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Flash Vacuum Pyrolysis of 2-Picoline *N*-Oxide. Formation of 2-Picolyl Radical

The flash vacuum pyrolysis of 2-picoline *N*-oxide was found to give 2-picoline, pyridine, 2-vinylpyridine, bis(2-pyridyl)methane, and 1,2-bis(2-pyridyl)ethane. From the mechanistic consideration of the formation of these products, intermediacy of 2-picolyl radical (*i.e.*, 2-pyridylmethyl radical) is strongly suggested.

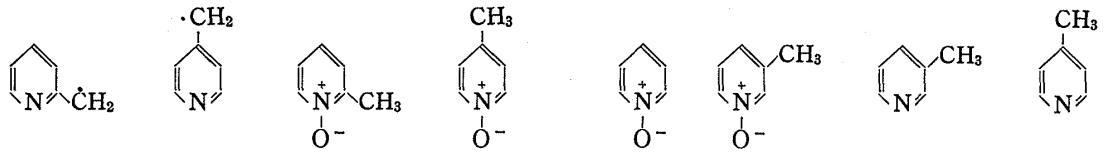
Keywords——flash vacuum pyrolysis; thermolysis; picoline *N*-oxides; heterocycles; radical reaction; radical coupling; picolyl radical; pyridylmethyl radical

Although 2-picolyl (2-pyridylmethyl)radical (**1**) and 4-picolyl (4-pyridylmethyl)radical (**2**) have been presumed to be intermediates in some reactions of 2-picoline *N*-oxide (**3**) and 4-picoline *N*-oxide (**4**) respectively, formation of radical **1** from **3** is still subtle.[1-5]

We wish to report an evidence for the formation of radical **1** from **3** by flash vacuum pyrolysis (fvp).[6]

Vaporized material **3** was introduced into an evacuated tube with a slight stream of a carrier and pyrolysed through a hot-zone (quartz tube, ϕ=10 mm, l=150 mm). The yields of the products at various conditions are shown in Table.

In runs a and b, N_2 was used as the carrier and the decomposition of **3** was observed when the temperature of the hot-zone was 550° or above, while 98% of **3** was recovered at 500°. A complete decomposition was observed at 650° or above.[7]

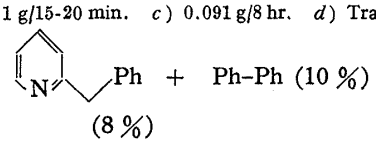
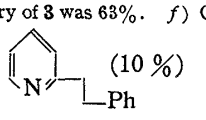
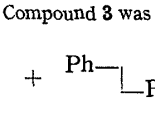


1 **2** **3** **4** **14** **15** **16** **17**

Chart 1

TABLE I. Fvp of 2-Picoline *N*-Oxide (**3**)[a]

Run	Conditions				Products (%)					
	Carrier	°C	mm Hg	Flow rate of **3**	**5**	**6**	**7**	**8**	**9**	Other products
a	N_2	550	1—5	[b]	6	4	2	2	10	—[e]
b	N_2	800	1—5	[b]	13	23	5	11	27	—[f]
c	—	800	0.1	[c]	32	23	tr[d]	tr	21	—[f]
d	PhH (4 g)	800	1—5	[b]	17	14	tr	7	27	[g,f]
e	PhMe (5 g)	800	1—5	[b]	16	15	2	5	34	[h,f]
f	MeOH (2 g)	800	1—5	[b]	31	6	tr	3	45	—[f]

[a] All products were isolated by distillation, vpc, column chromatography, and tlc. The yields were determined by pmr and/or vpc of the mixtures obtained from rough distillations of the original mixtures. The yields are based on the *N*-oxides consumed.
[b] 1 g/15-20 min. [c] 0.091 g/8 hr. [d] Trace. [e] Recovery of **3** was 63%. [f] Compound **3** was not recovered.
[g]  (8 %) **10** + Ph-Ph (10 %) **11**
[h]  (10 %) **12** +  (5 %) **13**

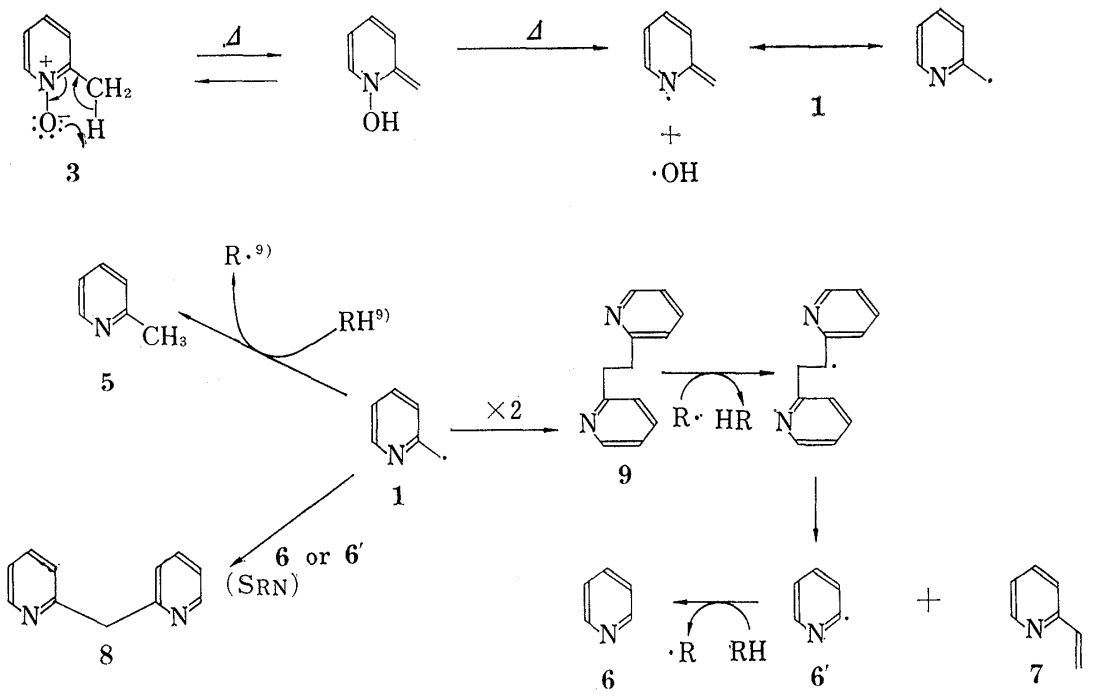


Chart 2

None of **5**—**9** was regarded as a precursor of the other products because the fvp of each of the individual compounds under similar conditions (800°) resulted in an almost quantitative recovery of the starting material. Compounds **7**—**9** are undoubtedly formed intermolecularly and an intermolecular ionic mechanism might be excluded for the formation of these compounds in view of the reaction under non-polar and low-pressure vapor-phase (very low concentrated) conditions applied here. Hence, not only the formation of these products (**7**—**9**) seems to be rationalized only by assuming the free radical **1** as a key intermediate, but also the formation of **5**[8] and **6** could be explained by intermolecular reactions of the radical. In run c, formation of the dimer **9** was recognized in spite of low concentration of **3** (namely, very slight stream of **3**, without carrier) and this shows a considerable stability of the radical **1**.

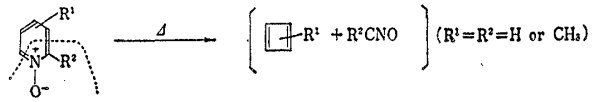
In order to obtain further evidences for the formation of **1**, vaporized organic compounds were employed as the carriers instead of N_2. The formation of compound **10** in run d evidently shows the presence of the radical **1** and that of **12** in run e supports a coupling reaction between radical **1** and benzyl radical formed *via* hydrogen abstraction from toluene. When **3** was pyrolyzed with methanol vapor (run f), yields of **5** and **9** appreciably increased. The increase of **5** might be due to ease of hydrogen abstraction of radical **1** from the methanol molecule (whose hydrogen atoms are highly labile in some radical reactions) and that of **9** can be explained by its less reactivity towards hydrogen abstraction (*i.e.*, lower reactivity of **9** than that of methanol towards R· in Chart 2[9]) and in subsequent decomposition to form **6** and **7**. Additionally, when a vapor of a described organic solvent was introduced during the pyrolysis of **3** (with N_2, 800°, 2 mmHg) from an inlet attached to a point just after the hot-zone, the yields of products **5**—**9** were practically the same as those in run b and no compounds such as **10**—**13** were obtained. This observation indicates that the described reactions were completed within the hot-zone.

Further, the fvp (650°)[7] of the other *N*-oxides, *i.e.*, pyridine *N*-oxide (**14**), 3-picoline *N*-oxide (**15**), and 4-picoline *N*-oxide (**4**) gave deoxygenated compounds, pyridine (**6**, 26%), 3-picoline (**16**, 15%), and 4-picoline (**17**, 6%), respectively, as major products.[10] And recoveries

of the starting materials were 60, 68, and 91%, respectively. These data show a higher reactivity of **3** compared with those of **14**, **15**, and **4**, and support that the mechanism of the reaction of **3** involves an interaction between the methyl group and the oxygen atom, on the formation of the radical **1**, in such a way as shown in Chart 2.[8]

References and Notes

1) The radicals **1** and **2** have been proposed to be the key intermediates in the acyloxy rearrangements of the *N*-oxides **3** and **4**.[2,3] While the presence of **1** is yet unlikely[3,4] in the reaction of **3** with acetic anhydride, **2** has been shown to be present in a similar reaction of **4**.[5]
2) E. Ochiai, "Aromatic Amine Oxides," Elsevier, New York, 1967.
3) A.R. Katritzky and J.M. Lagowski, "Chemistry of the Heterocyclic *N*-Oxides," Academic Press, New York, 1971.
4) H. Iwamura, M. Iwamura, T. Nishida, and I. Miura, *Tetrahedron Lett.*, **1970**, 3117.
5) H. Iwamura, M. Iwamura, M. Imanari, and M. Takeuchi, *Bull. Chem. Soc. Japan*, **46**, 3486 (1973) and references therein.
6) R.F.C. Brown, "Pyrolytic Methods in Organic Chemistry," Academic Press, New York, 1980.
7) The *N*-oxide **3** underwent a complete decomposition at 650° giving aforementioned products, although the data of fvp of **3** at 650° are eliminated in Table. The data will be shown in a future paper.
8) A heterolytic cleavage of the N–O bond of **3** also may be undeniable for the formation of **5** (at least in part).
9) RH represents molecules which bear one or more hydrogen atoms. R· means each radical involved in the reaction system.
10) Several attempts to detect compounds expected from a decomposition as given by



were failed, as well as in fvp of **3** (even in run c).

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Synthesis of Stereoisomeric Suc-Tyr-Leu-Val-*p*NA and Their Properties as Substrate and Inhibitor for Human Spleen Fibrinolytic Proteinase (SFP)[1]

Stereoisomeric analogues of Suc–Tyr–Leu–Val–*p*NA were synthesized in the conventional manner and their properties as the substrate and/or the inhibitor against human spleen fibrinolytic proteinase (SFP) were tested. Suc–D–Tyr–L–Leu–L–Val–*p*NA (II) was hydrolyzed to release *p*-nitroaniline with K_{cat}/K_m value (3700), whereas K_{cat}/K_m value of Suc–L–Tyr–L–Leu–L–Val–*p*NA (I) was 22647. Suc–L–Tyr–D–Leu–D–Val–*p*NA (III) inhibited the hydrolytic activity of SFP towards both the peptide (I) and fibrin.

Keywords——Suc–Tyr–Leu–Val–*p*NA; stereoisomer; peptide synthesis; synthetic substrate; synthetic inhibitor; human spleen fibrinolytic proteinase; inhibition of fibrinolysis