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186. Torizo Takahashi*1 and Kazuo Kariyone*2 : Studies on Insecticides. V. Synthesis of 2-Piperidone Derivatives.

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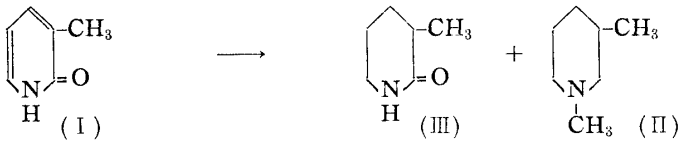
In previous papers,[1,2] a new procedure for converting 2-piperidone into proline derivatives was reported. The present paper describes the synthesis of some 2-piperidone derivatives which may be useful for *trans*-formation into prolines.

Grave[3] obtained 2-piperidone from 2-aminopyridine by catalytic hydrogenation, followed by diazotization and subsequent hydrolysis. Hydrogenation of 2(1*H*)-pyridone at a high temperature and high pressure to give 2-piperidone was described by Raeth.[4] Katada[5] prepared 2-piperidone from pyridine 1-oxide by treatment with boiling acetic anhydride, followed by immediate hydrogenation over 40% palladium-carbon.

A hydrogenation method through which 2(1*H*)-pyridone is reduced to 2-piperidones in the presence of Raney nickel in a better yield is described.

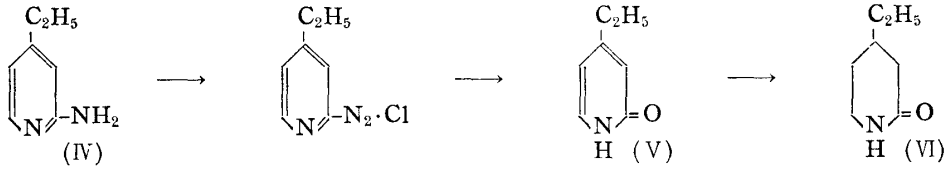


(I) (III) (II)

3-Methyl-2-piperidone (III) was obtained in 80% yield when 3-methyl-2(1*H*)-pyridone (I), prepared by the method of Boekelheide and Linn,[6] was hydrogenated over Raney nickel in methanol at 120 atm. and 200~240°. When the temperature was raised to 280°, partial reduction of the carbonyl group followed by methylation of the resulting 3-methylpiperidine was observed, giving 1,3-dimethylpiperidine (II) as a by-product.

In contrast to Raney nickel, the nickel and copper carbonate catalyst was not effective in hydrogenation of 3-methyl-2(1*H*)-pyridone at 290° and 120 atm., while 40% palladium-carbon was also found to be inactive for the hydrogenation of the pyridones (I) at room temperature and atmospheric pressure.

Hydrogenation of 4-ethyl-2(1*H*)-pyridone (V) by a similar method as for 3-methyl-2(1*H*)-pyridone furnished 4-ethyl-2-piperidone (VI) in 80% yield.



(IV) (V) (VI)

The starting material, 4-ethyl-2(1*H*)-pyridone (V), was prepared by diazotization of 2-amino-4-ethylpyridine (IV) followed by hydrolysis of the resulting diazonium compound. The 2(1*H*)-pyridone (V) thus obtained exhibited a carbonyl band at 1650 cm^{-1} in its infrared spectrum, as expected.

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1) T. Takahashi, K. Kariyone : Yakugaku Zasshi, **78**, 1306(1958).
2) *Idem* : *Ibid.*, **79**, 711(1959).
3) T. B. Grave : J. Am. Chem. Soc., **46**, 1468(1924).
4) C. Raeth : Ann., **489**, 107(1930).
5) M. Katada : Yakugaku Zasshi, **67**, 51(1947).
6) V. Boekelheide, W. J. Linn : J. Am. Chem. Soc., **76**, 1286(1954).

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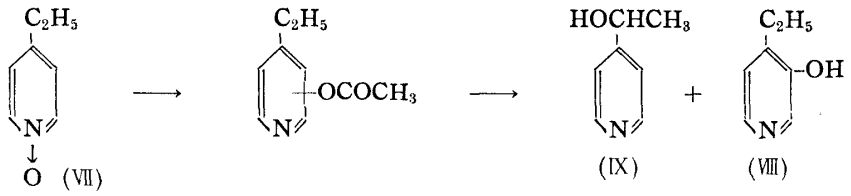
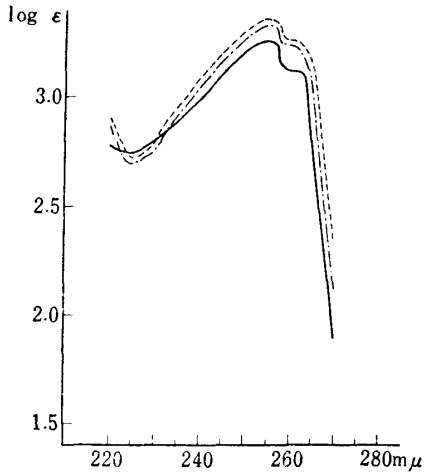


In this connection, the action of acetic anhydride on 4-ethylpyridine 1-oxide (VII) was examined.

Boekelheide and Linn,[6] and Bullitt and Maynard[7] reported previously that the only isolable product from the reaction mixture of 2- or 4-methylpyridine 1-oxide and acetic anhydride was 2- or 4-pyridinemethanol acetate, while Kobayashi and Furukawa[8] isolated 2-pyridinemethanol acetate and 6-methyl-2(1*H*)-pyridone in a ratio of about 5:2 when 2-methylpyridine 1-oxide was reacted with acetic anhydride. In contrast to the results of the above workers, Berson and Cohen[9] isolated from the reaction mixture of 4-methylpyridine 1-oxide with acetic anhydride two products which were shown to be 4-pyridinemethanol acetate and 3-hydroxy-4-methylpyridine.

In view of the above controversy, it seemed of interest to find out what would be the products of reaction of acetic anhydride with 4-ethylpyridine 1-oxide, and especially to know whether 4-ethyl-2(1*H*)-pyridone would be one of the products or not.

The reaction mixture afforded two products after saponification. The one which was not extractable with aqueous sodium hydroxide from chloroform solution gave an oxalate, which analyzed for $C_7H_9ON \cdot C_2H_2O_4$. The infrared srectrum of the free base exhibited a hydroxyl band at 3200 cm^{-1} (in Nujol) but no bands in the carbonyl region, and its ultraviolet spectrum was very similar to that of 4-ethylpyridine (Fig. 1).



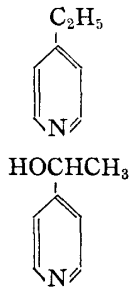


Fig. 1.

——— in MeOH

---------- in MeOH

– – – – – in *M*/10 MeONa (MeOH)

Based on these findings, along with the observation of Boekelheide and Linn[6] that 2-ethylpyridine 1-oxide gave 2-(1-acetoxyethyl)-pyridine on treatment with acetic anhydride, the structure of 4-(1-hydroxyethyl)pyridine (IX) was assigned to this base.

The second basic product which was extractable with sodium hydroxide solution from its chloroform solution was characterized as its neutral oxalate, $(C_7H_9ON)_2 \cdot C_2H_2O_4$. The base gave a red ferric chloride test suggesting that it is a 3-hydroxypyridine derivative. The infrared spectrum of the base showed two broad bands at about 1900 and 2500 cm^{-1}, characteristic of 3-hydroxypyridines,[10] and the ultraviolet spectrum in a sodium meth-

7) O. H. Bullitt, J. T. Maynard : J. Am. Chem. Soc., **76**, 1370(1954).
8) G. Kobayashi, G. Furukawa : This Bulletin, **1**, 347(1953).
9) J. A. Berson, T. Cohen : J. Am. Chem. Soc., **77**, 1281(1955).
10) S. F. Mason : J. Chem. Soc., **1957**, 4874.

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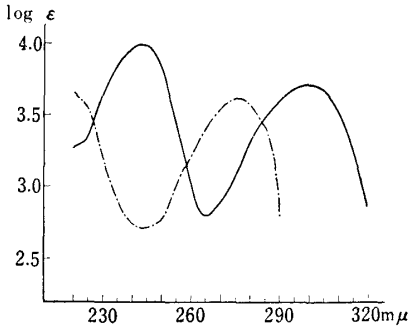


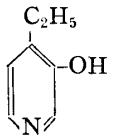


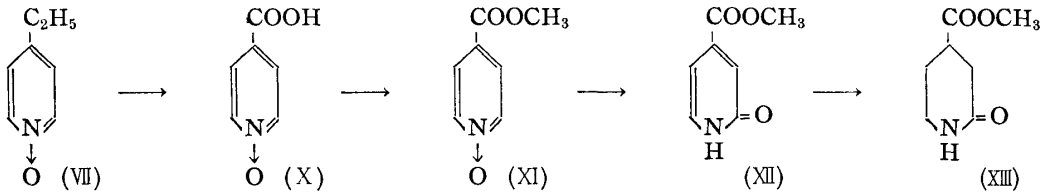
Fig. 2.

——— in MeOH

------ in *M*/10 NaOMe (MeOH)

oxide solution exhibited a striking bathochromic shift from that in methanol (Fig. 2).

All these results, together with the findings of Berson and Cohen[9] on the reaction products of 4-methylpyridine 1-oxide with acetic anhydride, suggested the identity of this base as 3-hydroxy-4-ethylpyridine (VIII). 2(1*H*)-Pyridones were not detected in the reaction mixture, contrary to expectations.



Treatment of methyl isonicotinate 1-oxide (XI) with acetic anhydride gave, though in a poor yield, 4-methoxycarbonyl-2(1*H*)-pyridone (XII) which was identified by direct comparison with a sample obtained by the method described by Bümler, Sorkin, and Erlenmeyer.[11] Methyl isonicotinate 1-oxide (XI) used for this reaction was most conveniently obtained by a permanganate oxidation of 4-ethylpyridine 1-oxide (VII) followed by esterification, since 4-ethylpyridine 1-oxide (VII) is, in contrast to 4-ethylpyridine, readily soluble in water and oxidation proceeds very smoothly.

Hydrogenation of 4-methoxycarbonyl-2(1*H*)-pyridone (XII) over Raney nickel gave 4-methoxycarbonyl-2-piperidone (XIII) in 50% yield.

Experimental

3-Methyl-2-piperidone (III) and 1,3-Dimethylpiperidine (II)—3-Methyl-2(1*H*)-pyridone was prepared according to the method of Boekelheide and Linn.[6] MeOH solution (250 cc.) of (I) (8.0 g.) was hydrogenated in a shaking autoclave over Raney Ni with H_2 with an initial pressure of 120 atm. at 280° for 6 hr. After removal of the catalyst, the filtrate was evaporated to dryness under a reduced pressure and the residue distilled to obtain two fractions, 2.5 g. of (III), b.p_{14} 140~150°, and 0.8 g. of (II), b.p_{14} 70~100°. (III) was redistilled for analysis to give a colorless oil, b.p_8 128~131°. *Anal.* Calcd. for $C_6H_{11}ON$: C, 63.68; H, 9.80; N, 12.37. Found: C, 63.99; H, 10.16; N, 11.94.

The picrate of 1,3-dimethylpiperidine was prepared in Et_2O and formed yellow needles, m.p. 105°. *Anal.* Calcd. for $C_{13}H_{18}O_7N_4$: C, 45.61; H, 5.39; N, 16.37. Found: C, 45.97; H, 5.52; N, 16.42.

4-Ethyl-2-piperidone (VI) and Methyl 2-Oxoisonipecotate (XIII)—The hydrogenation of (V) and (XII) was carried out in MeOH by the procedure similar to that described above. The reaction mixture was worked up in the usual manner and each product was distilled or crystallized as shown in Table

Table I.

Material (g.)		Raney Ni W-2 (g.)	MeOH (cc.)	Temp. (°C)	Recrystn. solvent	b.p. (°C/mm. Hg) or m.p. (°C)	Product	Yield (g.)	Mol. formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
(V)	6.0	1.5	260	260		124/4	(VI)	5.0	C_7H_9ON	68.27	7.37	11.37	67.95	7.32	10.99
(XII)	0.9	0.3	50	260	Me_2CO+ petr. benzine	115	(XIII)	0.5	$C_7H_{11}O_3N$	53.49	7.05	8.91	53.06	7.27	9.17

11) J. Bämler, E. Sorkin, H. Erlenmeyer: Helv. Chim. Acta, **34**, 496(1951).

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I. When the reduction temperature was kept at 180°, the starting material was recovered unchanged in almost quantitative yield.

4-Ethyl-2(1*H*)-pyridone (V)—To a solution of 2-amino-4-ethylpyridine (8.0 g.) in 10% HCl (120 cc.) a solution of $NaNO_2$ (6.5 g.) in H_2O (30 cc.) was added with stirring and cooling below 5°. After continued stirring for 0.5 hr., the mixture was gently heated to reflux. After 3 hr., the reaction mixture was evaporated to dryness under a reduced pressure, the residue was taken up in a small amount of H_2O, neutralized with K_2CO_3, and extracted with $CHCl_3$. The organic layer was dried, concentrated *in vacuo*, and the residue was crystallized from EtOH to colorless plates (5.5 g.), m.p. 126°. *Anal.* Calcd. for C_7H_9ON : C, 68.27; H, 7.37; N, 11.29. Found : C, 68.10; H, 7.37; N, 11.29.

Action of Acetic Anhydride on 4-Ethylpyridine 1-Oxide—A mixture of 4-ethylpyridine 1-oxide (13.0 g.) and Ac_2O (50 cc.) was refluxed for 3 hr., evaporated *in vacuo*, and the residue was distilled at 92~110°/6 mm. to yield a colorless oil (6.8 g.). This was hydrolyzed with 15% HCl (40 cc.) by refluxing for 8 hr. The reaction mixture was concentrated under a reduced pressure to 15 cc., neutralized with K_2CO_3, and extracted with $CHCl_3$. The organic layer was washed with 10% NaOH, dried, evaporated, and distilled at 108°/4 mm. to give a colorless solid (3.5 g.) of 4-(1-hydroxyethyl)-pyridine (IX) which melted at 63° after purification through its oxalate. *Anal.* Calcd. for C_7H_9ON: C, 68.27; H, 7.37; N, 11.37. Found : C, 67.97; H, 7.17; N, 11.08.

The oxalate was prepared in EtOH and formed needles (from EtOH), m.p. 153°. *Anal.* Calcd. for $C_9H_{11}O_5N$: C, 50.70; H, 5.20; N, 6.57. Found : C, 50.59; H, 5.48; N, 6.60.

The NaOH washing was acidified with HCl, neutralized with K_2CO_3, and extracted with $CHCl_3$. The $CHCl_3$ extract was dried, evaporated, and the residue was distilled at 135°/0.3 mm. to give a pale yellow solid (0.8 g.) of 4-ethyl-3-hydroxypyridine, m.p. 100°, after purification through its oxalate. *Anal.* Calcd. for C_7H_9ON : C, 68.27; H, 7.37; N, 11.39. Found : C, 67.86; H, 7.62; N, 11.34.

The oxalate was obtained by adding oxalic acid in EtOH to an EtOH solution of the base. It crystallized from 70% EtOH as prisms, m.p. 231°. *Anal.* Calcd. for $C_{16}H_{20}O_6N_2$: C, 57.13; H, 5.99; N, 8.33. Found : C, 57.38; H, 5.84; N, 8.23.

Isonicotinic Acid 1-Oxide (X)—To a solution of 4-ethylpyridine 1-oxide (8.4 g.) in H_2O (80 cc.), pulverized $KMnO_4$ (44 g.) was added in small portions with vigorous stirring under reflux. After continued refluxing and stirring for 5 hr., the reaction mixture was filtered, and MnO_2 was washed with hot H_2O. The filtrate and washings were combined, concentrated to 30 cc. under a reduced pressure, and 13.7 g. of H_2SO_4 was added carefully to the solution to separate crystals. The crystals were collected and recrystallized from EtOH to colorless needles (9.2 g.), m.p. 268°. *Anal.* Calcd. for $C_6H_5O_3N$: C, 51.80; H, 3.62; N, 10.07. Found : C, 51.49; H, 3.80; N, 9.62.

Methyl Isonicotinate 1-Oxide (XI)—A solution of isonicotinic acid 1-oxide (9.0 g.) in a mixture of MeOH (50 cc.) and H_2SO_4 (1.0 g.) was gently refluxed for 5 hr. After concentration to 10 cc., the mixture was diluted with H_2O (20 cc.), neutralized with K_2CO_3, and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over Na_2SO_4, evaporated to dryness under a reduced pressure, and the residual crystalline solid was recrystallized from Me_2CO to colorless needles (7.5 g.), m.p. 121°. *Anal.* Calcd. for $C_7H_7O_3N$: C, 54.94; H, 4.61; N, 9.15. Found : C, 55.17; H, 4.18; N, 9.17.

The picrate formed yellow needles, m.p. 107° (from EtOH). *Anal.* Calcd. for $C_{13}H_{10}O_{10}N_4$: C, 40.85; H, 2.64; N, 14.66. Found : C, 40.71; H, 2.75; N, 14.91.

4-Methoxycarbonyl-2(1*H*)-pyridone (XII)—A solution of (XI) (10 g.) in Ac_2O (150 cc.) was refluxed for 8 hr., concentrated *in vacuo*, and the residue was dissolved in a small amount of H_2O. This solution was neutralized with K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ layer was dried, evaporated to dryness *in vacuo*, and the residue was crystallized from Me_2CO. The dark colored crystals were purified by sublimation and repeated crystallizations from Me_2CO to pale yellow needles (0.7 g.), m.p. 210°. *Anal.* Calcd. for $C_7H_7O_3N$: C, 54.90; H, 4.61; N, 9.15. Found : C, 54.65; H, 4.76; N, 8.87.

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Summary

Hydrogenation of 2(1*H*)-pyridones was carried out in methanol over Raney nickel at 120 atm. and 200~240° and gave 2-piperidone derivatives.

When the reduction temperature was raised to 280°, hydrogenation of carbonyl group took place, followed by N-methylation of the resulting piperidine derivative was observed. On the other hand, when the reaction temperature was kept below 180°, the starting material was recovered unchanged.

By the action of acetic anhydride on 4-ethylpyridine 1-oxide, 4-(1-hydroxyethyl)pyridine and 4-ethyl-3-hydroxypyridine were obtained, while 4-methoxycarbonylpyridine 1-oxide gave 4-methoxycarbonyl-2(1*H*)-pyridone. (Received April 16, 1960)

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