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The Synthesis of 1-Methyl-2-pyridones from 2-Chloromethylpyridines

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The reaction of 2-chloromethylpyridine (Ia) and its homologs, 5-ethyl- (Ib), 6-methyl- (Ic), and 4-methyl-2-chloromethylpyridine (Id), with pyridine gave the corresponding 1-(2′-pyridylmethyl)-pyridinium chlorides (II), from which, on heating with dimethyl sulfate, 1-methyl-2-(pyridiniomethyl)-pyridinium salts (III) were obtained. The pyridinium salts were treated with aqueous alkali at a low temperature to yield 1-methyl- (IVa), 5-ethyl-1-methyl- (IVb), 1,6-dimethyl- (IVc), and 1,4-dimethyl-2-pyridone (IVd). The reaction sequence, in combination with the 1-oxidation of 2-picolines and followed by the reaction of the 1-oxides with tosyl chloride to yield 2-chloromethylpyridines, is recommended as a convenient route for the synthesis of 1-methyl-2-pyridones starting with 2-picolines.

There have been reported a variety of methods for the synthesis of 1-methyl-2-pyridones, of which the following procedures are typical. The method of Decker for the synthesis of 1-methylpyridones consists, as is well known, of the treatment of pyridines with dimethyl sulfate, followed by oxidation with ferricyanide. Berson and Cohen[1] obtained 1-methyl-2-pyridone by heating a mixture of 2-picoline methiodide and iodine in a pyridine solution and by treating the resultant dipyridinium salt with aqueous alkali. The 1-methylation of 2-pyridones has also been reported.[2,3]

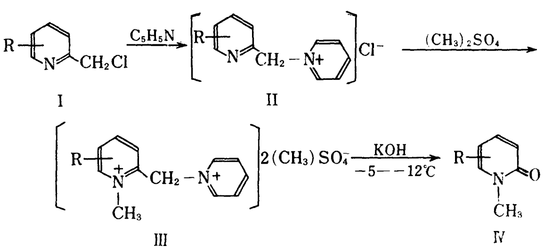
In previous papers,[4,5] we reported that the reaction of the 1-oxides of pyridine and thiazole derivatives bearing a methyl group at the 2-position with tosyl chloride gave 2-chloromethyl derivatives in a good yield, and suggested that the 2-chloromethylpyridines thus obtained might be used to synthesize a variety of pyridine derivatives.

In the present paper, a study of the conversion of 2-chloromethylpyridines into the corresponding 1-methyl-2-pyridones will be reported.

Results and Discussion

2-Chloromethylpyridine (Ia) and its homologs, 5-ethyl- (Ib) and 6-methyl-2-chloromethylpyridine (Ic), were prepared from the 1-oxides of the corresponding parent bases, that is, 2-picoline, 5-ethyl-2-picoline, and 2,6-lutidine respectively, by a reaction with tosyl chloride. 4-Methyl-2-chloromethylpyridine (Id) was also prepared by the same method from 2,4-lutidine 1-oxide. The identification of Id was not carried out with the free base, because of its facile decomposition during fractionation. The results of the elemental analysis of the picrate obtained from Id agreed with the calculated value required for the methyl-chloromethylpyridinium picrate. The position attacked by the chloride anion was not confirmed directly, but on the bases of the results of a series of reactions described below it was found that the 2-methyl group rather than the 4-methyl group was chlorinated.

The reaction of Ia—d with pyridine proceeded readily upon warming. The removal of the excess pyridine from the reaction mixture *in vacuo* gave a hygroscopic residue which consisted mainly of 1-(2′-pyridylmethyl)-pyridinium chlorides (IIa—d). Thus, on the addition of a silver nitrate solution to an aqueous solution of the residue, silver chloride was deposited immediately, and the dipicrates were subsequently obtained from the alcoholic solution of the residue.



Ia, IIa, IIIa, and IVa, $R=H$
Ib, IIb, IIIb, and IVb, $R=5\text{-}C_2H_5$
Ic, IIc, IIIc, and IVc, $R=6\text{-}CH_3$
Id, IId, IIId, and IVd, $R=4\text{-}CH_3$

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[1] J. A. Berson and T. Cohen, *J. Amer. Chem. Soc.*, **78**, 416 (1956).

[2] R. Adams and A. W. Schrecker, *ibid.*, **71**, 1186 (1949).

[3] D. J. Cook, R. E. Bowen, P. Sorter and E. Daniels, *J. Org. Chem.*, **26**, 4949 (1961).

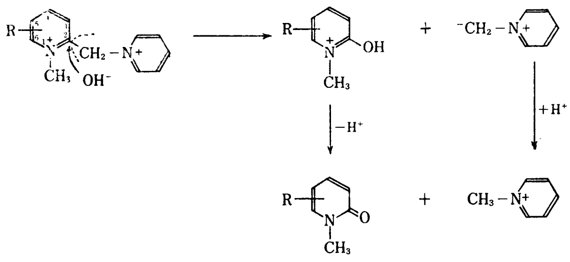
[4] E. Matsumura, *Nippon Kagaku Zasshi*, **74**, 363 (1953).

[5] E. Matsumura, T. Hirooka and K. Imagawa, *ibid.*, **82**, 616 (1961).

A gentle heating of the mixture of crude IIa—d and dimethyl sulfate gave, with the liberation of methyl chloride, a hygroscopic residue of crude 1-methyl-2-(pyridiniomethyl)-pyridinium salts (IIIa—d). The formation of the cation of III was confirmed by an elemental analysis of the dipicrate formed from an ethanolic solution of the residue.

On the treatment of crude IIIa—d with an aqueous potassium hydroxide solution at a low temperature, 1-methyl-2-pyridones (IVa—d) were obtained.

In the cation of III, *i.e.*, the 1-methyl-2-(pyridiniomethyl)-pyridinium ion, the 2-position is greatly activated to be attacked by a nucleophilic reagent due to the quaternization of the nitrogen atoms of both the pyridine rings. Therefore, the attack by a hydroxide ion under mild conditions at that site, resulting in the cleavage of the C_2-methylene linkage and eventually in the formation of 1-methyl-2-pyridones, proceeds through the course depicted in Scheme 1. This step in the reaction sequence is essentially the same as that proposed by Berson and Cohen.1)



IV

Scheme 1

IVa, IVc and IVd were identified as the corresponding picrates by a mixed-melting-point determination with authentic samples.3,6) The fact that VId was obtained from Id confirmed that the chloromethyl and methyl groups in Id were, as expected, attached to the 2- and 4-positions respectively. In the case of the reaction sequence starting with Ib, the structure of the resulting IVb was established by the following observations. The elemental analysis of the IVb supported the required molecular formula, the melting point of the picrate agreed with that reported by Sugasawa and Kirisawa,7) and the IR spectrum of IVb showed its absorption maximum at $1660\ cm^{-1}$, suggesting the presence of a carbonyl group. Sugasawa and Kirisawa7) reported that the oxidation of 3-ethylpyridine by the method of Decker afforded a mixture in which 1-methyl-3-ethyl-2-pyridone greatly predominated over the 5-ethyl isomer (IVb). Therefore, they synthesized IVb by a tedious method which involved the conversion of 3-ethylpyridine into 3-acetylpyridine, subsequent Decker's oxidation to 1-methyl-5-acetyl-2-pyridone, and the reconversion of the acetyl into the ethyl group. Also, IVc and IVd, which could not be prepared by the direct Decker method and which were, therefore, prepared by the same tedious procedure, were easily obtained by the present method.

This method is thus recommended as a convenient route for the synthesis of 1-methyl-2-pyridones starting with 2-picolines, since 2-chloromethylpyridines can readily be obtained by the reaction of 2-picoline 1-oxides with tosyl chloride.

Experimental

2-Chloromethyl-4-methylpyridine (Id). A solution of 2,4-lutidine 1-oxide (12.0 g) and tosyl chloride (24.1 g) in dry benzene (70 m*l*) was allowed to stand at room temperature for 15 min. After the subsequent removal of the solvent, the residue was heated at 70°C for 2 hr, and then at 100°C for 1 hr. Water was added to the cooled reaction mixture, the excess tosyl chloride was removed by filtration, and the filtrate, after the adjustment of the pH to 6.0 with sodium carbonate, was steam-distilled. The distillate was extracted with ether, the extract was dried over sodium sulfate, and the solvent was removed *in vacuo* to give crude Id as a stimulative oil (9.8 g, 68.0%); this oil was used for the next step without purification. Picrate: mp 138—139°C.

Found: C, 42.37; H, 3.03; N, 15.22%. Calcd for $C_{13}H_{11}O_7N_4Cl$: C, 42.10; H, 3.00; N, 15.11%.

1-Methyl-2-pyridone (IVa). A mixture of dry pyridine (10.0 g) and Ia (8.0 g) was heated at 80°C for 5 hr. At the end of the reaction time, a dark red, oily material separated at the bottom of the reaction vessel. The removal of the excess pyridine *in vacuo* and the washing of the residue with ether gave crude IIa as a hygroscopic syrup. Dipicrate: mp 168—169°C.

Found: C, 43.84; H, 2.51; N, 17.96%. Calcd for $C_{23}H_{16}O_{14}N_8$: C, 43.96; H, 2.57; N, 17.83%.

A mixture of dimethyl sulfate (23.8 g) with the crude IIa was kept for 20 min at room temperature and then heated at 80°C for 3 hr until a homogeneous solution was formed; this gave a hygroscopic syrup consisting mainly of IIIa. Dipicrate: mp 192—193°C.

Found: C, 44.75; H, 2.91; N, 17.15%. Calcd for $C_{24}H_{18}O_{14}N_8$: C, 44.87; H, 2.83; N, 17.44%.

A solution of potassium hydroxide (17.1 g) in water (150 m*l*) was stirred, drop by drop, into a solution of crude IIIa in water (76 m*l*) over a period of 3 hr at 2—5°C; the stirring was then continued for another 2 hr at the same temperature. The mixture was extracted with ether using a continuous extractor, the extract was evaporated, and the residue was distilled *in vacuo* to yield IVa as a yellow oil (4.5 g, 65.0%) boiling at 117°C/10 mmHg. The melting point of the picrate of IVa (142—143°C) was undepressed in a mixed-melting-point determination with an authentic sample.

1-Methyl-5-ethyl-2-pyridone (IVb). A solution of dry pyridine (9.5 g) and Ib (15.5 g) in ether (106

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6) E. A. Prill and S. M. McElvain, "Organic Syntheses", Coll. Vol. II, p. 487.

7) S. Sugasawa and M. Kirisawa, *Chem. Pharm. Bull.* (Tokyo), **4**, 139 (1956).

m*l*) was allowed to stand at room temperature for 30 min. After the removal of the solvent, the residue was heated at 50°C for 6 hr, and then at 80°C for 3 hr. The same treatment as with IIa gave a hygroscopic oil of IIb. Dipicrate: mp 155°C.

Found: C, 45.48; H, 3.06; N, 17.17%. Calcd for $C_{25}H_{20}O_{14}N_8$: C, 45.74; H, 3.07; N, 17.07%.

A mixture of dimethyl sulfate (36.8 g) and the crude IIb was heated at 80°C for 3 hr to give a hygroscopic syrup consisting mainly of IIIb. Dipicrate: mp 163°C.

Found: C, 46.39; H, 3.34; N, 16.58%. Calcd for $C_{26}H_{22}O_{14}N_8$: C, 46.57; H, 3.31; N, 16.71%.

A solution of potassium hydroxide (20.7 g) in water (186 m*l*) was stirred, drop by drop, into a solution of crude IIIb in water (392 m*l*) over a period of 2 hr at −7——10°C; the stirring was then continued for another 2 hr at the same temperature. Subsequent treatment similar to that used with IVa gave IVb as a yellow oil (8.4 g, 64.0%) boiling at 114—115°C/3 mmHg. The product showed its absorption maximum at 1660 cm^{-1} in the IR spectrum, and the picrate recrystallized from ethanol melted at 122—123°C.[7] Picrate: mp 122—123°C.

Found: C, 45.90; H, 3.85; N, 15.30%. Calcd for $C_{14}H_{14}O_8N_4$: C, 46.00; H, 3.94; N, 15.31%.

1,6-Dimethyl-2-pyridone (IVc). A mixture of dry pyridine (23.3 g) and Ic (13.8 g) was allowed to stand at room temperature for 30 min, and then heated at 60°C for 3 hr and subsequently at 70°C for 2 hr. The removal of the excess pyridine *in vacuo* gave hygroscopic crystals of IIc. Dipicrate: mp 179°C.

Found: C, 44.83; H, 2.98; N, 17.48%. Calcd for $C_{24}H_{18}O_{14}N_8$: C, 44.87; H, 2.83; N, 17.44%.

A mixture of dimethyl sulfate (27.6 g) and crude IIc was heated at 80°C for 3 hr, subsequent treatment like that of IIIa gave IIIc as hygroscopic crystals. Dipicrate: mp 186°C.

Found: C, 45.52; H, 3.03; N, 17.12%. Calcd for $C_{25}H_{20}O_{14}N_8$: C, 45.72; H, 3.07; N, 17.07%.

A solution of potassium hydroxide (24.2 g) in water (217.8 m*l*) was stirred, drop by drop, into a solution of crude IIIc in water (278 m*l*) over a period of 2 hr at −10——12°C. The stirring was then continued for another 4 hr at the same temperature. Subsequent treatment similar to that of IVa gave IVc as hygroscopic crystals (7.5 g, 62.8%) boiling at 116—117°C/3 mmHg.

Found: C, 68.27; H, 7.36; N, 11.37%. Calcd for C_7H_9ON: C, 68.27; H, 7.36; N, 11.68%.

The IR spectrum of IVc agreed with that of the authentic sample,[2] and the melting point of the picrate of IVc (133—134°C) was undepressed upon a mixed-melting-point determination with an authentic sample.

1,4-Dimethyl-2-pyridone (IVd). A mixture of dry pyridine (11.7 g) and Id (15.0 g) was heated at 80°C for 5 hr. Subsequent treatment similar to that of IIa gave IId as a hygroscopic oil. Dipicrate: mp 185.5—186.5°C.

Found: C, 45.01; H, 2.92; N, 17.55%. Calcd for $C_{24}H_{18}O_{14}N_8$: C, 44.87; H, 2.83; N, 17.44%.

A mixture of dimethyl sulfate (37.8 g) and IId in water (295 m*l*) was heated at 80°C for 3 hr. When it was then treated as IIIa had been, a hygroscopic syrup of IIId was obtained. Dipicrate: mp 202.5°C.

Found: C, 45.41; H, 3.17; N, 17.30%. Calcd for $C_{25}H_{20}O_{14}N_8$: C, 45.74; H, 3.07; N, 17.07%.

A solution of potassium hydroxide (26.6 g) in water (234 m*l*) was stirred, drop by drop, into a solution of IIId over a period of 2 hr at −7——10°C, after which the stirring was continued for 3 hr. Subsequent treatment of the mixture much like that of IVa gave IVd of hygroscopic crystals (6.9 g, 53.6%) boiling at 110—111°C/3 mmHg. The IR spectrum of IVd was identical with that of the authentic sample,[2] and the melting point of the picrate of IVd was undepressed by a mixed-melting-point determination with an authentic sample. Picrate: mp 163—164°C.

Found: C, 44.32; H, 3.36; N, 15.62%. Calcd for $C_{13}H_{12}O_4N_8$: C, 44.32; H, 3.43; N, 15.91%.