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Studies on 1-Alkyl-2(1*H*)-pyridone Derivatives. XIX.[1] Reactivity of 1-Methyl-2(1*H*)-thiopyridone and Its Derivatives

Hiroshi Tomisawa and Chao Hsiung Wang

Tohoku College of Pharmacy[2]

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Reactivity of 1-methyl-2(1*H*)-thiopyridone (I), 1-methyl-2(1*H*)-thioquinolone (III), and 2-methyl-1(2*H*)-thioisoquinolone (V) was compared with that of the corresponding oxygen compounds, 1-methyl-2(1*H*)-pyridone (II), 1-methyl-2(1*H*)-quinolone (IV), and 2-methyl-1(2*H*)-isoquinolone (VI). In deuteration, I was less reactive than II, III entirely failed to react, and V reacted under a stronger reaction condition than VI. Bromination of I and V was carried out but they did not produce the expected products, although II and VI reacted easily. Grignard reaction as an example of the nucleophilic substitution reactions on III, which was most inactive to the electrophilic substitution reactions, revealed that III is more inactive than IV to this reaction and the yield was not good even under a more drastic condition.

We reported the reaction of 1-methyl-2(1*H*)-thiopyridone (I) with formaldehyde and hydrochloric acid[3] in the preceeding paper. It was thereby found that one of the largest difference from the same reaction of 1-methyl-2(1*H*)-pyridone[4] (II) is the position of substitution with a hydroxymethyl group and the other is the reaction condition. Therefore, comparative examinations were made on the reactivity of sulfur and oxygen compounds, using I, II, and their derivatives. Comparisons were made between I and II, 1-methyl-2(1*H*)-thioquinolone (III) and 1-methyl-2(1*H*)-quinolone (IV), and 2-methyl-1(2*H*)-thioisoquinolone (V) and 2-methyl-1(2*H*)-isoquinolone (VI).

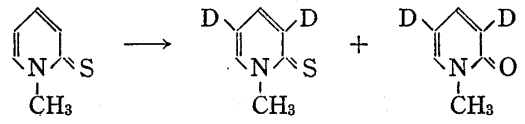
Deuteration

One of the electrophilic substitution reactions is the deuteration with D_2SO_4 in D_2O. This reaction is advantageous among all electrophilic substitutions in that the steric effect does not have to be taken into consideration because of the small D^+, and is the most simple reaction. Luckily, there is a report of Kawazoe and Yoshioka[5] on this reaction with pyridone, quinolone, and isoquinolone, but the reaction has not been attempted on I, III, and V. Therefore, the reaction was carried out on these sulfur compounds in comparison with the result of oxygen compounds reported by Kawazoe and Yoshioka.

Deuteration of I is summarized in Table I. In contrast to the deuteration of II resulting in the formation of 3,5-dideuterio compound by reaction at 180° for 15 hr (Kawazoe's data give 1 hr),[5] deuteration of I progressed only to 60% at 180° for 20 hr, to 80% for 40 hr, and it required 48 hr for complete deuteration. In other words, Table I clearly indicates the difference in the reactivity of I and II. Deuteration of I also gave only the 3,5-dideuterio compound, as in the case of II,[5] suggesting that the reactivity of 3- and 5-positions is about the same. In the reaction of II with formaldehyde and hydrochloric acid,[4] 5-methylol compound alone was formed while the same reaction of I gave 3-methylol compound as the main product[3] (Chart 1). This result must be due to factors other than the difference in reactivity

1) Part XVIII: H. Tomisawa, T. Suzuki, H. Sawada, H. Hongo, R. Fujita, H. Kato, and C.H. Wang, *Chem. Pharm. Bull.* (Tokyo), **21**, 2602 (1973).
2) Location: *Komatsushima, Sendai, 983, Japan.*
3) H. Tomisawa, K. Kōsaka, H. Hongo, R. Fujita, and C.H. Wang, *Chem. Pharm. Bull.* (Tokyo), **21**, 2590 (1930).
4) H. Tomisawa, Y. Kobayashi, H. Hongo, and R. Fujita, *Chem. Pharm. Bull.* (Tokyo), **18**, 932 (1970).
5) Y. Kawazoe and Y. Yoshioka, *Chem. Pharm. Bull.* (Tokyo), **16**, 715 (1968).

TABLE I



I I_D II_D

Concentration of D_2SO_4 in D_2O (%)	Temperature (°C)	Time (hr)	Ratio of I_D:II_D		Total deuteration degree (%)
5	180	48	5	3	100
10	180	40	75	32	80
10	180	20	4	1	59
10	170	30	13	3	85
10	170	15	17	3	60
30	180	35			0
80	180	30			0
10	150	4			0
40	150	4			0
10[a)]	180	15(1)	0	1	100

a) II→II_D ( ) by Kawazoe and Yoshioka[5)]

of I and II. Deuteration of I at a higher temperature and for a longer period of time results in the hydrolysis of thioketone to form the derivative of II, and this is clearly indicated in the result shown in Table I.

II yield 46% I yield 22%

Chart 1

The report of Katritzky and others[6)] that II reacts as the free base when acid concentration is low and the rate of deuteration becomes faster was found to be true also in the case of I and deuteration did not progress at all when the concentration of D_2SO_4 was above 30%.

Kawazoe and Yoshioka[5)] carried out deuteration of 2-quinolone obtaining 6,8-dideuterio compound first and then 3,5,6,8-tetradeuterio compound and determined the order of reactivity of IV (Chart 2). Deuteration of III is summarized in Table II, and the reaction conditions used by Kawazoe for IV, *i.e.*, the reaction using 75% D_2SO_4 at 140°, did not give the desired result. Therefore, based on the theory of Katritzky and others[6)] for II, expecting the reaction of a free base, the concentration of D_2SO_4 was lowered from 50% to 30, 20, 10, and 5% but deuteration of III did not materialize.

Considering the fact that the reaction of IV with formaldehyde and hydrochloric acid was the most difficult among II, IV, and VI, the unsuccessful deuteration of III among I, III, and V may indicate the similarity between the oxygen compounds and sulfur compounds.

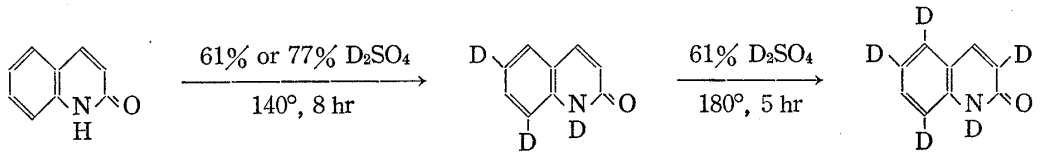
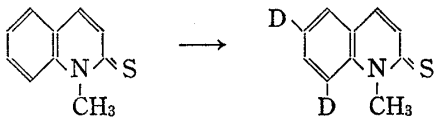


Chart 2

6) P. Bellingham, C.D. Johnson, and A.R. Katritzky, *J. Chem. Soc.* (*B*), **1967**, 1226.

TABLE II



III

Concentration of D_2SO_4 in D_2O (%)	Temperature (°C)	Time (hr)	Total deuteration degree (%)
5	120	5	0
5	150	4	0
10	150	4	0
10	120	48	0
20	120	48	0
20	150	4	0
30	150	4	0
30	180	5	0
50	150	4	0
75	140	5	0
75	140	15	0
61[a)]	140	8	100

a) IV→IV_D by Kawazoe and Yoshioka[5)]

The reaction of VI by Kawazoe and Yoshioka[5)] is shown in Chart 3. Deuteration was most facile in 4-position, followed by 5- and 7-positions. Deuteration of V is summarized in Table III. Reaction conditions used by Kawazoe for VI did not succeed in the case of V but the use of a low concentration of the acid and reaction at a high temperature gave

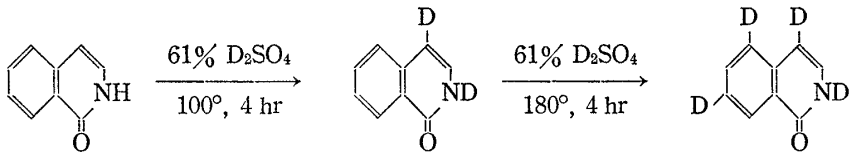
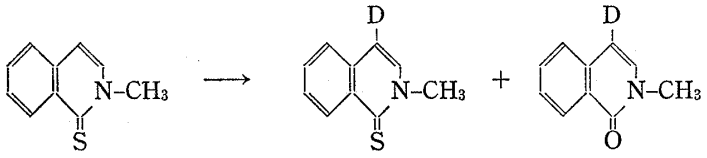


Chart 3

TABLE III



V V_D VI_D

Concentration of D_2SO_4 in D_2O (%)	Temperature (°C)	Time (hr)	Ratio of V_D:VI_D		Total deuteration degree (%)
20	180	5	9	4	partial
30	120	8	9	1	4-position complete
30	180	2	12	5	4-position complete
40	120	8	9	7	4-position complete
50	120	4	12	4	4-position complete
50	150	4	13	7	4-position complete
50	150	15	1	4	4-position complete
60	100	4			0
96.5	120	2			0
96.5	150	2			0
61[a)]	100	4			100

a) VI→VI_D by Kawazoe and Yoshioka[5)]

4-deuterio compound. In all the reactions listed in Table III, deuteration of other positions did not materialize. Reaction at a high temperature and for a longer period of time resulted in hydrolysis of V, which would not be desirable as a method for the preparation of deuterio compounds. The authentic sample of 4-deuterio-2-methyl-1(2*H*)-thioisoquinolone (V_D) was obtained by deuteration of VI and treatment of its product with phosphorus pentasulfide.

Since the reaction with D_2SO_4 in D_2O was invariably accompanied by hydrolysis, the reaction with D_2SO_4 in anhydrous CH_3COOD was attempted (Table IV). As was expected, hydrolysis did not occur in this reaction but deuteration also did not progress, even under the reaction conditions by which deuteration did progress in D_2O, such as the reaction of I with 10% D_2SO_4 at 180° for 40 hr or of V with 40% D_2SO_4 at 150° for 4 hr. This means that deuteration without hydrolysis did not succeed.

Table IV

Compound	Concentration of D_2SO_4 in CH_3COOD (%)	Temperature (°C)	Time (hr)	Deuteration degree (%)
I	0	180	5	0
I	10	150	4	0
I	10	180	16	0
I	10	180	20	0
I	10	180	40	0
III	0	150	4	0
III	0	180	5	0
III	70	180	4	0
III	70	200	2	0
V	0	180	5	0
V	10	150	4	0
V	40	150	4	0
V	70	120	4	0
V	70	150	2	0

Bromination

Bromination was attempted on I and V which were successfully deuterated. The reaction on II was carried out according to the report of Sass and Wisloki,[7] and the use of excess bromine at 0—5° gave 3,5-dibromo-1-methyl-2(1*H*)-pyridone in a quantitative yield. Its treatment with phosphorus pentasulfide afforded the 3,5-dibromo derivative of I as an authentic sample.

Bromination of I under the same conditions failed to give the bromo compound and, as shown in Table V, the reaction at a maximum temperature of 180° for 48 hr did not afford a product that could be identified with an authentic sample by nuclear magnetic resonance (NMR) spectrum and thin-layer chromatography (TLC).

Bromination of V at a low temperature according to the report of Muchowski and others[8] did not give a brominated product and the reaction at 125° for 4 hr gave a dibromo-isoquinoline in *ca.* 23% yield, and not the bromo-thioisoquinolone compound. The dibromo-isoquinoline compound was also detected in TLC under the reaction conditions marked with [b] in Table V. This product was assumed to be 1,4-dibromoisoquinoline from its spectral data.

7) M. Sass and W. Wisloki, *J. Prakt. Chem.* [2], **84**, 440 (1911).
8) D.E. Horning, G. Lacasse, and J.M. Muckowski, *Can. J. Chem.*, **49**, 2785 (1971).

TABLE V

Bromination compound	Bromine molar ratio	Temperature (°C)	Reaction time (hr)	Bromination degree (%)
I	1	room	24	0
I	2.5	150	5	0
I	2.5	180	15	0
I	3	0—5	1.5	0
I	3	180	20	0
I	3	180	48	0
V	1	room	1.5	0
V	2.2	60	2	0
V	2.2	60	4	0
V	2.2	80	4	*a*)
V	2.2	100	4	*a*)
V	3	room	1.5	0
V	3	125	4	*b*)
V	3	150	4	*a*)

a) These compounds were detected by TLC.
b) 1,4-dibromoisoquinoline in 23% yield

Grignard Reaction

The foregoing electrophilic substitution reactions have shown that I, III, and V have markedly poor reactivity than the corresponding oxygen compounds, II, IV, and VI. Of these, III had the lowest reactivity in the electrophilic substitution reaction and, expecting its high reactivity to the nucleophilic substitution reactions, Grignard reaction was attempted on III. The reaction of IV, the oxygen compound corresponding to III, with phenylmagnesium bromide had been reported by Tomisawa and others,[9] and the reaction conditions giving the maximum yield (*ca.* 30%) were used for the reaction of III. III was allowed to stand with the Grignard reagent at room temperature for 1 hr and then boiled for 2 hr, and the product obtained was 1-methyl-2-phenylquinolinium salt, same as in the case of IV, though its yield was a mere 2.5%, recovering the starting material in 75%. When the reaction at room temperature was shortened to 20 min and the boiling lengthened to 4 hr, the highest yield of *ca.* 18% of this reaction was obtained. The yield never reached that (*ca.* 30%) of IV and recovery of the starting material was still large at 55%. Contrary to expectations, III most unreactive to the electrophilic substitution reactions was also proved to be more inactive than IV in nucleophilic substitution reaction.

Experimental[10]

Preparation of 4-Deuterio-2-methyl-1(2*H*)-isoquinolone——A mixture of 3.84 g of 2-methyl-1(2*H*)-isoquinolone, 4.35 g of D_2O, and 9.2 g of D_2SO_4 was heated at 100° for 4 hr. The reaction mixture was poured into ice water, basified with K_2CO_3, and the aqueous layer was extracted with benzene. The extract was dried over $MgSO_4$, the solvent was evaporated, and the residue was recrystallized from hexane to 4-deuterio-2-methyl-1(2*H*)-isoquinolone as colorless plates, mp 53—54°. Yield, 3.5 g (90.6%). NMR (in $CDCl_3$) ppm: 3.6 (3H, singlet, N-CH_3), 7.1 (1H, singlet, C3-H), 7.32—7.78 (3H, multiplet, C5, C6, C7-H), 8.48 (1H, broad doublet, J=8 cps, C8-H).

Preparation of 4-Deuterio-2-methyl-1(2*H*)-thioisoquinolone——A mixture of 0.3 g of 4-deuterio-2-methyl-1(2*H*)-isoquinolone, 0.9 g of P_2S_5, and 20 ml of pyridine was refluxed for 4 hr, pyridine was distilled off under a reduced pressure, and hot water was added to the residue. After stirring this mixture, H_2O was evaporated and the residue was extracted with warm CS_2. The solvent was evaporated from the extract and the residue was recrystallized from MeOH to 0.14 g (42.4%) of 4-deuterio-2-methyl-1(2*H*)-thioisoquinolone

9) H. Tomisawa, H. Hongo, and H. Haruta, *Yakugaku Zasshi*, **87**, 554 (1967).
10) All melting points are uncorrected.

as yellow prisms, mp 109—110°. NMR (in $CDCl_3$) ppm: 4.05 (3H, singlet, N-CH_3), 7.4 (1H, singlet, C3-H), 7.43—7.65 (3H, multiplet, C5, C6, C7-H), 9.05 (1H, broad doublet, J=8 cps, C8-H).

Preparation of 3,5-Dibromo-1-methyl-2(1*H*)-thiopyridone——A mixture of 0.4 g of 3,5-dibromo-1-methyl-2(1*H*)-pyridone and 0.4 g of P_2S_5 was heated at 130° for 4 hr. The cooled reaction mixture was basified with NaOH solution and the aqueous layer was extracted with benzene. The extract was dried over $MgSO_4$, benzene was evaporated, and the residue was recrystallized from benzene to 0.25 g (59%) of 3,5-dibromo-1-methyl-2(1*H*)-thiopyridone as yellow prisms, mp 129—133°. *Anal.* Calcd. for $C_6H_5NSBr_2$: C, 25.46; H, 1.78. Found: C, 25.45; H, 1.60. NMR (in $CDCl_3$) ppm: 4.06 (3H, singlet, N-CH_3), 7.90—8.05 (2H, multiplet, C4, C6-H).

Reaction of 2-Methyl-1(2*H*)-thioisoquinolone and Bromine——A mixture of 1.4 g of 2-methyl-1(2*H*)-thioisoquinolone, 4 g of Br_2, and 13.3 g of AcOH was sealed in a tube and heated at 125° for 4 hr. The reaction mixture was basified with K_2CO_3 solution and the aqueous layer was extracted with $CHCl_3$. The extract was dried over $MgSO_4$, $CHCl_3$ was evaporated, and the residue was extracted with warm benzene. The benzene extracted was chromatographed over silica gel and the benzene eluate afforded 0.7 g (22.8%) of 1,4-dibromoisoquinoline as pale yellow needles, mp 99—100°. *Anal.* Calcd. for $C_9H_5NBr_2$: N, 4.88. Found: N, 4.90. NMR (in $CDCl_3$) ppm: 7.55—8.4 (4H, multiplet, C5, C6, C7, C8-H), 8.45 (1H, singlet, C3-H). Mass Spectrum (*m/e*): 285 (M^+), 206 (M-Br), 127 (M-Brx2).

Reaction of 1-Methyl-2(1*H*)-thioquinolone (III) and Phenylmagnesium Bromide——C_6H_5MgBr was prepared from 2.9 g of C_6H_5Br, 0.45 g of Mg, and 30 ml of tetrahydrofuran. To C_6H_5MgBr being stirred under ice cooling, 20 mg of Cu_2Cl_2 and then 2 g of III in 30 ml of tetrahydrofuran were added and the mixture was allowed to stand at room temperature for 1 hr and then refluxed for 2 hr. The reaction mixture was cooled in ice water, 20 ml of 10% HCl was added, and the mixture was extracted with benzene. The extract was dried over $MgSO_4$, benzene was evaporated, and 1.5 g (75%) of the starting III was recovered. The aqueous layer was acidified with 35% HCl, excess KI was added, and the mixture was extracted with $CHCl_3$. The $CHCl_3$ layer afforded 0.9 g (2.5%) of 1-methyl-2-phenylquinolinium iodide.

The above reaction was also carried out with a large excess of C_6H_5MgBr and using 2.4 g of $CuAc_2 \cdot H_2O$ in place of Cu_2Cl_2, and standing at room temperature for 20 min and then boiled for 4 hr, from which 17.7% of the quinolinium salt was obtained besides 55% recovery of III.

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