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Studies on 1-Alkyl-2(1*H*)-pyridone Derivatives. XVIII.[1] Reaction of 1-Methyl-2(1*H*)-quinolone with Phosphoryl Chloride and N,N-Dimethylaniline

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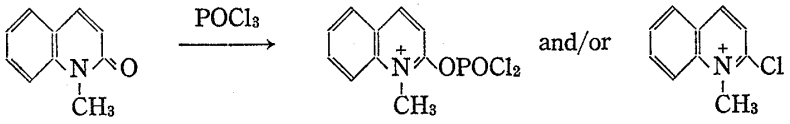
Reaction of 1-methyl-2(1*H*)-quinolone with phosphoryl chloride and dimethylaniline was successfully carried out. The two products, 2-[4′-(dimethylamino)phenyl]quinolinium chloride (V) and 2-[4′-(dimethylamino)phenyl]quinoline (VI), were obtained in good yield, 76.2% for V and 2.6% for VI, which can be change the ratio between those two products of the reaction condition changed. The structure of products were confirmed by the corresponding Grignard reactions. The same reaction of 1-methyl-2(1*H*)-thioquinolone was attempted with low yield and only one product (VI).

1-Methyl-2(1*H*)-quinolone (I) is an interesting compound as a synthetic intermediate and is obtained easily in a high yield from quinoline, and some electrophilic substitution reactions[3,4] have been carried out on I in order to introduce a carbon chain. We attempted the reaction of I with phosphoryl chloride and dimethylformamide, *i.e.*, the Vilsmeyer reaction, but the reaction did not materialize. At first it was considered that, since I has an amide structure similar to dimethylformamide in its molecule, I might form a quinolinium salt[5] (III; IIIa and/or IIIb) by the action of phosphoryl chloride, as shown in Chart 1, which would lower the reactivity of the ring against electrophilic substitution. However, Muchowski



I IIIa IIIb

Chart 1

and others[6] succeeded in the Vilsmeyer reaction of 2-methyl-1(2*H*)-isoquinolone and Sugasawa and others[7] that of 4-methoxy-1-methyl-2(1*H*)-pyridone, with the introduction of a formyl group into 4-position in the former and 3-position in the latter. It seems probable that the unsuccessful Vilsmeyer reaction of I is due to the low reactivity of I to electrophilic reaction. In fact, comparison of the reaction of 2-methyl-1(2*H*)-isoquinolone,[8] 1-methyl-2(1*H*)-pyridone,[4] and I[4] with hydrochloric acid and formaldehyde shows that their reactivity falls in that order. Therefore, formation of III from I and phosphoryl chloride was examined.

In general, the reaction of 1-methyl-2(1*H*)-pyridone and phosphoryl chloride is thought to produce a pyridinium salt as an intermediate, as shown in Chart 2, but this compound

1) Part XVII: H. Tomisawa, K. Kōsaka, H. Hongo, R. Fujita, H. Kato, and C.H.Wang, *Chem. Pharm. Bull.* (Tokyo), **21**, 2590 (1973).
2) Location: *Komatsushima, Sendai.*
3) H. Tomisawa, M. Watanabe, R. Fujita and H. Hongo, *Chem. Pharm. Bull.* (Tokyo), **18**, 919 (1970).
4) H. Tomisawa, Y. Kobayashi, H. Hongo and R. Fujita, *Chem. Pharm. Bull.* (Tokyo), **18**, 932 (1970).
5) B.C. Challis and J. Challis, "The Chemistry of Amides," Interscience Publishers, London, 1970, p. 805.
6) D.E. Horning, G. Lacasse and J.M. Muchowski, *Can. J. Chem.* **49**, 2785 (1971).
7) T. Sugasawa, T. Toyoda and K. Sasakura, *Abstr. Papers*, 16*th Symp. Chem. Natural Products*, 1972, p. 304.
8) H. Tomisawa, K. Saito, H. Hongo and R. Fujita, *Chem. Pharm. Bull.* (Tokyo), **18**, 937 (1970).

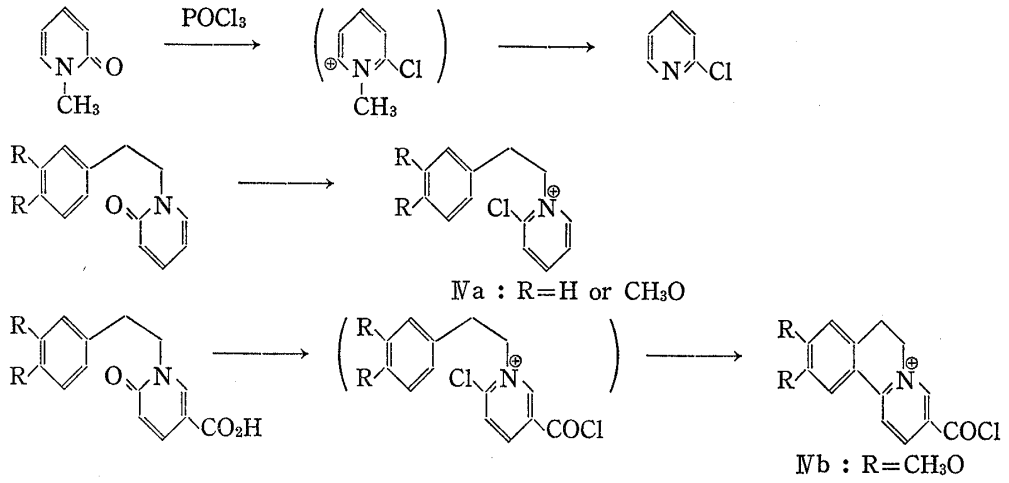


Chart 2

undergoes demethylation and 2-chloropyridine[9,10] is obtained. When there is a β-phenethyl group in 1-position of pyridone (Chart 2), 2-chloro-1-phenethylpyridinium salt[10,11] (IVa) is formed, *i.e.*, IIIb-type compound is stable and reaction with the benzene ring does not progress. When R is a methoxy group, which increases the reactivity of the benzene ring, and R′ is a carboxyl group, which increases the reactivity of the III-type intermediate compound, then, and only then, the intramolecular cyclization takes place to form IVb. Considering the limited condition for this intramolecular cyclization, it would seem quite difficult for the intermolecular reaction to take place between III and aromatic compounds. On the other hand, Ban and Kimura[12] reported that the indole ring quite easily reacted with III-type compounds, as shown in Chart 3.

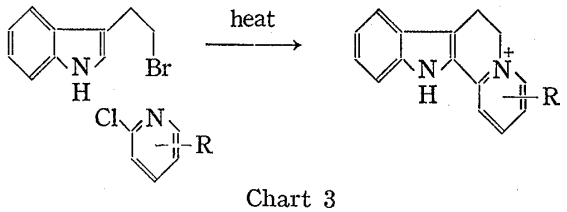


Chart 3

With reference to these reports and to know the limit of the reactivity of III, reaction of III with N,N-dimethylaniline was attempted and some observations were made.

A mixture of I and phosphoryl chloride was heated at *ca.* 100° for 1 hr, dimethylaniline was added to it, and the mixture was heated at 120° for 4 hr to give two products (V and VI).

V was obtained as a fine red crystalline powder of mp 205—207° (decomp.) in 76.2% yield, and its elemental analytical values corresponded to $C_{18}H_{19}N_2Cl \cdot H_2O$. The infrared (IR) spectrum of V did not show the absorption of a carbonyl, so that V was considered to be I with introduction of a substituent in 2-position. The nuclear magnetic resonance (NMR) spectrum of V showed a singlet signal at 3.60 ppm for $N(CH_3)_2$ and a singlet signal at 4.60 ppm for a methyl bonded to ring nitrogen, with signals for 10 H due to protons in the aromatic ring. Consequently, the presence of a (dimethylamino)phenyl group in 2-position of 1-methylquinolinium chloride was assumed as the structure of V but the position of dimethylamino group in the benzene ring could not be determined from the spectra of V. Therefore synthesis of V from another route was attempted by the reaction of I with *p*-(dimethylamino)phenylmagnesium bromide. In this reaction,[13] 1-methylquinolinium salt with *p*-(dimethylamino)-phenyl group in 2-position, without doubt, was produced (Chart 4).

9) E. Fischer, *Ber.*, **17**, 2396 (1884).
10) R.H. Wiley, N. Smith and L. Knabeschuh, *J. Am. Chem. Soc.*, **75**, 4482 (1953).
11) S. Sugasawa, S. Akaboshi and Y. Ban, *Chem. Pharm. Bull.* (Tokyo), **7**, 263 (1959); J.A. Berson and T. Cohen, *J. Am. Chem. Soc.*, **78**, 416 (1956).
12) Y. Ban and T. Kimura, *Chem. Pharm. Bull.* (Tokyo), **16**, 549 (1968).
13) H. Tomisawa, H. Hongo and H. Haruta, *Yakugaku Zasshi*, **87**, 554 (1967).

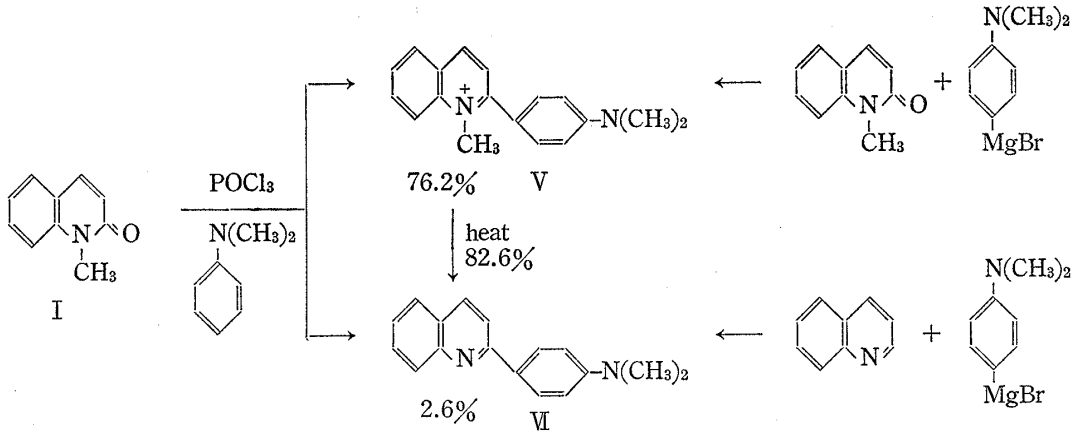


Chart 4

This sample and V agreed completely in their IR and NMR spectra, when both were treated with potassium iodide and derived easily to the respective quinolinium iodides. Therefore, the structure of V would be 2-[4′-(dimethylamino)phenyl]quinolinium chloride.

VI was obtained in 2.6% yield as pale yellow needles, mp 177—178°. The IR spectrum of VI lacked the absorption for a carbonyl, while the NMR spectrum of VI was approximately similar to that of V except for the disappearance of a signal at 4.60 ppm in the latter for N–CH_3. Therefore, VI was assumed to be the ring N-demethylated compound and its sample was synthesized by another route. Reaction of quinoline and *p*-(dimethylamino)phenylmagnesium bromide, followed by dehydrogenation gave 2-[4′-(dimethylamino)phenyl]quinoline[14,15] which was found to be identical with VI by IR spectral comparison and mixed mp determination (Chart 4). Since VI is a demethylated compound of V, increased yield of VI may be expected by a more drastic reaction condition. Therefore, the foregoing reaction was carried out at 170° for 16 hr, by which the yield of VI was increased to 28.2% but that of V decreased inversely to 29%, which was not a desirable result as a whole. Demethylation of V proceeds easily at about 225° and the yield is *ca.* 83%. By taking this demethylation reaction into consideration, VI should be obtained in a maximum yield of *ca.* 65%. The yield of VI by synthesis reported is 50—65% from the reaction of quinoline and *p*-(dimethylamino)phenyllithium by Gilman and others,[14] and *ca.* 60% by the reaction of quinoline 1-oxide, benzoyl chloride, and dimethylaniline reported by Hamana and Hoshino.[15] These yields are approximately the same as that of VI in the present method. Methylation of VI takes place in the dimethylamino group to form 2-[4′-(trimethylamino)phenyl]quinoline iodide, and V can not be obtained from VI. Formation of V by the reaction of I and Grignard reagents is not in a good yield. Considering these facts, the present method seems the most suitable for the preparation of V.

Thus, III obtained from I and phosphoryl chloride reacts with the *para* position of N,N-dimethylaniline to give V and VI in a good yield. It is hoped that the reaction of III with other compounds will be carried out to know the limit of this reaction.

The same reaction was also carried out with 1-methyl-2(1*H*)-thioquinolone (VII), a sulfur derivative easily obtained from I. The product obtained was merely 2.2% of V and 8.4% of I, probably formed during the post-treatment, and the starting material was recovered in *ca.* 52% yield. This shows sulfur compound is less reactive than oxygen compound, and is the same result as it of our previous work.[16]

14) H. Gilman, J.L. Towle and S.M. Spatz, *J. Am. Chem. Soc.*, **68**, 2017 (1946).
15) M. Hamana and O. Hoshino, *Yakugaku Zasshi*, **84**, 35 (1964).
16) H. Tomisawa and C.H. Wang, *Chem. Pharm. Bull.* (Tokyo), **21**, 2607 (1973).

Experimental[17]

Reaction of 1-Methyl-2(1*H*)-quinolone (I) with Phosphoryl Chloride and N,N-Dimethylaniline——A mixture of 3 g of I and 3.9 g of $POCl_3$ was heated at 100° (bath temp.) for 30 min and then at 120° for 1 hr. To this mixture, 4.4 g of N,N-dimethylaniline was added and the mixture was again heated at 120° for 4 hr. To the cooled mixture, 12.5 g of ice water and 9.6 g of $KHCO_3$ were added and the precipitate formed was collected by filtration. The filtrate was extracted with benzene, the extract was dried over $MgSO_4$, and benzene was evaporated, leaving 2.7 g of a residue. The collected precipitate was extracted with EtOH, the extract was dried over $MgSO_4$, and EtOH was evaporated. This residue was extracted with acetone, the extract was dried over $MgSO_4$, and acetone was evaporated. Recrystallization of this residue from EtOH gave 4.5 g (76.2%) of 2-[4-(dimethylamino)phenyl]-1-methylquinolinium chloride (V) as reddish crystalline powder, mp 205—207° (decomp.). *Anal.* Calcd. for $C_{18}H_{19}N_2Cl \cdot H_2O$: C, 68.24; H, 6.68; N, 8.84. Found: C, 67.82; H, 6.25; N, 9.05. IR ν_{max}^{KBr} cm^{-1}: 1610, 1585, 830, 810. NMR (in CF_3COOH) ppm: 3.60 (6H, singlet, $\overset{+}{N}Me_2$), 4.60 (3H, singlet, $\overset{+}{N}Me$), 8.00—8.54 (9H, multiplet, aromatic H), 9.10 (1H, doublet, $J=9$ Hz, aromatic H).

The residue obtained from the benzene extract was chromatographed over a column of silica gel (Kieselgel Merk, 0.05—0.2 mm, 70—325 mesh) and the column was eluted with benzene–$CHCl_3$ (3:1). The solvent was evaporated from the effluent and the residue was recrystallized from benzene to 0.12 g (2.6%) of 2-[4′-(dimethylamino)phenyl]quinoline (VI) as pale yellow needles, mp 177—178° (mp 174—176°[15]). When the foregoing reaction was carried out at 170° for 16 hr, 1.02 g (29%) of V and 0.88 g (28.2%) of VI were obtained.

Formation of 2-[4′-(Dimethylamino)phenyl]-1-methylquinolinium Iodide from V——To a solution of 85 mg of V dissolved in 15 ml of H_2O, a solution of 610 mg of KI in 15 ml of H_2O was added and the mixture was warmed at 60° for 20 min. The mixture was cooled, the precipitate was collected by filtration, and recrystallized from H_2O. The iodide was obtained as a reddish crystalline powder, mp 222—224° (decomp.). Yield, 74 mg (70.7%).

Preparation of 2-[4′-(Dimethylamino)phenyl]-1-methylquinolinium Bromide by the Grignard Reaction——To a solution of the Grignard reagent, obtained by the reaction of 7.4 g of *p*-bromo(dimethylamino)benzene and 0.9 g of Mg in 50 ml of tetrahydrofuran, a solution of 2 g of I in 10 ml of tetrahydrofuran and 50 mg of Cu_2Cl_2 was added and the mixture was allowed to stand at room temperature of 2 hr. To this mixture 10% HCl was added, the solvent was evaporated, and 20 ml of H_2O and 2 g of NaOH were added to the residue. The precipitate formed was collected by filtration, extracted with EtOH and then with acetone, and the residue from these extracts was recrystallized from $CHCl_3$–acetone to 1.7 g (39.5%) of the objective compound as a fine red crystalline powder, mp 224—226° (decomp.). *Anal.* Calcd. for $C_{18}H_{19}N_2Br$: C, 62.98; H, 5.58; N, 8.16. Found: C, 62.67; H, 5.50; N, 8.06.

Preparation of VI by the Grignard Reaction——To a solution of the Grignard reagent, obtained from 7.3 g of *p*-bromodimethylaniline, 1.2 g of Mg, and 50 ml of tetrahydrofuran, 5 g of quinoline in 10 ml of tetrahydrofuran was added and the mixture was allowed to stand at room temperature for 3 hr. K_2CO_3 solution was added to the reaction mixture which was extracted with benzene. The extract was dried over $MgSO_4$, the solvent was evaporated, and 6.6 g of a residue was obtained. To this residue, 40 g of nitrobenzene and 0.3 g of Pd-C were added and the mixture was heated at 100° (bath temp.) for 8 hr. The cooled reaction mixture was extracted with 10% HCl, the aqueous layer was basified with K_2CO_3, and extracted with benzene. The extract was dried over $MgSO_4$, the solvent was evaporated, and 1.8 g of residue so obtained was recrystallized several times from benzene and acetone and *ca.* 30 mg of VI was obtained as pale yellow needles, mp 177—178°.

Demethylation of V——Heating of 300 mg of V at 224—229° (bath temp.) for 3 min resulted in decomposition with bubbling. The product was extracted with benzene and evaporation of the solvent from the extract afforded 202 mg (82.6%) of VI.

Reaction of 2-[4′-(Dimethylamino)phenyl]quinoline and Methyl Iodide——A mixture of 0.1 g of 2-[4′-(dimethylamino)phenyl]quinoline, 0.57 g of MeI, and 2 ml of benzene was sealed in a tube and the tube was heated at 90° (bath temp.) for 8 hr. When cooled, the precipitate formed was collected by filtration and recrystallized from MeOH to 0.145 g (92.4%) of 2-[4′-(trimethylamino)phenyl]quinoline iodide as brown scales, mp 202—204°. *Anal.* Calcd. for $C_{18}H_{19}N_2I$: C, 55.40; H, 4.91; N, 7.18. Found: C, 55.36; H, 4.65; N, 7.17. NMR (in CF_3COOH) ppm: 3.85 (9H, singlet, $\overset{+}{N}Me_3$), 8.0—8.75 (9H, multiplet, aromatic H), 9.22 (1H, doublet, $J=9$ Hz, aromatic H).

Reaction of 1-Methyl-2(1*H*)-thioquinolone (VII) with Phosphoryl Chloride and N,N-Dimethylaniline——A mixture of 1 g of VII and 1.2 g of $POCl_3$ was heated at 100° (bath temp.) for 3 hr and then at 110° for 1 hr, excess $POCl_3$ was distilled off, and 1.3 g of N,N-dimethylaniline was added. This mixture was heated at 120° for 4 hr, 8 g of ice water and 2.1 g of NaOH were added to the mixture, and the precipitated inorganic

17) All melting points are uncorrected.

matter was filtered off. The filtrate was extracted with benzene, the extract was dried over $MgSO_4$, and the solvent was evaporated. Addition of benzene to 1.999 g of a residue so obtained precipitated insoluble matter. This precipitate was filtered off and evaporation of the filtrate left 1.771 g of a residue. The precipitate collected by filtration was extracted with EtOH, the extract was dried over $MgSO_4$, and EtOH was evaporated. This residue was extracted with acetone, the extract was dried over $MgSO_4$, and acetone was evaporated. The residue was recrystallized from EtOH to 40 mg (2.2%) of V as reddish crystalline powder, mp 205—207° (decomp.).

The residue from the filtrate was chromatographed over a column of silica gel (Kieselgel Merk, 0.05—0.2 mm, 70—325 mesh) and the column was eluted with benzene. Evaporation of the eluate gave 518 mg (51.8%) of the starting VII. Elution of the column with $CHCl_3$ gave 76 mg (8.4%) of I.

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