Summary

5-Hydroxytetralone-(1) gave a green fluorescence when heated in sulfuric acid with hexoses, oligosaccharides, or polysaccharides which contains hexose units in their molecule. The reaction was sensitive and specific for hexose, and interfered by only a few substances. The limit of the detection of hexoses, oligosaccharides, and polysaccharides was tabulated, and a new syntheses of the reagent was described.

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U.D.C. 547.821.411

40. Ikuo Suzuki : Rearrangement Reaction of Picolyl Ethers with Sodium Amide. I.

(*National Hygienic Laboratory**)

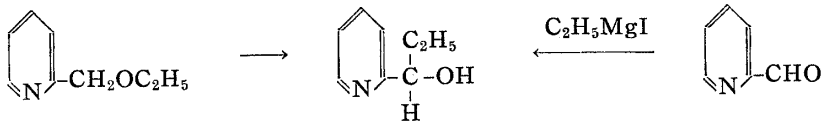
It has been found that α- or γ-ethers of picolyl compounds (Table I) undergo interesting rearrangement reaction by sodium amide in Decalin, xylene, or benzene, details of which are set in the present paper.

TABLE I. Properties of Picolyl Ethers used as the Starting Material

	Methyl (α)	Methyl (γ)	Ethyl (α)	Ethyl (γ)	Ethyl (β)
b.p. (°C/mm.)	45~55/4	62~65/4	63~64/5	75~80/5	77~78/5
Picrate, m.p. (°C)	81~83	107~109	119~121	112~114	108~109
Yield (%)	69.1	76.2	86.5	81.6	79.8

	sec-Butyl (α)	*sec*-Butyl (γ)	Phenyl (α)	Phenyl (γ)	Benzyl (α)	Benzyl (γ)
b.p. (°C/mm.)	73~75/5	81~83/5	140~143/5	145~150/3	150~160/7	153~158/6
Picrate, m.p. (°C)	101~103	107~109	170~171	171~172	117~119	145~146
Yield (%)	44.0	63.3	72.4	47.0	85.2	82.5

Reaction of ethyl α-picolyl ether and ethyl γ-picolyl ether with equivalent amount of sodium amide, in Decalin or benzene, respectively yields a viscous oil of $b.p_4$ 66~77°(picrate, m.p. 98~100°) and of $b.p_6$ 125~126°(picrate, m.p. 113~115°). These oily products were found to be respectively identical with ethyl-α-pyridylcarbinol and ethyl-γ-pyridylcarbinol, obtained from α- and γ-pyridylaldehydes by the application of ethylmagnesium iodide in ether.



(and the same with 4-position)

The same reactions were carried out with the α- and γ-substituted compounds of benzyl, *sec*-butyl, methyl, and phenyl picolyl ethers, and ethyl β-picolyl ether, and the results listed in Table II were obtained.

As can be seen from these tables, benzyl ether underwent rearrangement to the pyridylcarbinol with a slightly better yield than the ethyl ether, while *sec*-butyl ether gave a poor yield. Further, ethyl β-picolyl ether and the methyl and phenyl ethers failed to yield the rearrangement products (cf. Table III).

It should be noted from the foregoing experimental results that picolyl ethers undergo rearrangement only when they are α- or γ-substituents, and no such reac-

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Table II. Reaction Conditions for the Rearrangement

Carbinol obtained	Solvent	React. time (hr.)	React. [a] temp.(°C)	Yield (%)	Recov. (%)	Resin. prod. (%)	b.p. (°C/mm.)	Picrate m.p.(°C)	HCl-salt m.p. (°C)
Ethyl-α- [b] pyridyl-	Decalin	8	140~150	30	nil	50	66~77/6	98~100	142~145
	Benzene	3	boiling	45.5	nil	36.3			
Ethyl-γ- pyridyl-	Decalin	15	140~150	40	26.7	trace	125~126/6	113~115	132
	Benzene	5	boiling	11.7	53.3	trace			
Benzyl-α- [c] pyridyl-	Xylene	5	130~140	50	nil	25	137~142/3	119~121	
Benzyl-γ- [c] pyridyl-	Xylene	5	130~140	35	25	30	—	162~163	
sec-Butyl-α-pyridyl-	Xylene	5	130~140	40	nil	30	84~88/2	—	121~123
sec-Butyl-γ-pyridyl-	Xylene	5	130~140	36.6	33.3	6.6	124~127/5	142~144	

a) Reaction temperature indicates that of the bath.

b) Reported $b.p_{49}$ 135° (L. Lautenschlager: Ber., **51**, 603(1918)). $b.p_{13}$ 112~113°, picrate, m.p. 94~95° (K. Hess: Ann., **441**, 126(1925)).

c) Reported m.p. 104° (Rath: Ber., **57**, 841(1924)); m.p. 104~105° (N. Sperber, *et al.*: J. Am. Chem. Soc., **71**, 887(1949). The compounds obtained in the present experiments: Benzyl-α-pyridylcarbinol, m.p. 101~103°; benzyl-γ-pyridylcarbinol, m.p. 144~145.5°.

Table III. Reaction failing to yield the Carbinol

Picolyl Ether	Solvent	React. time (hr.)	React. temp. (°C)	Recovery (%)	Resinous Product (%)
Ethyl β-	Xylene	4	150~160	80	trace
	Benzene	3	boiling	50	45
Methyl α-	Xylene	3	140~150	23.3	66.6
	Benzene	3	boiling	80	trace
Methyl γ-	Xylene	3	140~150	53.3	20
Phenyl α-	Xylene	4	130~140	40	35
Phenyl γ-	Xylene	4	130~140	50	20

Examination of the resinous product is in progress.

tion is observed in the β-compounds. This indicates that in the reaction with $NaNH_2$, the carbanion formed from the radical activated by the polar effect of nitrogen becomes the field of rearrangement. The fact that such carbanions form the field of rearrangement is already known and some examples may be cited below.

1) Stevens[1] obtained α,β-diphenylethyldimethylamine by the application of sodium methoxide on dibenzyldimethylammonium chloride and α,β-diphenylethylmethylaniline by the application of sodium amide to phenyldibenzylmethylammonium iodide.

$$(C_6H_5CH_2)_2\overset{+}{N}(CH_3)_2 \xrightarrow[140°]{NaOCH_3} C_6H_5-\underset{\displaystyle CH_2C_6H_5}{\overset{\displaystyle H}{\overset{|}{\underset{|}{C}}}}-N(CH_3)_2$$

$$(C_6H_5CH_2)_2\overset{+}{N}(C_6H_5)CH_3 \xrightarrow[160\sim170°]{NaNH_2} C_6H_5-\underset{\displaystyle CH_2C_6H_5}{\overset{\displaystyle H}{\overset{|}{\underset{|}{C}}}}-N(C_6H_5)CH_3$$

2) Wittig[2] reported that he obtained methylphenylcarbinol by the application of phenyllithium to benzyl methyl ether.

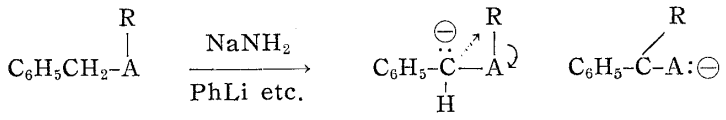
$$C_6H_5CH_2OCH_3 \xrightarrow{\phi Li} C_6H_5-CH(OH)CH_3$$

3) In 1951, Hauser and Kantor[3] obtained benzylphenylcarbinol by the application of potassium amide to dibenzyl ether in liquid ammonia, and further examined

1) T. Thomson, T. S. Stevens: J. Chem. Soc., **1932**, 1932.
2) G. Wittig: Ann., **550**, 260(1942).
3) C. R. Hauser, S. W. Kantor: J. Am. Chem. Soc., **73**, 1437(1951).

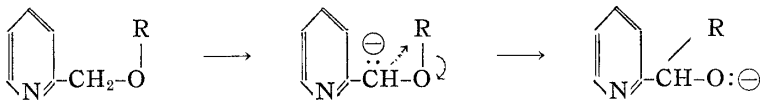
the same reactions with benzyl allyl, diallyl, benzyl *sec*-butyl, and benzyl methyl ethers.

Wittig, Hauser, and Kantor explain the mechanism of this rearrangement in the following manner. (i) This rearrangement does not go through an intermediate product of aldehyde which undergoes Grignard reaction with metalloalkyl compound to form the secondary alcohol. (ii) This reaction first forms a carbanion as an intermediate by the action of sodium alkoxide, sodium or potassium amide, or phenyllithium, and results in the rearrangement of the alkyl or benzyl group. (iii) It is not that the rearranging radical liberates as a carbonium cation but that the carbanion electron attacks the carbon with a low electron density in the rearranging radical, which severs between that carbon and the hetero atom ($\overset{+}{N}$ or O), and the rearrangement reaction is hereby completed (1-2 shift).



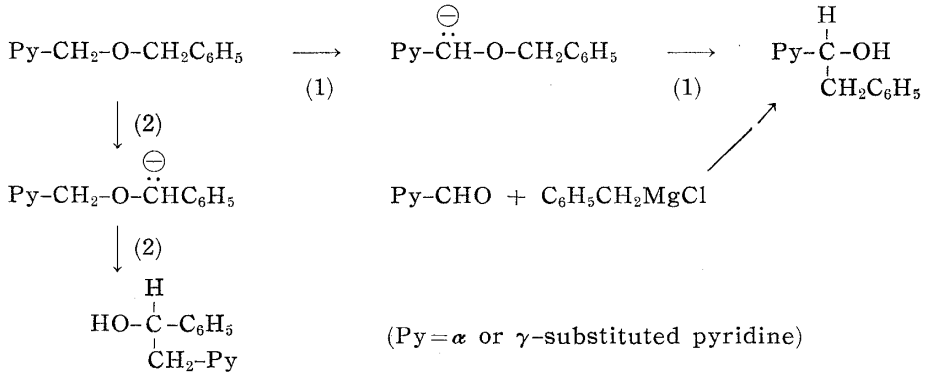
A=Hetero atom ($\overset{+}{N}$, O) R=alkyl, benzyl.

The rearrangement of the picolyl ethers found by the present writer may be explained by assuming that a kind of a Stevens rearrangement had taken place, as shown below :



It follows, therefore, that the carbanion does not form in ethyl β-picolyl ether, in which the effect of nitrogen is small, and the rearrangement does not take place. As can be seen from Table II, the yield of the rearrangement is always better in the α-compounds than in the γ. On the other hand, there is a larger formation of resinous substances in α-compounds. The electron pair of the carbanion attacks the carbon with a low electron density so that it is natural that the yield of the rearrangement product decreases in the order of benzyl, ethyl, and *sec*-butyl picolyl ethers, though not strictly speaking, and a carbon with low electron density is not formed in phenyl ether that a rearrangement product could not be isolated. However, failure of the methyl ethers to undergo such rearrangement, or the failure to isolate such rearrangement products, requires further study.

In benzyl picolyl ethers, the rearrangement product differs according to whether the carbanion forms with the carbon directly bonded to the pyridine ring or to the benzyl group.



(Py=α or γ-substituted pyridine)

In reaction (1), benzylpyridylcarbinol is formed, while phenylpicolylcarbinol is formed by reaction (2). The product obtained from the present experiment was

found to be identical with benzylpyridylcarbinol, prepared from pyridine-2(or -4)-aldehyde and phenylmagnesium chloride. This has shown that the effect of the pyridine ring is stronger and the carbanion forms, as in reaction (1), resulting in rearrangement.

Ethyl-α- or-γ-pyridylcarbinol thereby obtained is chlorinated by the application of phosphoryl chloride, and the chloro compound can be reduced by catalytic reduction with palladium-carbon to 2- or 4-propylpyridine (cf. Table IV).

$$\text{Py-CH(OH)-C}_2\text{H}_5 \xrightarrow[\text{POCl}_3]{} \text{Py-CH(Cl)-C}_2\text{H}_5 \xrightarrow[\text{H}_2]{} \text{Py-CH}_2\text{C}_2\text{H}_5$$

TABLE IV.

Pyridine compound	Yield (%)	b.p.(°C/mm.) (bath temp.)	Picrate (m.p. °C)	Other Salt
2-(α-Chloropropyl)-	68.9	80~90/4	138~140(Plates)	
4-(α-Chloropropyl)-	70.1	90~95/3	111~113(Needles)	
2-Propyl-	76.9	185~195/760	62~64 (Needles)[a]	Pt-salt, m.p. 160~163[a]
4-Propyl-	64.1	200~210/760	130~132(Needles)[b]	

a) Reported b.p_{755} 165~166°, picrate, m.p. 64°, platinum salt, m.p. 163~164°(R. P. Mariella, *et al.*: J. Am. Chem. Soc., **70**, 1494(1948)).

b) Reported b.p_{20} 80°; picrate, m.p. 131°(J. P. Wibaut: Rec. trav. chim., **72**, 513(1953)). Reported picrate, m.p. 131°(S. Goldschmidt, M. Minsinger: Chem. Ber., **87**, 956(1954)).

The writer expresses his gratitude to Dr. T. Kariyone, Director of the Laboratory, for giving him facilities for the present study. He is also deeply indebted to Prof. Eiji Ochiai of the University of Tokyo for his constant and kind guidance throughout the course of this study, to Prof. J. F. Bunnet of the University of North Carolina, and to Assistant Prof. T. Okamoto, also now at the University of North Carolina, for many helpful suggestions regarding the literature, and to Dr. T. Itai for kind encouragement. The writer also feels grateful to Mr. S. Sako for carrying out a part of the experiments and to Miss Y. Ishigaki for the microanalytical data reported herein.

Experimental

General Method of the Synthesis of Alkyl or Benzyl α-Picolyl Ethers—A mixture of 5 g. of 2-chloromethylpyridine, b.p_4 55~57°, dissolved in 5 volumes of corresponding dehyd. alcohols and equivalent amount of Na dissolved in corresponding dehyd. alcohols was warmed on a water bath for ca. 1 hr., cooled, and NaCl formed was removed by filtration. The filtrate was evaporated under reduced pressure and the residual oil was distilled *in vocuo*. All ethers are colorless liquid.

General Method of the Synthesis of Alkyl or Benzyl γ-Picolyl Ethers—A mixture of 5 g. of 4-chloromethylpyridine hydrochloride, m.p. 171°, dissolved in 10~20 volumes of corresponding dehyd. alcohols and equivalent amount of Na dissolved in corresponding dehyd. alcohols was treated as in α-compounds. All ethers are colorless liquid.

Synthesis of Phenyl α-Picolyl Ether—To a solution of 4.3 g. of phenol dissolved in 150 cc. of dehyd. EtOH, 1.2 g. Na was added, followed by EtOH solution of 6 g. of 2-chloromethylpyridine, and the mixture was heated on a water bath for 1 hr. After cooling, the solution was filtered, and the filtrate was distilled under a reduced pressure, from which 0.2 g. of oil, b.p_5 64°, was obtained. This is ethyl α-picolyl ether. Yield, 6.3 g.(72.4%) of b.p_5 140~143°. The oil solidified on standing to needles of m.p. ca. 30°. This is phenyl α-picolyl ether.

Synthesis of Phenyl γ-Picolyl Ether—To a solution of 1.2 g. of phenol dissolved in 50 cc. of dehyd. EtOH, 0.9 g. of Na, followed by a solution of 3 g. of 4-chloromethylpyridine hydrochloride dissolved in 50 cc. of dehyd. EtOH, were added, and the mixture was heated on a water bath for 1 hr. The treatment of this reaction mixture as for the α-compound afforded 0.9 g. of ethyl γ-picolyl ether as an oil, b.p_3 70~74°. Then 1.6 g. (47%) of oil, b.p_3 145~150°, was obtained which, on standing, solidified into needles melting at about 25°. This is phenyl γ-picolyl ether.

Reaction of Various Ethers with Sodium Amide.—a) In Decalin: To a solution of 0.02 mole of picolyl ethers dissolved in 3 volumes of Decalin, equivalent amount of $NaNH_2$ was added, and the mixture was heated in an oil bath (cf. Table II for temperature and time). After cooling, the mixture was poured into ice water, acidified with HCl, and extracted with ether to remove Decalin. The solution was basified with K_2CO_3, extracted with ether, and the solvent was evaporated from ether extract after drying. The residual oil was distilled *in vacuo*.

b) In benzene and xylene: To a solution of 0.02 mole of picolyl ethers dissolved in 2~3 volumes of benzene or xylene, equivalent amount of finely pulverized $NaNH_2$ was added and

Analytical Data of the Picrates of Pyridyl Ethers
Py-CH_2-O-R (Py=α or γ-substituted pyridine)

R	Mol. formula	C%		H%		N%		Appearance (Recrystn. solvt.)
		Calcd.	Found	Calcd.	Found	Calcd.	Found	
CH_3 (α)	$C_{13}H_{12}O_8N_4$	44.32	44.48	3.40	3.65	15.91	15.45	Needles (AcOEt)
CH_3 (γ)	$C_{13}H_{12}O_8N_4$	44.32	44.13	3.40	3.60	15.91	15.88	Needles (AcOEt)
C_2H_5 (α)	$C_{14}H_{14}O_8N_4$	45.90	46.42	3.83	3.82	15.30	15.05	Needles (MeOH + benzene)
C_2H_5 (β)	$C_{14}H_{14}O_8N_4$	45.90	46.04	3.83	4.23	15.30	14.75	Needles (MeOH + benzene)
C_2H_5 (γ)	$C_{14}H_{14}O_8N_4$	45.90	46.01	3.83	3.68	15.30	15.35	Needles (EtOH)
sec-Butyl (α)	$C_{16}H_{18}O_8N_4$	48.73	48.70	4.57	4.55	14.21	14.63	Needles (MeOH)
sec-Butyl (γ)	$C_{16}H_{18}O_8N_4$	48.73	48.45	4.57	4.19	14.21	13.95	Needles (MeOH)
C_6H_5 (α)	$C_{18}H_{14}O_8N_4$	52.17	52.00	3.38	3.03	13.53	13.01	Needles (MeOH)
C_6H_5 (γ)	$C_{18}H_{14}O_8N_4$	52.17	52.32	3.38	3.47	13.53	13.33	Needles (MeOH)
$C_6H_5CH_2$ (α)	$C_{19}H_{16}O_8N_4$	53.27	52.95	3.74	3.69	13.08	13.11	Needles (MeOH)
$C_6H_5CH_2$ (γ)	$C_{19}H_{16}O_8N_4$	53.27	52.93	3.74	3.76	13.08	12.58	Prisms (acetone)

the mixture was heated in an oil bath (cf. Table II or III for temperature and time). After cooling, the mixture was poured into ice water, extracted with $CHCl_3$, and the $CHCl_3$ residue was distilled *in vacuo*.

Analytical Data of Pyridylcarbinols, their Picrates, and Hydrochlorides
Py-CH(OH)-R (Py=pyridyl)

R	Mol. formula	C%		H%		N%		Appearance (Recrystn. solvt.)
		Calcd.	Found	Calcd.	Found	Calcd.	Found	
C_2H_5 (α) Picrate	$C_{14}H_{14}O_8N_4$	45.90	46.05	3.83	3.71	15.30	14.67	Needles (AcOEt)
C_2H_5 (γ) Picrate	$C_{14}H_{14}O_8N_4$	45.90	46.18	3.83	4.14	15.30	15.98	Needles (EtOH)
C_2H_5 (γ) HCl-salt	$C_8H_{12}ONCl$	55.33	55.60	6.92	6.77	8.07	8.23	Scalies (AcOEt + MeOH)
C_2H_5 (γ) HCl-salt	$C_8H_{12}ONCl$	55.33	54.65	6.92	6.89	8.07	7.78	Scalies (AcOEt + MeOH)
sec-Butyl (α) HCl-salt	$C_{10}H_{16}ONCl$	59.55	59.14	7.94	7.63	6.95	7.56	Needles (AcOEt + MeOH)
sec-Butyl (γ) Picrate	$C_{16}H_{18}O_8N_4$	48.73	48.49	4.57	4.29	—	—	Prisms (MeOH)
$C_6H_5CH_2$ (α) Picrate	$C_{19}H_{16}O_8N_4$	53.27	52.92	3.74	3.76	13.08	12.84	Needles (EtOH)
$C_6H_5CH_2$ (γ) Picrate	$C_{19}H_{16}O_8N_4$	53.27	53.17	3.74	3.97	13.08	12.81	Needles (MeOH + AcOEt)
$C_6H_5CH_2$ (α)	$C_{13}H_{13}ON$	78.44	78.17	6.53	6.62	7.04	7.10	Scalies (benzine)
$C_6H_5CH_2$ (γ)	$C_{13}H_{13}ON$	78.44	78.29	6.53	6.40	7.04	7.16	Needles (benzene + MeOH)

No depression of m.p. observed on admixture with alkyl- or benzylcarbinol picrate (or HCl-salt, free base), obtained by the Grignard reaction described later.

Grignard Reaction of α- or γ-Pyridylaldehydes—To a solution of α- or γ-pyridylaldehyde dissolved in dehyd. ether, a dehyd. ether solution of magnesiumalkyl or -aryl halide was added dropwise under stirring, and the mixture was heated in a water bath for 30 mins. After all were added, the mixture was acidified with conc. HCl on cooling, basified with 10% NaOH, and extracted with ether. The ether residue was distilled *in vacuo*.

Carbinol obtained Py-CH(OH)-R	Yield %	Grignard Reagt.	Appearance
C_2H_5 (α)	70.3	C_2H_5MgI	Pale yellow viscous oil
C_2H_5 (γ)	39.0	C_2H_5MgI	Pale yellow viscous oil
sec-butyl (α)	39.0	$CH_3(C_2H_5)CHMgBr$	Pale yellow viscous oil
sec-butyl (γ)	20.0	$CH_3(C_2H_5)CHMgBr$	Pale yellow viscous oil
$C_6H_5CH_2$ (α)	29.6	$C_6H_5CH_2MgCl$	White crystals
$C_6H_5CH_2$ (γ)	11.0	$C_6H_5CH_2MgCl$	White crystals

Chlorination of Ethyl-α- or γ-Pyridylcarbinol—To a solution of 0.5 g. of ethylpyridylcarbinol (α- or γ-) in 3 cc. of $CHCl_3$, 1 g. of $POCl_3$ was added dropwise under cooling and the mixture was heated on a water bath for 1 hr. After cooling, the reaction mixture was poured into ice water, basified with K_2CO_3, and extracted with $CHCl_3$. The $CHCl_3$ residue was distilled in an oil bath

(cf. Table IV). *Anal.* Calcd. for $C_8H_{10}NCl \cdot C_6H_3O_7N_3$(2-(α-Chloropropyl)pyridine picrate): C, 43.69; H, 3.38; N, 14.56. Found: C, 43.60; H, 3.39; N, 14.18. *Anal.* Calcd. for $C_8H_{10}NCl \cdot C_6H_3O_7N_3$(4-(α-chloropropyl)pyridine picrate). Found: C, 43.46; H, 3.36; N, 14.25.

Reduction of α- or γ-Chloro Compounds—A solution of 0.5 g. of chloro compounds, obtained by the above method, dissolved in 10% HCl was catalytically reduced with Pd-C (30%). After removal of the catalyst, HCl solution was distilled off, the residue was dissolved in a small amount of water, basified with 10% NaOH, and extracted with ether. The ether residue was distilled in an oil bath (cf. Table IV). *Anal.* Calcd. for $C_8H_{11}N \cdot C_6H_3O_7N_3$(2-Propylpyridine picrate): C, 48.00; H, 4.00; N, 16.00. Found: C, 47.93; H, 4.09; N, 16.10. *Anal.* Calcd. for $C_8H_{11}N \cdot C_6H_3O_7N_3$(4-Propylpyridine picrate): C, 48.00; H, 4.00. Found: C, 48.10; H, 4.51.

Summary

Alkyl- or benzylpyridylcarbinols (α or γ) were obtained from alkyl or benzyl (α or γ) picolyl ethers by the application of sodium amide in Decalin, xylene, or benzene. This indicates that the sodium amide forms a carbanion by the polar effect of nitrogen and the carbanion electron attacks the carbon with a low electron density in the rearranging radical, thus the rearrangement takes place. Ethyl, benzyl, *sec*-butyl (α or γ)-picolyl ethers underwent the rearrangement to carbinols, but rearrangement product could not be isolated from ethyl β-picolyl ether, in which the effect of nitrogen is small, and from phenyl (α or γ) picolyl ethers, in which a carbon with a low electron density is not formed. In benzyl picolyl ethers, the carbanion is formed from the carbon directly bonded to the pyridine ring, and benzyl-(α or γ)-pyridylcarbinol is obtained by the rearrangement reaction.

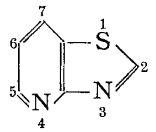
(Rceived March 19, 1956)

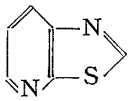
U.D.C. 547.789.6' 834

41. Torizo Takahashi and Kan-ichi Ueda: Sulfur-containing Pyridine Derivatives. XLVIII.* Synthesis of Thiazolo[5,4-*c*]pyridines.

(*Pharmaceutical Institute, Medical Faculty, University of Kyoto***)

In thiazolopyridine system formed by the fusion of pyridine and thiazole rings, there are following four possible isomers, except for the [3,2-*a*] series.


Thiazolo[4,5-*b*]pyridine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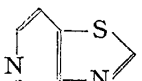
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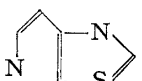
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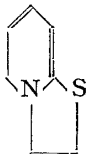
[3,2-*a*]

Previous reports on thiazolopyridines were confined to the [4,5-*b*], [5,4-*b*], and [4,5-*c*] series. The synthesis of thiazolopyridines of these series was demonstrated by earlier workers. The method may be divided broadly into two classes: (1) Application of the procedure used by Kaufmann[1] in the synthesis of aminobenzothiazoles from aniline derivatives to aminopyridines by thiocyanation, and (2) cyclization of *o*-aminopyridinethiols with suitable reagents such as acid anhydride, acid halide, urea, and thiophosgene.

Similar method was adopted by Bernstein *et al.*,[2] who synthesized thiazolo[4,5-

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1) H. P. Kaufmann, *et al.*: Arch. Pharm., **266**, 197 (1928).; **273**, 31(1935); Ber., **67**, 944(1934).

2) J. Bernstein, B. Stearns, E. Shaw, W. A. Lott: J. Am. Chem. Soc., **69**, 1151(1947).