Notes

UDC 547.824.07

Tetsuji Kametani*1 and Yukio Nomura*1 : Studies on the Syntheses of Heterocyclic Compounds. LIV.[1] Formation of N-Alkyl-2-pyridone by Alkali Treatment of N-Alkyl-2-chloropyridinium Salt.

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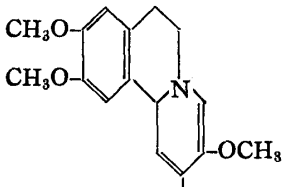
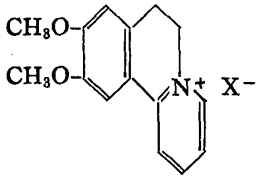
Synthesis of benzoquinolizine derivatives has recently been undertaken especially for the purpose of synthetic approach to rotundine alkaloid, the main alkaloid of *Stephania rotunda* LOUREIRO, to which formula 2-methyl-3,9,10-trimethoxy-6,7-dihydro-11b*H*-benzo-[*a*]quinolizine (1)[2,3] has been given by H. Kondo and Matsuno. In general, cyclization of N-substituted 2-pyridone by the Bischler-Napieralski reaction is thought to be not so easy as in the case of N-substituted 2-piperidone.[4~6]



(I)

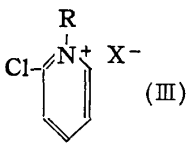


(II)

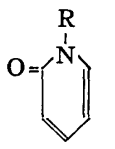
Cyclization was attempted on the pyridone (IV) in order to synthesize benzoquinolizine derivative (II) as a model experiment to synthesis of rotundine (I), but the expected compound (II) was not obtained.[5,6]

Contrary to expectation, N-substituted 2-chloropyridinium salt (III) was obtained and this was easily converted to the corresponding 2-pyridone (IV) by treatment with sodium hydroxide solution. Accordingly, this reaction was examined in another case of N-alkyl-2-chloropyridinium iodide (III), by the result of which a new reaction of N-substituted 2-pyridone (IV) from N-alkyl-2-halopyridinium salt was developed.

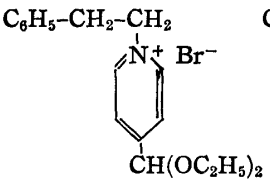
Many methods have been reported for synthesis of N-alkyl- or N-aralkyl-2-pryidone. For instance, a modification of the oxidation reaction to convert 1-(β-phenethyl)-4-formyl-pyridinium bromide diethyl acetal (V) to a pyridone (VI) by treatment with an excess of potassium ferricyanide, followed by the addition of benzene and a very large



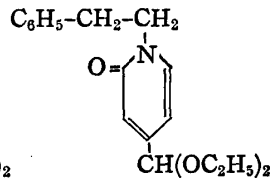
(III)



(IV)



(V)



(VI)

(IIIa) R=CH_3

(IIIb) R=CH_2-CH_2-(3,4-dimethoxyphenyl)

(IVa) R=CH_3

(IVb) R=CH_2-CH_2-(3,4-dimethoxyphenyl)

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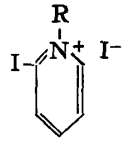
1) T. Kametani, K. Fukumoto : Yakugaku Kenkyu, **36**, 412(1958).
2) H. Kondo, T. Matsuno : Yakugaku Zasshi, **64A**, 28; **64B**, 113, 274(1944).
3) S. Sugasawa, K. Mizukami : This Bulletin, **6**, 312(1958).
4) J. A. Berson, T. Cohen : J. Am. Chem. Soc., **78**, 416(1956).
5) S. Sugasawa, S. Akaboshi, Y. Ban : This Bulletin, **7**, 263(1959).
6) Y. Ban, O. Yonemitsu, T. Oishi, S. Yokoyama, M. Nakagawa : *Ibid.*, **7**, 609(1959).

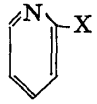
excess of sodium hydroxide solution was successfully carried out.[7]

Furthermore, a new method of converting 2-methylpyridine to 2-pyridone (IVa) has recently been described, this reaction affording a selective method for introducing pyridone oxygen at a predetermined site.[4]

As regards the synthesis of N-alkyl-2-chloropyridinium salt (III), an attempt was made to condense methyl or ethyl iodide with 2-chloropyridine (IX) prepared from 2-aminopyridine (VIII) by the Sandmeyer reaction, but, in this case, N-methyl- or N-ethyl-2-iodopyridinium iodide (VIIa or VIIb) was found to be formed by iodoalkylation of 2-chloropyridine in the presence of excess alkyl iodide according to the method of O. Fischer.[8] The objective N-methyl- or N-ethyl-2-pyridone was obtained by alkali treatment of iodo derivative.

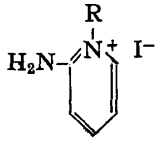


(VIIa) $R=CH_3$
(VIIb) $R=C_2H_5$

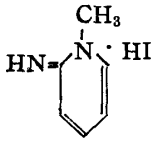


(VIII) $X=NH_2$
(IX) $X=Cl$

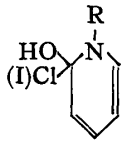
In general, 2-chloropyridine (IX) is prepared by treatment of N-methyl-2-pyridone with phosphoryl chloride. As is well known, (IVa) gives 2-chloropyridine (IX) when heated with phosphoryl chloride.[8,10] In the synthesis of 2-halopyridinium salt, however, yield was not so good that attempt was made to prepare N-alkyl-2-aminopyridinium salt (Xa or Xb) by condensation of 2-aminopyridine with methyl or ethyl iodide, in order to simplify the synthesis of N-alkyl-2-pyridone from (Xa) or (Xb).



(Xa) $R=CH_3$
(Xb) $R=C_2H_5$



(XI)



(XII)

Chichibabin[11] obtained N-methyl-2-imino-1,2-dihydropyridine hydriodide (XI) in place of (Xa) and, in addition, N-substituted 2-pyridone was obtained by refluxing with sodium hydroxide solution for 6 hours.

The mechanism of the reaction of Chichibabin is thought to be different from the present procedure of going through 2-chloropyridinium salt. N-Methyl-2-imino-1,2-dihydropyridine (XI) did form and its diazotization with excess of conc. hydrochloric acid and sodium nitrite was tried, but it was not successful. Iodoethylation of 2-aminopyri dine failed to give (Xb). It is possible that N-alkyl-2-imino-1,2-dihydropyridine cannot be converted to its tautomer, the 2-amino form (Xa), because the nitrogen atom is substituted by alkyl group. Accordingly, this 2-imino compound will not be diazotized.

N-Methyl- or N-ethyl-2-pyridone was obtained by treatment of the corresponding N-alkyl-2-iodopyridinium iodide (VIIa or VIIb) with 10% sodium hydroxide solution at room temperature or by slightly warming on a water bath. From N-aralkyl-2-chloropyridinium iodide, the objective N-aralkyl-2-pyridone was obtained. This reaction is thought to go through the carbinol base (XII), which is spontaneously formed as an intermediate after the quaternary ammonium salt is first liberated by 10% sodium hydroxide and

7) S. Sugasawa, T. Tatsuno : This Bulletin, **2**, 193(1954).
8) O. Fischer : Ber., **31**, 611(1898); *ibid.*, **32**, 1298(1899).
9) C. Rath : Ann., **486**, 76(1931).
10) R.G. Fargher, R. Furness : J. Chem. Soc., **107**, 688(1915).
11) A.E. Chichibabin, R.A. Konowalowa, A.A. Konowalowa : Ber., **54**, 817(1921).

which undergoes dehydrochlorination to the objective 2-pyridone derivative (IVa or IVb). Therefore, if N-substituted 2-halopyridinium salt, that is, the quaternary ammonium salt containing halogen next to nitrogen in the pyridine ring, can be formed easily, the objective N-substituted 2-pyridone should easily be produced. This reaction is now being examined with 2-chloroquinoline and 1-chloroisoquinoline, and these results will be reported subsequently.

Experimental*2

1-Methyl-2(1*H*)-pyridone (IVa)—a) By Alkaline Treatment of 1-Methyl-2-iodopyridinium Salt (VIIa): A mixture of 1 g. of 2-chloropyridine and 1 cc. of MeI was refluxed with 5 cc. of Me_2CO on a water bath for about 3.5 hr. and yellowish white crystals precipitated. The mixture was cooled, the precipitate was collected, washed with Me_2CO, and dried to 0.5 g. of a crude methiodide of m.p. 197~199° (decomp.).*3,4 0.3 g. of this methiodide was treated with 10% NaOH at room temperature and extracted with Et_2O and $CHCl_3$. This extract was dried, evaporated, and 0.2 g. of an oil was obtained which formed a picrate of m.p. 135~140°. It formed yellowish needles, m.p. 141~142°, after several recrystallizations from EtOH. The m.p. agreed with that reported in the literature.[12]

b) Preparation from 1-Methyl-2-picolinium Salt by Berson's Method: A mixture of 2.2 g. of 1-(2-picolyl)pyridinium iodide methiodide and 10 cc. of water was treated dropwise with 0.6*N* NaOH, the resulting deep blood-red solution was treated as usual, and 0.2 g. of its picrate was obtained, which agreed with an authentic sample mentioned above.

1-Ethyl-2-iodopyridinium Iodide (VIIb)—A mixture of 1.8 g. of 2-chloropyridine and 2.8 g. of EtI was heated on a water bath without a solvent and a considerable amount of crystals separated after 3 hr.'s heating. The reaction mixture was allowed to stand overnight. On the following day, the precipitate was collected by suctional filtration, washed with Me_2CO, and 1.3 g. of white needles, m.p. 148~155°, was obtained. The filtrate was heated for an additional 2 hr. and 0.2 g. of (VIIb) was formed. Total yield, 1.5 g. From the filtrate, 0.5 g. of the unreacted product was recovered by evaporation of the reddish brown solution to dryness in a reduced pressure. 1-Ethyl-2-iodopyridinium salt was purified from EtOH and colorless needles, m.p. 158~159°, were obtained. *Anal.* Calcd. for $C_7H_9NI_2$: C, 23.29. H, 2.54. Found: C, 23.32; H, 2.39.

1-Ethyl-2(1*H*)-pyridone (Preparation by Alkaline Treatment of N-Ethyl-2-iodopyridinium Iodide)—A mixture of 281.3 mg. of 2-iodo derivative (VIIb) and 30 cc. of 10% NaOH solution was shaken, by which the white crystalline iodide gradually dissolved in alkali, giving a clear solution. To make sure, it was gently warmed for 0.5 hr. After it was allowed to stand at room temperature overnight, the reaction mixture was extracted with $CHCl_3$ in the presence of excess K_2CO_3, dried over Na_2CO_4, and $CHCl_3$ was evaporated, affording 127 mg. of an oil. $HgCl_2$ complex: m.p. 111~112.5°.[13] Yield, 259.9 mg. of crude complex or 95.5% of theoretical amount from iodide.

1-(3,4-Dimethoxyphenethyl)-2-picolinium Bromide—A mixture of 3,4-dimethoxyphenethyl bromide and 0.6 g. of 2-picoline was heated for about 4 hr. on a water bath and the reaction mixture solidified to give 2.1 g. of colorless crystals of m.p. 170~180°. After recrystallization from EtOH and Et_2O, it melted at 180° (sint. 173°). *Anal.* Calcd. for $C_{16}H_{20}O_2NBr \cdot \frac{1}{2}H_2O$: C, 55.34; H, 6.09. Found: C, 55.23; H, 6.05. This bromide was treated with AgCl and then with sodium picrate and its O-picrate was obtained as yellowish needles of m.p. 112~113° after recrystallization from EtOH. *Anal.* Calcd. for $C_{16}H_{20}O_2N \cdot C_6H_2O_7N_3$: C, 54.32; H, 4.56. Found: C, 54.61; H, 4.48.

1-(3,4-Dimethoxyphenethyl)-2(1*H*)-pyridone (IVb)—By Hydrolysis of 1-(2-pyridylmethyl)pyridinium Iodide Methiodide: To a suspension of 1.7 g. of the bromide in 20 cc. of pyridine, a solution of 1.3 g. of I_2 in 10 cc. of pyridine was added dropwise. In this case, it took about 10 min. for the addition, while heating and stirring. After addition, the reaction mixture was heated an additional 3 hr. The precipitated solid, 1.7 g. of a yellow-orange crystals of m.p. 193~195°, was collected and the mother liquor was concentrated. The concentrate was combined with the foregoing crystals obtained above and the whole was dissolved in 30 cc. of H_2O. This solution was extracted with Et_2O in order to remove excess of I_2. A solution of 0.5 g. of NaOH dissolved in 5 cc. H_2O was added to the above solution of 1-(2-pyridylmethyl)pyridinium iodide methiodide and a deep blood-red solution resulted. In this case, a red substance formed soon disappeared and reddish, clear solution was obtained. This solution was allowed to stand overnight in an ice-box and then extracted with $CHCl_3$ in the presence

*2 All m.p.s are not corrected.
*3 Chichibabin recorded m.p. 207° (decomp.) for this 2-iodo derivative.
*4 In this case excess of MeI gave better yield.
12) O. Fischer, N. Neundlinger: Ber., **46**, 2544(1913).
13) V. Pechmann, O. Blatzer: *Ibid.*, **24**, 3147(1891).

of K_2CO_3. The extract was dried and $CHCl_3$ was evaporated. The residue was again extracted with benzene several times. After the evaporation of benzene, 0.8 g. (61.5%) of a brown, viscous oil was obtained, fairly soluble in AcOEt. Chloroplatinate: Yellow crystals, m.p. 100~103. *Anal.* Calcd. for $C_{15}H_{17}O_3N \cdot \frac{1}{2}H_2PtCl_6 \cdot 2H_2O$: C, 41.70; H, 4.97. Found: C, 41.93; H, 4.65.

1-(3,4-Dimethoxyphenethyl)-2-chloropyridinium Iodide (IIIb)—A mixture of 0.5 g. of the pyridone (IVb) and 3 cc. of $POCl_3$ was refluxed in the presence of 5 cc. of toluene, gently in an oil bath for 2 hr. during which time the evolution of HCl was hardly observed and the color of the mixture turned dark brown. Excess of $POCl_3$ and toluene were mostly removed *in vacuo* and the residue was dissolved in 5 cc. of H_2O, its solution being decolorized with activated charcoal. From one part of its solution, a yellow crystalline chloroplatinate, m.p. 192~194° (decomp.), was formed. From an aqueous solution, the iodide was precipitated by the addition of 0.7 g. of KI and this was collected on a filter. This was purified from EtOH, forming yellow needles of m.p. 160~161°.[4] *Anal.* Calcd. for $C_{15}H_{17}O_2NCl$I: C, 44.42; H, 4.22. Found: C, 44.41, 44.08; H, 4.48, 3.99.

A solution of 108.2 mg. of the above iodide in 10 cc. of MeOH was converted to the corresponding chloride by heating for 1.5 hr. with 300 mg. of AgCl, and 73 mg. of the chloride was obtained as a white powder of m.p. 139~141°. The latter was converted as usual to the corresponding O-picrate. This was collected and purified from EtOH, forming brownish yellow crystals of m.p. 153~154°, which showed positive Beilstein test. *Anal.* Calcd. for $C_{15}H_{16}O_2NCl \cdot C_6H_2O_7N_3$: C, 49.76; H, 3.78. Found: C, 49.96; H, 3.74.

The authors gratefully acknowledge the advice and stimulating discussions of Professor Emeritus S. Sugasawa of the University of Tokyo and technical assistance of Mr. Keiichiro Fukumoto, University of Osaka, in some of the experimental work.

Summary

1-Methyl- or 1-ethyl-2(1*H*)-pyridone was formed by alkaline treatment from their corresponding 1-alkyl-2-chloropyridinium salt of 2-iodo derivative.

(Received July 7, 1959)

UDC 547.571.07

Hideaki Shirai and Noriichi Oda: New Synthesis of 2-Nitro-5-methoxybenzaldehyde.

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In connection with the synthesis of 2-methoxyphenanthrene, it was necessary to prepare 2-nitro-5-methoxybenzaldehyde (IV). The aldehyde has been previously prepared by two routes; one by the reaction of *m*-methoxybenzaldehyde with nitric acid[1] and the other by the nitration of bis-(*m*-formylphenyl) carbonate, followed by hydrolysis and subsequent methylation.[2] The former, however, involves rather troublesome separation of isomers and the latter consists of many steps.

A new convenient synthesis of the aldehyde was now achieved by means of the Reissert reaction. 2-Nitro-5-methoxybenzoic acid (I), needed in this synthesis as the starting material, was prepared by the method of Makino, *et al.*[3] from *m*-cresol. The chloride of (I) was converted into the Reissert compound (III), in the mixture of quinoline, hydro-

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1) H. H. Hodgson, H. G. Beard: J. Chem. Soc., **1927**, 2380.
2) M. E. Smith, E. Elisberg, M. L. Sherrill: J. Am. Chem. Soc., **68**, 1301(1946).
3) K. Makino, H. Takahashi: *Ibid.*, **76**, 4994(1954).