-$(CH_2)_2N$(iso-$C_3H_7)_2$	b 165~170	50	$C_{16}H_{25}ON_3$	69.80	69.44	9.09	9.06	15.30	15.58

of NH in the region of 3100~3400 cm^{-1}.

Assuming that this lactam formation would also be effected with ammonia, the lactone (IV) was reacted with ammoniacal ethanol or liquid ammonia but contrary to anticipation, 2-hydroxymethylnicotinamide (XXV), m.p. 146~147°, was produced in either case. It was also found that the amide (XXV) reverted to the lactone (IV) by liberation of ammonia when heated at its melting point.



(IV) (XXV)

As the mechanism for lactam formation described above, the following reaction route may be cosidered. 2-Hydroxymethylnicotinamide derivative would be the reaction intermediate which may undergo dehydration to form the lactam. In this connection, it seemed of interest to see whether N-benzyl-2-hydroxymethylnicotinamide (XXVI), a model compound, would undergo deamination like (XXV) to form the lactone (IV) or dehydration to form the lactam (XXIIIb), and attempt was made to prepare (XXVI) by the route shown in Chart 3.

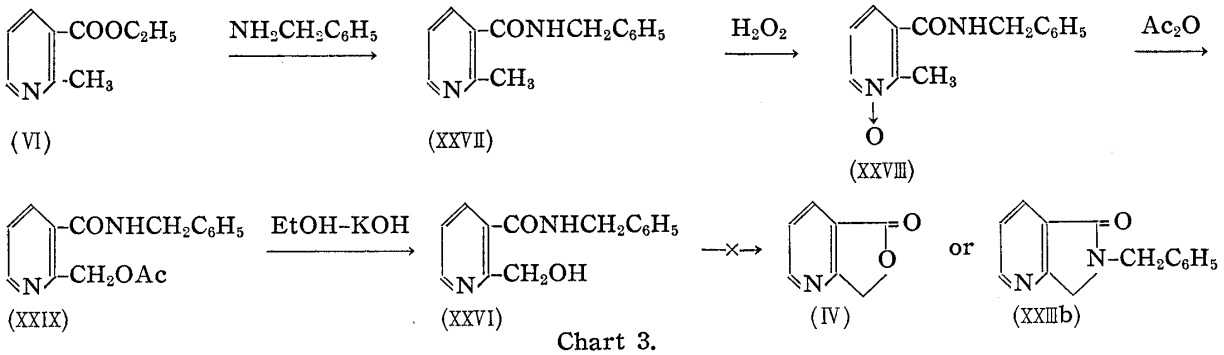
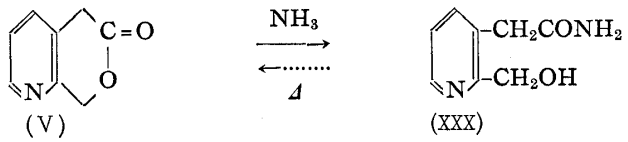


Chart 3.

From series of reactions illustrated in Chart 3, a viscous oily substance considered to be N-benzyl-2-hydroxymethylnicotinamide (XXVI) was obtained. Low-pressure distillation of this oily product gave an extremely small amount of sublimable crystals whose infrared spectrum failed to establish its identity with either (IV), (XXIIIb), or the unreacted (XXVI).

Application of ethanolic ammonia to 2-hydroxymethylpyridine-3-acetic acid lactone (V) afforded, similar to the other lactone (IV), 2-hydroxymethylpyridine-3-acetamide



(V) (XXX)

(XXX) of m.p. 154~155°. Heating of (XXX) to 160° and maintenance of the fused state for 30 minutes ended in almost complete recovery of the starting material, contrary to the case of the five-membered lactone (IV), although some ammonia odor was detected during the procedure. The foregoing experimental evidences have shown that the behavior of acid amides (XXV and XXX) to deammoniation differs according to whether the acid amide group has a methylene or not and that the mode of reactions differs on whether the amide group has a substituent or not, as in the case of (XXVI). Accordingly, these results might suggest that the afore-mentioned formation of a lactam is probably effected through some different mechanism.

Reduction of the lactam derivatives mentioned above with lithium aluminium hydride in ether afforded derivatives (XXXI and XXXII) showing fluorescence in ultraviolet rays, as indicated in Tables III and IV.

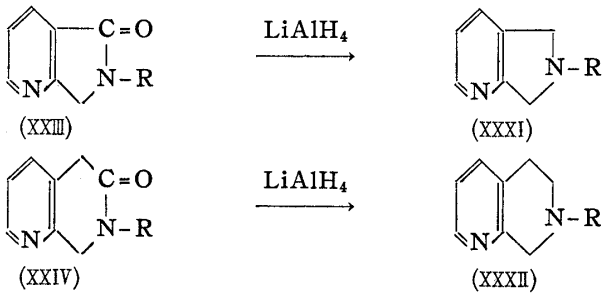
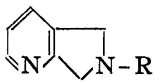
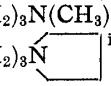


Table III. 

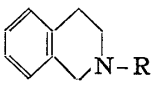
Compd. (XXXI)	R	b.p. (°C/mm.Hg)	Yield (%)	Mol. formula	Analysis (%) C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
a	C_6H_5-	m.p. 145.5~146.5	58.4	$C_{13}H_{12}N_2$	79.56	79.66	6.16	6.37	14.28	14.20
b	$C_6H_5CH_2$-	161~163/3	73.7	$C_{14}H_{14}N_2$	79.96	79.91	6.71	6.66	13.32	13.18
c	$-(CH_2)_2N(CH_3)_2$ i)	135~136/6	61.2	$C_{11}H_{17}N_3$	69.07	68.92	8.96	8.87	21.97	21.86
d	$-(CH_2)_2N(C_2H_5)_2$	132~133/4	55.0	$C_{13}H_{21}N_3$	71.19	70.82	9.65	9.68	19.16	19.08
e	$-(CH_2)_2N(iso\text{-}C_3H_7)_2$	134/3.5	58.2	$C_{15}H_{25}N_3$	72.82	72.63	10.19	10.37	16.99	17.25
f	$-(CH_2)_2$  ii)	153~154/3	49.5	$C_{13}H_{19}N_3$						
g	$-(CH_2)_3N(CH_3)_2$ iii)	115~122/1.5	49.0	$C_{12}H_{19}N_3$	70.20	69.56	9.33	9.26	20.47	20.24
h	$-(CH_2)_3$  iv)	130~132/0.01	47.0	$C_{14}H_{21}N_3$						

i) Hydrochloride, m.p. 261~262°. Calcd. for $C_{11}H_{17}N_3 \cdot 2HCl$: C, 50.02; H, 7.22; N, 15.91. Found: C, 50.06; H, 7.09; N, 15.94. Methiodide, m.p. 205°. Calcd. for $C_{13}H_{23}N_2I_2$: C, 32.85; H, 4.88; N, 8.84. Found: C, 33.19; H, 4.98; N, 9.02.

ii) Hydrochloride, m.p. 264~266°. Methiodide, m.p. 178.5~179.5°. Dipicrate. Calcd. for $C_{25}H_{25}O_{14}N_9$: C, 44.45; H, 3.73; N, 18.66. Found: C, 44.26; H, 3.89; N, 18.63.

iii) Hydrochloride, m.p. 263~264°. Methiodide, m.p. 228~230°.

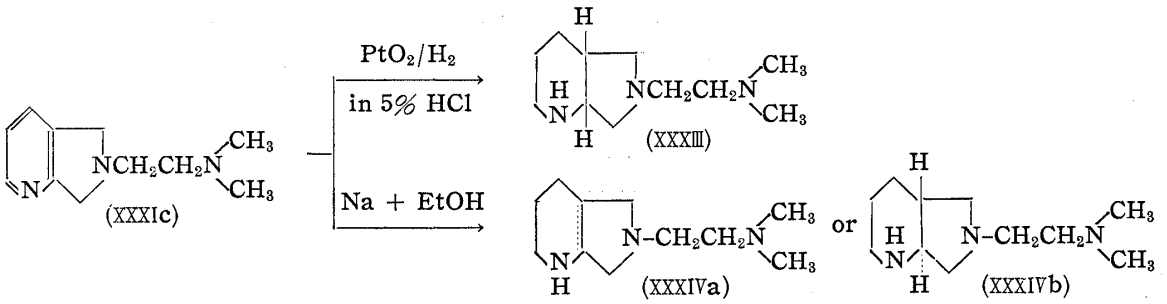
iv) Methiodide, m.p. 215°. Tripicrate, m.p. 211~212°(decomp.). Calcd. for $C_{32}H_{30}O_{21}N_{12}$: C, 41.83; H, 3.26; N, 18.28. Found: C, 42.12; H, 3.18; N, 18.08.

Table. IV. 

Compd. (XXXII)	R	b.p.$_1$ (°C) (bath temp.)	Yield (%)	Mol. formula	Analysis (%) C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
a	$-(CH_2)_2N(CH_3)_2$	110~120	60	$C_{12}H_{19}N_3$	70.30	70.27	9.26	9.61	20.50	20.34
b	$-(CH_2)_2N(C_2H_5)_2$	120~130	63	$C_{14}H_{23}N_3$	72.15	72.05	9.89	9.86	18.10	18.01
c	$-(CH_2)_2N(iso\text{-}C_3H_7)_2$	130~140	45	$C_{16}H_{27}N_3$	73.60	73.45	10.34	10.23	16.10	16.28

Pharmacological tests revealed that some of the derivatives listed in Tables III and IV possessed a fairly strong hypotensive action. Details on this point will be reported at a later date.

Hydrogenation of the pyridine ring was attempted with 2-(2-dimethylaminoethyl)-2,3-dihydro-1*H*-pyrrolo[3,4-*b*]pyridine (XXXIc) by catalytic reduction over platinum oxide in 5% hydrochloric acid and by metallic sodium in dehydrated ethanol. Reduction products thereby obtained were both oils, one of b.$p_{2.5}$ 97~99° (bath temp.) (picrate : m.p. 219° (decomp.)) and the other of b.p_2 97~99° (picrate : m.p. 245~246° (decomp.)).



(XXXIc) (XXXIII) (XXXIVa) (XXXIVb)

From the result of reduction of the ring in 3,4-cyclopentenopyridine by Prelog[9] and Ayerst[10] under similar conditions, (XXXIII) is thought to be a *cis* derivative. On the other hand, Prelog and others considered that the product obtained by reduction of 3,4-cyclopentenopyridine is a *trans* derivative but this conclusion was pointed out as erroneous by Ayerst who proved that a double bond still remained in the reduction product. From these facts, there remains the possibility that (XXXIV) might take a or b structure. There is still no conclusive evidences for either of these structures and the question will be left for further studies.

Experimental

Ethyl 2-Acetoxymethylnicotinate (VIII)—To a solution of 100 g. of (VI) in 1.2 L. of glacial AcOH, 120 g. of 30% H_2O_2 was added, the mixture was heated at 80~85° for 5 hr., and another 60 g. of 30% H_2O_2 was added. Heating was continued at the same temperature for further 5 hr. AcOH and excess of H_2O_2 were removed *in vacuo* and crude oily 1-oxide (VII) so obtained was added slowly into Ac_2O boiling gently. The reaction mixture was refluxed for 30 min. after addition and concentrated *in vacuo* to remove excess Ac_2O. Water was added to the residue, neutralized with Na_2CO_3, and extracted with $CHCl_3$. $CHCl_3$ solution was dried over Na_2SO_4 and evaporated. The residue was distilled *in vacuo* to give 90 g. (66.5%) of the acetate (VIII), b.p_3 133~136°. IR ν_{max}^{Liq} cm^{-1} : 1725, 1740 (sh.) (-CO_2Et, -CH_2OAc); 1280 (-CH_2OAc), 1230 (-CO_2Et). *Anal.* Calcd. for $C_{11}H_{13}O_4N$: C, 59.18; H, 5.87; N, 6.28. Found : C, 59.32; H, 5.95; N, 6.11.

2-Hydroxymethylnicotinic Acid (X)—A solution of 170 g. of (VIII) dissolved in a solution of 290 g. of KOH in 3 L. of commercial dehyd. EtOH was refluxed for 7 hr., and crystals that precipitated on cooling were collected. This product was dissolved in a small amount of water and the solution was adjusted to pH 3 with 30% H_2SO_4, followed by addition of excess EtOH. This EtOH solution was heated to boil and filtered to remove insoluble K_2SO_4. Needle crystals of m.p. 153~154° (decomp.) precipitated on cooling and were collected. The filtrate was concentrated to obtain further crop of crystals. Total weight, 63.0 g. of (X). IR ν_{max}^{Nujol} cm^{-1} : 2440, 1930, 1690 (COOH), 3250, 1055 (OH). UV λ_{max}^{EtOH} 265 mμ (ε 3200). *Anal.* Calcd. for $C_7H_5O_3N$: C, 54.90; H, 4.61; N, 9.15. Found : C, 55.02; H, 4.57; N, 9.38.

CO_2 was introduced into the filtrate of EtOH solution, K_2CO_3 that deposited was filtered off, and the filtrate was concentrated to dryness under a reduced pressure. The residue was dissolved in water and the aqueous solution was neutralized to pH 2 with dil. H_2SO_4. A white precipitate that deposited was collected and recrystallized from water to 15.3 g. of 2-methyl-5-hydroxynicotinic acid

9) V. Prelog, O, Metzler : Helv. Chim. Acta, **29**, 1170(1946).
10) G.G. Ayerst, K. Schoffield : J. Chem. Soc., **1958**, 4097.

(XI) as colorless plates, m.p. 305~307°(decomp.). IR ν_{max}^{Nujol} cm^{-1} : 1660(COOH), 1700~2800(broad). UV λ_{max}^{EtOH} 297 mμ (ε 4710), $\lambda_{max}^{EtOH\text{-}0.1N\ NaOH\ (1:1)}$ 311 mμ (ε 4870).

Hydrolysis of (VIII) with 30% H_2SO_4—A solution of 10 g. of (VIII) dissolved in 50 cc. of 30% H_2SO_4 was refluxed for 3 hr. and the reaction mixture was neutralized to pH 2 with $NaHCO_3$ when cooled. Insoluble material was collected and recrystallized from water to 0.75 g. of (XI), m.p. 305~307° (decomp.). The filtrate was extracted with $CHCl_3$ and the $CHCl_3$ solution was dried over Na_2SO_4, followed by evaporation of the solvent, leaving 2.5 g. of crude lactone (IV). It recrystallized from EtOH to needles, m.p. 141~142°. IR ν_{max}^{Nujol} 1780 cm^{-1} (lactone). UV λ_{max}^{EtOH} 269 mμ (ε 5040).

Lactonization of (X)—(X) was converted quantitatively to the lactone (IV) by sublimation at its decomposition point. The product was recrystallized from EtOH to needles, m.p. 141~142°.

2-Methyl-5-hydroxypyridine (XII) from (XI)—600 mg. of (XI) was heated at 310~320° at atmospheric pressure. The carbonised material was obtained as a major product with some sublimed product, which was eluted with acetone to give 110 mg. of crude crystals. It was dissolved in EtOH and treated with charcoal to give colorless crystals of m.p. 168~168.5°. It showed no m.p. depression with authentic sample of 2-methyl-5-hydroxypyridine[5] and was also identical in infrared spectrum.

2-Methyl-3-hydroxymethylpyridine (XIII)[11]—A mixture of 60 g. of $LiAlH_4$ in 1.3 L. of dehyd. Et_2O was refluxed for about 1 hr. A solution of 200 g. of (VI) in 1.2 L. of dehyd. Et_2O was added dropwise into this mixture with ice-cooling and the whole was refluxed for 3 hr. Water was added to decompose excess $LiAlH_4$, Et_2O solution was dried over Na_2SO_4, and evaporated off to give an oily residue. The decomposed Li salt was extracted with 500 cc. of warm EtOH and the extract was concentrated to give further oily residue. The combined oil was distilled *in vacuo*, $b.p_9$ 139~140° (119 g.). An oil, $b.p_5$ 35°, with strong odor of pyridine was obtained by redistillation of a low-boiling fraction. The picrate of this oil, m.p. 187~188°, showed no m.p. depression with the authentic sample of 2,3-lutidine picrate.[7] *Anal.* Calcd. for $C_{15}H_{14}O_9N_4$: C, 46.63; H, 3.60; N, 16.66. Found : C, 46.65; H, 3.69; N, 16.88.

2-Methyl-3-cyanomethylpyridine (XVI)—A solution of 111 g. of (XIII) dissolved in small volume of benzene was added gradually into 322 g. of $SOCl_2$ with stirring and ice-cooling, and the mixture was refluxed for 2.5 hr. Excess $SOCl_2$ was evaporated *in vacuo*, the residue was dissolved in 240 cc. of 60% EtOH, and a solution of 174 g. of KCN and 11.3 g. of KI in 1090 cc. of 60% EtOH was added with refluxing and stirring. The mixture was further refluxed for 5 hr. The inorganic salt that deposited on cooling was filtered off and the filtrate was concentrated *in vacuo*. The residue was dissolved in a small amount of water, extracted several times with $CHCl_3$, the $CHCl_3$ solution was dried over K_2CO_3, and the solvent was distilled off. The residue was distilled *in vacuo*. $b.p_{10}$ 136~137° (88.6 g.). n_D^{26} 1.5255. IR $\nu_{max}^{CHCl_3}$ 2270 cm^{-1} (—C≡N). UV λ_{max}^{EtOH} mμ (ε) : 263(3340), 270(2680). Picrate, m.p. 149~149.5°. *Anal.* Calcd. for $C_{14}H_{11}O_7N_5$: C, 46.55; H, 3.05; N, 19.40. Found : C, 46.69; H, 3.25; N, 19.51.

Ethyl 2-Methylpyridine-3-acetate (XVII)—Dry HCl gas was introduced for 1.5 hr. into a solution of 45 g. of (XVI) dissolved in a mixture of 157 g. of dehyd. EtOH and 88 cc. of dehyd. Et_2O, with stirring and ice-cooling. The reaction mixture was further refluxed and stirred for another 5 hr., continuing the introduction of HCl gas. The inorganic salt that deposited on cooling was filtered off and the filtrate was concentrated *in vacuo*, leaving an oil. The oil was dissolved in a small amount of water, made alkaline with K_2CO_3, and the aqueous solution was extracted with $CHCl_3$. The residue obtained on evaporating the solvent was distilled *in vacuo* to give 43.4 g. of oil, $b.p_7$ 124~125°, n_D^{25} 1.4982. IR $\nu_{max}^{CHCl_3}$ 1730 cm^{-1} (Ester). UV λ_{max}^{EtOH} mμ (ε) : 264(4260), 269(3330 sh). *Anal.* Calcd. for $C_{10}H_{13}O_2N$: C, 67.00; H, 7.26; N, 7.82. Found : C, 66.97; H, 7.18; N, 7.68. Picrate, m.p. 154.5~155.5°. Calcd. for $C_{16}H_{16}O_9N_4$: C, 47.00; H, 3.92; N, 13.70. Found : C, 46.85; H, 4.05; N, 13.71.

Ethyl 2-Methylpyridine-3-acetate 1-Oxide (XVIII)—A solution of 43.4 g. of (XVII) and 47 g. of 30% H_2O_2 dissolved in 83 cc. of AcOH was heated at 80~85° on a water bath for 6 hr. Another 24 g. of 30% H_2O_2 was added, the reaction mixture was further heated for 5 hr., and worked up as in the case of (VII). The product, 33 g. of oil, $b.p_4$ 140~150°, solidified to give crystals of m.p. 54~59°. UV λ_{max}^{EtOH} 263 mμ (ε 10900). *Anal.* Calcd. for $C_{10}H_{13}O_3N \cdot \frac{1}{2}H_2O$: C, 58.80; H, 6.87; N, 6.86. Found: C, 58.32; H, 6.67; N, 7.35.

Ethyl 2-Acetoxymethylpyridine-3-acetate (XIX)—A solution of 26.7 g. of (XVIII) in a small amount of Ac_2O was added dropwise into refluxing Ac_2O, further refluxed for 30 min., and worked up as in the case of (XIX) to give 24.2 g. of oil, $b.p_7$ 171~173°, n_D^{26} 1.4942. UV λ_{max}^{EtOH} mμ (ε) : 263(3280), 269(2880). *Anal.* Calcd. for $C_{12}H_{15}O_4N$: C, 60.75; H, 6.33; N, 5.91. Found : C, 60.45; H, 6.26; N, 5.89. Picrolonate, m.p. 122~123°(decomp.). *Anal.* Calcd. for $C_{22}H_{23}O_9N_5$: C, 52.70; H, 4.69; N, 13.97. Found: C, 52.78; H, 4.62; N, 14.11.

2-Hydroxymethylpyridine-3-acetic Acid Lactone (V)—A solution of 5.9 g. of (XIX) and 8.3 g. of

11) Y. Sato : This Bulletin, **7**, 244(1959).

KOH dissolved in 110 cc. of EtOH was refluxed for 9 hr. The reaction mixture was acidified with 22% EtOH-HCl and neutralized again with $NaHCO_3$. Inorganic salt that deposited was filtered off and the filtrate was concentrated *in vacuo*. The residue was extracted with $CHCl_3$, the extract was evaporated to remove the solvent, leaving the residue which was sublimed at 135~150°/3 mm. Hg to give 1.3 g. of crude crystals. Recrystallization from EtOH yielded the crystals of m.p. 118~119°. UV λ_{max}^{EtOH} mμ (ε): 264 (3580), 270 (2890). IR ν_{max}^{KBr} 1730 cm^{-1} (lactone). *Anal.* Calcd. for $C_8H_7O_2N$: C, 64.40; H, 4.70; N, 9.40. Found: C, 64.46; H, 4.84; N, 9.42.

2-(2-Dimethylaminoethyl)-2,3-dihydro-1-oxopyrrolo[3,4-*b*]pyridine (XXIIIc)—A mixture of 11.9 g. of the lactone (IV) and 12.0 g. of 2-dimethylaminoethylamine placed in a sealed tube was heated at 200~210° for 7 hr. When cool, the reaction mixture was washed with K_2CO_3 solution to remove unreacted lactone and extracted with $CHCl_3$. The residue was distilled *in vacuo* to 16.8 g. of an oil, b.$p_{0.045}$ 130°, which solidified to yield crystals of m.p. 72~73°. Other derivatives shown in Tables I and II were prepared by the same procedure.

2-Hydroxymethylnicotinamide (XXV)—A solution of 0.5 g. of the lactone (IV) in 50 cc. of dehyd. EtOH was saturated with dry NH_3 gas with cooling. After standing overnight, the solvent was removed, leaving crude crystals which recrystallized from EtOH to 0.45 g. of crystals, m.p. 146~147°. UV λ_{max}^{EtOH} 263 mμ (ε 2960). IR ν_{max}^{KBr} cm^{-1}: 3130, 3635 (OH, NH_2), 1670 (-$CONH_2$). *Anal.* Calcd. for $C_7H_8O_2N_2$: C, 55.20; H, 5.26; N, 18.41. Found: C, 55.35; H, 5.30; N, 18.50.

Heating of 0.3 g. of (XXV) at around 150° resulted in vigorous gas evolution with melting. Heating was stopped after completion of gas evolution. When cool, the solidified product was recrystallized from EtOH to 0.24 g. of crystals, m.p. 141~142°, which showed no depression with authentic sample of the lactone (IV).

N-Benzyl-2-methylnicotinamide (XXVII)—A mixture of 8 g. of (VI) and 10.3 g. of benzylamine was heated at 150~160° for 30 hr. Excess benzylamine and unreacted (VI) were removed *in vacuo*. The residue solidified on standing in a refrigerator and was recrystallized from AcOEt to 9.3 g. of (XXVII), m.p. 117~118°. UV λ_{max}^{EtOH} 265 mμ (ε 4260). IR ν_{max}^{KBr} cm^{-1}: 1635 (CONH-), 3290 (-NH-). *Anal.* Calcd. for $C_{14}H_{14}ON_2$: C, 74.40; H, 6.20; N, 12.40. Found: C, 74.31; H, 6.24; N, 12.40.

N-Benzyl-2-methylnicotinamide 1-Oxide (XXVIII)—4.1 g. of 30% H_2O_2 was added into the solution of 9.3 g. of (XXVII) in 30 cc. of glacial AcOH and heated at 80° for 6 hr. After another 3 g. of 30% H_2O_2 was added, the reaction mixture was further heated for 5 hr. and concentrated to remove the solvent. A small amount of water was added to the residue and concentrated again. This procedure was repeated once more to give an oily residue. The residue was dissolved in a small amount of water and the aqueous solution was made alkaline to give crude crystals on standing. Recrystallization from AcOEt yielded 8.4 g. of (XXVIII), m.p. 175~176°. UV λ_{max}^{EtOH} 265 mμ (ε 11900). IR ν_{max}^{KBr} cm^{-1}: 1660 (-CONH-), 3240 (-NH-). *Anal.* Calcd. for $C_{14}H_{14}O_2N_2$: C, 69.50; H, 5.78; N, 11.58. Found: C, 69.54; H, 5.75; N, 11.85.

N-Benzyl-2-Acetoxymethylnicotinamide (XXIX)—A suspension of 3.6 g. of (XXVIII) in 4.6 g. of Ac_2O was heated gradually. A vigorous reaction occurred suddenly at around a bath temperature of 110°. The reaction mixture became completely homogeneous and was further heated at 130~140° for 40 min., concentrated *in vacuo* to remove excess Ac_2O, and 5 cc. of H_2O was added to the residue. The solution was made alkaline with Na_2CO_3 and extracted with $CHCl_3$. The solvent was removed after drying and the residue was distilled *in vacuo* to give 1.0 g. of a viscous orange oil, b.$p_{0.02\sim0.03}$ 220~230°(bath temp.). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3300 (NH), 1735 (OAc), 1660 (-CONH-), 1235 (OAc). Picrolonate: m.p. 147~148°(decomp.). *Anal.* Calcd. for $C_{26}H_{24}O_8N_6$: C, 56.99; H, 4.41; N, 15.32. Found: C, 56.86; H, 4.13; N, 15.37.

Hydrolysis of (XXIX) with EtOH-KOH—A mixture of 0.8 g. of (XXIX) added to a solution of 1.0 g. KOH in 20 cc. of EtOH was refluxed for 11 hr. After concentration of the reaction mixture, the oil separated on adding water to the residue was extracted with $CHCl_3$, which was dried and evaporated. The residue was distilled to give crystals sublimating gradually at 80°(bath temp.) at 0.1~0.2 mm. Hg. Infrared spectrum of this unidentified material lacked the absorption of a lactam of (XXIIIb) and lactone of (IV).

2-Hydroxymethylpyridine-3-acetamide (XXX)—A solution of 2.0 g. of the lactone (V) dissolved in 150 cc. of EtOH was saturated with NH_3. The needles, deposited on standing at room temperature for 2 days, was filtered off. The filtrate was concentrated to give further crop of crystals. Total amount of crystals of (XXX), m.p. 154~155°, weighed 2.1 g. There was no change in m.p. after recrystallization from EtOH. UV λ_{max}^{EtOH} 263 mμ (ε 3450). IR ν_{max}^{Nujol} cm^{-1}: 1670 (-$CONH_2$), 1070 (OH), 3350 (OH), 3160, 3090 (NH).

0.5 g. of the amide (XXX) was heated to melt at 160° for 30 min. The solidified product, on cooling, was recrystallized from EtOH, recovering about one-half the amount of (XXX) used. The lactone (V) could not be obtained, although odor of NH_3 was noticed slightly during this reaction.

2-(2-Dimethylaminoethyl)-2,3-dihydro-1*H*-pyrrolo[3,4-*b*]pyridine (XXXIc)—Under ice-cooling and stirring, a solution of 18.0 g. of the lactam (XXIIIc) in 300 cc. of dehyd. ether was added to 1.2 L. of

dehyd. ether in which 22 g. of $LiAlH_4$ was suspended, and the mixture was stirred for 30 hr. and finally at room temperature for 10.5 hr. Water was added to decompose excess $LiAlH_4$, the deposited precipitate was collected, and washed several times with ether. The combined ether solution was dried over K_2CO_3 and evaporated. Residual red oil was distilled to give 8.7 g. of (XXXIc), $b.p_6$ 135~136°. *Anal.* Calcd. for $C_{11}H_{17}N_3$: C, 69.07; H, 8.96; N, 21.97. Found: C, 68.92; H, 8.87; N, 21.86.

Other derivatives shown in Tables III and IV were prepared by the same procedure.

***cis*-8-(β-Dimethylaminoethyl)-2,8-diazabicyclo[4. 3. 0]nonane (XXXIII)**—500 mg. of (XXXIc) was hydrogenated over 250 mg. of PtO_2 in 5% HCl. About 3 moles of H_2 was absorbed. The catalyst was filtered off, the reaction mixture was made alkaline with NaOH, and extracted with ether. Ether solution was dried over K_2CO_3 and evaporated, leaving 430 mg. of residue. This was distilled *in vacuo* to give an oil, $b.p_{2.5}$ 97~99° (bath temp.). Tripicrate: m.p. 219°(decomp.), as recrystallized three times from water. *Anal.* Calcd. for $C_{29}H_{32}O_{21}N_{12}$: C, 39.37; H, 3.64; N, 19.00. Found: C, 39.45; H, 3.61; N, 18.90.

***trans* (?)-8-(β-Dimethylaminoethyl)-2,8-diazabicyclo[4. 3. 0]nonane (XXXIV)**—A solution of 4.0 g. of (XXXI) dissolved in 400 cc. of dehyd. EtOH was refluxed, 28.2 g. of small pieces of Na was added in small portions, and the reaction mixture was further refluxed for 30 min. after Na had dissolved completely. When cool, water was added, the solution was made weakly acid with dil. HCl, and concentrated *in vacuo*. The residue was made strongly alkaline with NaOH and extracted with ether. Ether solution was dried over K_2CO_3 and evaporated, leaving a red residue. This was distilled *in vacuo* to give an oil of $b.p_2$ 97~99°. Tripicrate: m.p. 245~246°(decomp.). *Anal.* Calcd. for $C_{29}H_{32}O_{21}N_{12}$: C, 39.37; H, 3.64; N, 19.00. Found: C, 39.51; H, 3.57; N, 19.42.

The authors express their gratitude to Mr. M. Matui, the Director of this Laboratory, and to Prof. K. Tsuda of the Institute of Applied Microbiology, University of Tokyo, for kind guidance and encouragement in this work. They are indebted to Mr. T. Nishimura for technical cooperation, to Messrs. H. Shindo, O. Amakasu, H. Higuchi, and N. Higosaki for measurement and analyses of infrared and ultraviolet spectra, and to Misses T. Onoe, T. Furukawa, and H. Ohtsuka for elemental analyses.

Summary

New type 2,3-disubstituted pyridine lactones were prepared from 2-methylnicotinic acid. The lactones, 2-hydroxymethylnicotinic acid lactone and 2-hydroxymethylpyridine-3-acetic acid lactone, were reacted with various amines to form the corresponding lactams, and the lactams were reduced with lithium aluminium hydride, yielding pyrrolopyridine and 1,7-naphthyridine derivatives which possessed a fair degree of hypotensive action.

(Received September 28, 1959)