agree with that of Fretwurst[2].

The quantitative investigation on the metabolic process of EHB is in progress.

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Summary

A metabolite of ethylhexabital isolated from the urine of rabbits receiving ethylhexabital was identified with an oxidation product of ethylhexabital with chromic acid. This metabolite is about 1/22 as toxic as ethylhexabital and has no hypnotic action. The chemical structure of EHB-M was disscussed and assumed as 5-cyclohexenonyl-5-ethylbarbituric acid.

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47. **Nobuo Ikekawa, Yoshihiro Sato, and Taizo Maeda**: Studies on the Coal Tar Bases. VII[1]. Basicity of Methylpyridines.

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It is well established that the methyl group in the α- or γ-position of the pyridine ring is more reactive than that in the β-position because of the influence of the nitrogen forming the pyridine nucleus. On the other hand, it is interesting that the basicity of methylpyridine is changed by a change in the position and number of the methyl group on the pyridine ring, namely, the effect of the methyl group on the basicity of the nitrogen of pyridine ring. In the previous papers of this series[2], synthesis of polymethylpyridines was described and some of the pyridines were isolated from coal tar bases of low-temperature coke[3]. The present investigation was undertaken to determine the dissociation constants of all methylpyridine isomers and to compare the basicity of these isomers.

Although the literature contains several references to the determination of the dissociation constants of pyridine and picoline, the values mentioned are varied. Brown and his coworkers studied the basicity of pyridine, three picolines, and 2,6-lutidine toward trifluoroboride[4] and trimethyl boride[5]. Herington[6] determined the dissociation constants of these bases from absorption spectra. Recently, Gero and Markham[7] compared the pK_a values of pyridine and five methylpyridines obtained from pH titration curves in aqueous solution and concluded that the pK_a value of methylpyridine was obtainable from the following experimental equation

$$pK_a = pK_{py} + 0.82\,\gamma + 0.73\,\alpha - 0.03\alpha(\alpha-1)$$

in which pK_{py} represents the pK_a of pyridine (5.23) and γ or α is the number of methyl group in γ- or α-position, respectively. A methyl group manifests its electron-donating character by increasing the electron density at the N atom (expressed in the pK_a) by a

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* Hakata, Fukuoka (池川信夫, 佐藤良博, 前田泰三).

[1] Part VI: This Bulletin, **1**, 283(1953).

[2] K. Tsuda, *et al.*: *Ibid.*, **1**, 122, 126, 142, 283(1953).

[3] N. Ikekawa: *Ibid.*, **1**, 149(1953).

[4] H. C. Brown, H. I. Schlesinger, S. Z. Cardon: J. Am. Chem. Soc., **64**, 325(1942).

[5] H. C. Brown, G. K. Barbars: *Ibid.*, **69**, 1137(1947).

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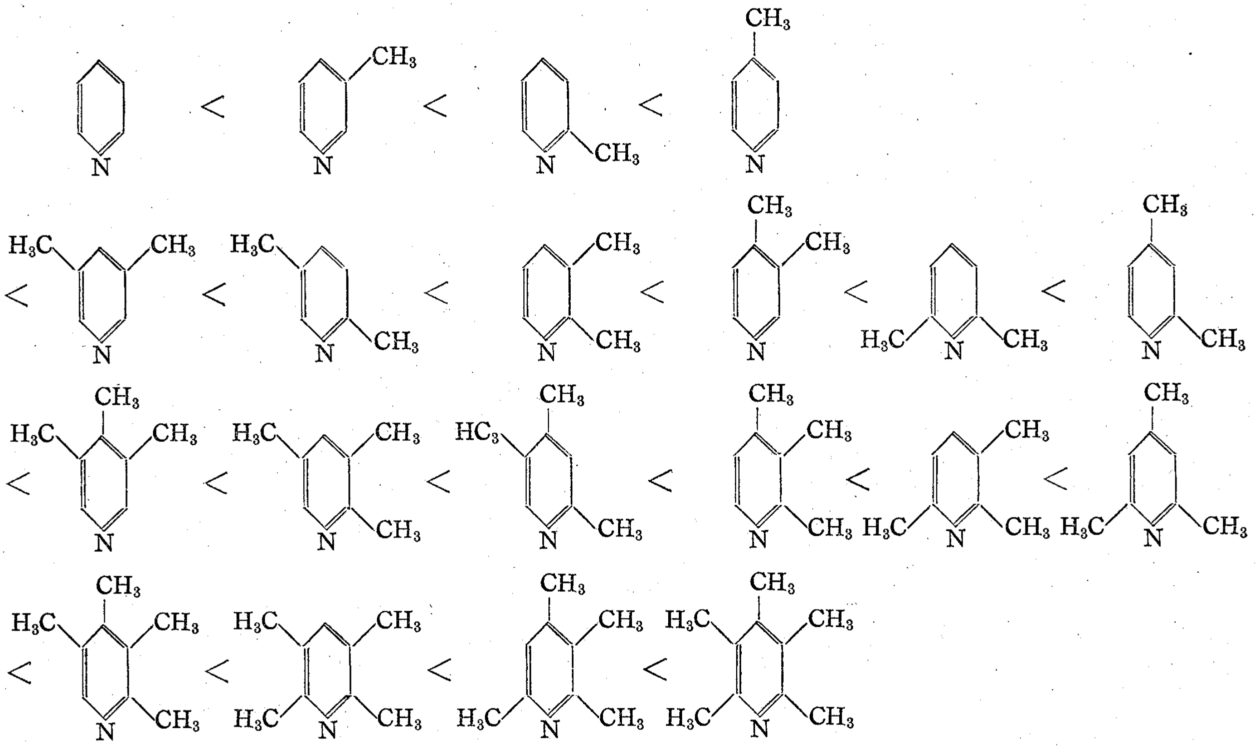
[7] A. Gero, J. J. Markham: J. Org. Chem., **16**, 1835(1951).

constant of 0.73 if the methyl group is in the α-position, and of 0.82, if it is in the γ-position. If two methyl groups are in the α-position, they increase the fundamental basicity of the ring by less than twice the α-constant, necessitating the correction of 0.03 for the α-constants. The dissociation constants of methylpyridines not mentioned in the literature referred to above have not been determined by any worker.

By a method almost similar to Gero's, the authors determined the dissociation constants of the pyridine and 19 kinds of methylpyridine isomers by potentiometric titration of the bases dissolved in dilute ethanol with hydrochloric acid. In the points of half-neutralization on the titration curves which are shown in Fig. 1, $[B]=[BH^+]$, and therefore the pH of the solution, is equal to pK_a of the conjugate acid of the base. These pK_a values and corresponding K_B values are listed in Table I. The data in Table I indicate that introduction of a methyl group into a pyridine ring increases the basicity of methylpyridine step by step and the methyl group attached to α- or γ-position is more effective than that attached to the β-position. In mono- and dimethylpyridines, the magnitude of the effect increases in the order of $\beta<\alpha<\gamma$, but in tri- and tetramethylpyridines, in the order $\beta<\gamma<\alpha$.



It is difficult to explain the effect of the methyl group on the basicity of pyridines but if the basicity of N atom of pyridine is assumed to remain unchanged in methylpyridine and the increased degree of basicity (expressed in pK_a) is assumed to indicate the effect of the methyl group, we can introduce a mathematical relationship between the effect of α-, β-, and γ-methyl group on the basicity, and from this point of view, the pK_a value of methylpyridine is shown in the following equation

$$pK_a = pK_{apy} + n_\alpha \cdot A_\alpha + n_\beta \cdot B_\beta + n_\gamma \cdot C_\gamma$$

where pK_{apy} represents the pK_a of pyridine (5.30) and A_α, B_β, or C_γ, the increased degree when a methyl group is introduced into the α-, β-, or γ-position, respectively, and n denoting the number of α-, β-, or γ-methyl group in pyridine. The value of A_α, B_β, or C_γ varies according to the number of methyl groups in the pyridine ring as shown in Fig. 2. The column headed by $pK_{a(calc.)}$ in Table I gives the calculated pK_a values which are the sum of A_α, B_β, and C_γ values shown in Fig. 2. It will be seen that the agreement

TABLE I. Physical Constants of Methylpyridines

	Compound	pK_a	$pK_{a(calc.)}$	Dissoc. const.	d_4^{15}*	n_D^{15}**
I	Pyridine	5.30	(5.30)	2.00×10^{-9}	0.9840	1.5100
II	β-Picoline	5.85	(5.85)	7.08×10^{-9}	0.9578	1.5052
III	α- 〃	5.95	(5.95)	8.91×10^{-9}	0.9488	1.5035
IV	γ- 〃	6.10	(6.10)	1.26×10^{-8}	0.9577	1.5043
V	3,5-Dimethylpyridine	6.34	(6.36)	2.19×10^{-8}	0.9432	1.5055
VI	2,5- 〃	6.55	(6.55)	3.55×10^{-8}	0.9346	1.4966
VII	2,3- 〃	6.56	(6.55)	3.63×10^{-8}	0.9569	1.5062
VIII	3,4- 〃	6.61	(6.60)	4.07×10^{-8}	0.9623	1.5127
IX	2,6- 〃	6.72	(6.74)	5.25×10^{-8}	0.9278	1.5001
X	2,4- 〃	6.80	(6.79)	6.31×10^{-8}	0.9332	1.5022
XI	3,4,5-Trimethylpyridine	7.10	(7.06)	1.26×10^{-7}	0.9616	1.5103
XII	2,3,5- 〃	7.15	(7.10)	1.41×10^{-7}	0.9613	1.5110
XIII	2,4,5- 〃	7.28	(7.33)	1.91×10^{-7}	0.9384	1.5095
XIV	2,3,4- 〃	7.38	(7.33)	2.40×10^{-7}	0.9605	1.5185
XV	2,3,6- 〃	7.40	(7.37)	2.51×10^{-7}	0.9294	1.5058
XVI	2,4,6- 〃	7.63	(7.60)	4.27×10^{-7}	0.9204	1.5012
XVII	2,3,4,5-Tetramethylpyridine	7.78	(7.82)	6.03×10^{-7}	0.9595	1.5215
XVIII	2,3,5,6- 〃	7.91	(7.92)	8.13×10^{-7}	—	—
XIX	2,3,4,6- 〃	8.10	(8.13)	1.26×10^{-6}	0.9388	1.5132
XX	Pentamethylpyridine	8.75	(8.70)	5.62×10^{-6}	—	—

* Measured with a pycnometer.
** Measured with the Abbé refractometer.

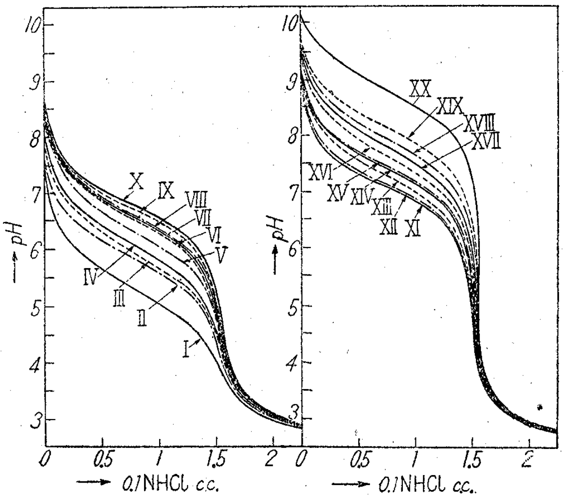


Fig. 1. Titration Curve of Methylpyridines (10% EtOH solution) I~XX → Table I.

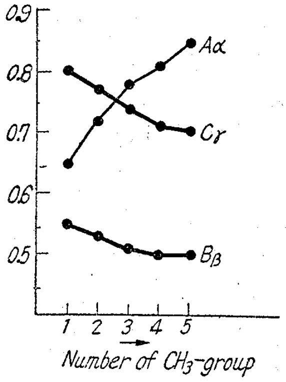


Fig. 2. Effect of Methyl Group in Pyridines

between the observed and calculated pK_a values is relatively good.

A simple equation like the one reported by Gero[7] is not always applicable to all methylpyridine isomers, because he did not measure the dissociation constants of pyridines which possess the methyl group in β-position. The introduction of a methyl group into pyridine ring increases the electron availability at the N atom through operation of the inductive effect produced, and the magnitude may be expected to increase in the order of $\gamma<\beta<\alpha$ because of the decreasing distance of methyl group from N atom. The hyperconjugative effect of methyl group may also bring about an increase in the strength of the basicity of methylpyridines, and the magnitude of this effect may change in the order of $\alpha,\ \gamma\gg\beta$. These total effects are presented as the basicity of methylpyridines, but the effect of the methyl group cannot be explained by such effect alone. It may be concluded from these results that the effect of γ-methyl group in polymethylpyridine is reduced by the interaction between that methyl group and other methyl groups. On the other hand, the effect of α-methyl group increases as the number of methyl group introduced into pyridine nucleus becomes greater. It was explained by Gero that the weaker basicity of 2,6-dimethylpyridine compared to that of 2,4-dimethylpyridine depends upon the steric hindrance of the two methyl groups in α-position. However, it was found from the present experiments that their steric hindrance was not so considerable in comparison with the basicity of all methylpyridine isomers towards hydrochloric acid. Brown and Dewar[8] reported that their calculated values of the charge density of N in picoline nucleus were parallel to the values of their dissociation constants which were measured by Herington[6] (β-picoline$\leqslant$α-picoline$<$γ-picoline), but no resolution have yet been obtained of polymethylpyridine by quantum mechanism. The absolute value of the effect of a methyl group in α-, β-, or γ-position cannot be determined from these results but its relative value is shown in Fig. 2.

The authors express their thanks to Prof. Kyosuke Tsuda for his suggestion of this investigation and for his unfailing guidance during the course of this work.

Experimental

Material—Following 8 pyridines were isolated from coal tar: Pyridine, α-, β-, and γ- picolines, and 2,6-, 2,4-, 2,3-, and 3,5-lutidines[3]. Following compounds were synthetically prepared as previously reported[2]: 2,5- and 3,4-lutidines, 2,3,4-, 2,3,5-, 2,3,6-, 2,4,5-, and 3,4,5-collidines, 2,3,-4,6-, 2,3,4,5-, and 2,3,5,6-tetramethylpyridines. 2,4,6-Collidine was prepared by the method of Hantzsch[9] and pentamethylpyridine by that of Karrer[10].

Method—The above pure samples were freshly distilled before use and 0.005 M solution was prepared by diluting with CO_2-free 10% EtOH. In order to obtain a uniform condition, all bases were diluted with 10% EtOH solution, for pentamethylpyridine is insoluble in water. Titration was carried out on the Coleman Model 3D pH meter equipped with the external electrode assembly. Each of the above solutions (30 cc.) was titrated with 0.1 N HCl in a 50-cc. beaker fitted with a tube introducing the N_2 gas at $15°\pm0.5°$(room temp.). Addition of acid was made from a buret having a capacity of 10 cc. and graduated at intervals of 0.05 cc. The fine-pointed tip of the buret was kept below the surface of the solution being titrated. During the titration, the solution was slightly bubbled by N_2 introduced for stirring and preventing absorption of atmospheric CO_2. The pH meter (accuracy ±0.02 pH) was frequently standardized against buffer of pH 4.10.

Summary

The dissociation constants of pyridine and 19 kinds of methylpyridines were determined by the titration method and the effect of methyl groups on basicity was compared.

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