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Studies on 1-Alkyl-2(1*H*)-pyridone Derivatives. XXIV.[1] The Friedel-Crafts Reaction of 1-Methyl-2(1*H*)-pyridone and Its Derivatives with Acid Anhydride

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The Friedel-Crafts reactions of 1-methyl-2(1*H*)-pyridone (I), 2-methyl-1(2*H*)-isoquinolone (II), and 1-methyl-2(1*H*)-quinolone (III) with acid anhydride, principally benzoic anhydride, were carried out. In the case of I and II, reaction with acid anhydride gave the products in a good yield, but in the case of III, the reaction with acid anhydride gave products in much less yield than that with acid chloride.

The Friedel-Crafts reaction of 1-methyl-2(1*H*)-pyridone (I) was attempted by Adams, *et al.*,[3] but did not succeed. Actually the reaction of I with acyl chloride in the presence of aluminum chloride at the boiling point of the acyl chloride was unsuccessful, except by the use of cyclohexanecarbonyl chloride[1] and benzoyl chloride.[4] The fact that only acyl chlorides with a high boiling point gave the acyl products in a good yield seems to suggest that the yield of the Friedel-Crafts reaction of I would depend on the boiling point of the acyl chloride used. The carbonyl of acid anhydride is less reactive than that of acid chloride, but the boiling point of acid anhydride is higher than that of the corresponding chloride. Therefore, the Friedel-Crafts reaction of I with aliphatic acid anhydride under various conditions was attempted and the reaction in the presence of sulfuric acid gave the objective products in the best yield.[1] The boiling point of benzoyl chloride (197.9°) is high enough for the Friedel-Crafts reaction of I, but the fact that the combination of I, aliphatic acid anhydride, and sulfuric acid gave the products in the best yield prompted us to attempt the reaction of I, 2-methyl-1(2*H*)-isoquinolone (II), and 1-methyl-2(1*H*)-quinolone (III) with benzoic and some other acid anhydrides. As the reaction temperature, 120° and 180° were selected, because the reaction of benzoyl chloride with II and III at 120° and that with I at 180° gave the products in a good yield.[4] Aluminum chloride and sulfuric acid were used as the catalyst. The structures of all the products were identified from the similarity of their infrared spectra with their authentic samples and their melting points were undepressed on admixture with their authentic samples.

The results of the reaction of I with benzoic anhydride (except No. 11) are shown in Table I. Experiments with No. 4 and 11 showed a difference in the reactivity between benzoic anhydride and benzoyl chloride, but, comparison of experiments No. 6 and No. 11 showed that the use of acid anhydride with prolonged reaction time gave products in a similar yield to that of acid chloride. Experiment No. 9 (sulfuric acid catalyst) reveals that the yield of 5-benzoylpyridone (IV) and 3,5-dibenzoylpyridone (VI) improved by about 7% and 33%, respectively, when using benzoic anhydride compared with those of benzoyl chloride (No. 11).

The yield of VI from monobenzoylpyridone (IV and V) was also improved about 10 times under reaction conditions similar to that of No. 9 in Table I, as shown in Table II.

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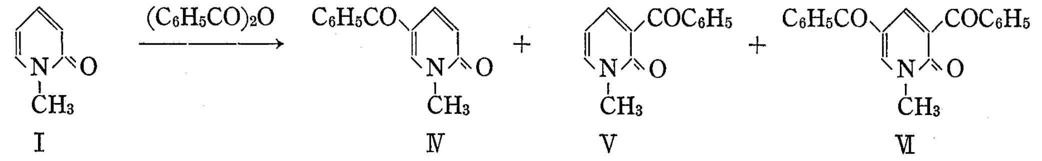
[1] Part XXIII: R. Fujita, *Chem. Pharm. Bull.* (Tokyo), 23, 501 (1975).

[2] Location: *Komatsushima, Sendai, 983, Japan.*

[3] R. Adams, J. Hine, and J. Campbell, *J. Am. Chem. Soc.*, 71, 387 (1949).

[4] H. Tomisawa, R. Fujita, H. Hongo, and H. Kato, *Chem. Pharm. Bull.* (Tokyo), 22, 2091 (1974).

TABLE I. Reaction Conditions and Yields



Expt. No.	Temp. (°C)	Catalyst	Period (days)	Yield (%)			
				IV	V	VI	Recovery
1	120	$AlCl_3$	9	2.6	0.8	—	66.7
2	120	H_2SO_4	9	—	—	—	66.7
3	120	H_2SO_4	12	1.0	0.3	—	60.0
4	180	$AlCl_3$	3	17.2	5.7	1.6	30.3
5	180	$AlCl_3$	4	25.5	4.9	1.9	16.7
6	180	$AlCl_3$	5	27.1	10.2	1.6	13.3
7	180	$AlCl_3$	9	1.2	1.0	—	—
8	180	H_2SO_4	4	20.0	0.8	2.8	11.7
9	180	H_2SO_4	5	38.2	2.7	36.7	—
10	180	H_2SO_4	9	10.0	2.2	2.5	—
11[a]	180	$AlCl_3$	2	30.9	12.4	3.8	7.1

a) The best condition in which benzoyl chloride was used as a reagent.[4]

TABLE II. Reaction Conditions and Yields of VI from IV or V

Compound No.	Reagent	Temp. (°C)	Catalyst	Period (days)	Yield (%)	Recovery (%)
IV	$(C_6H_5CO)_2O$	180	H_2SO_4	5	41.1	—
	$(C_6H_5CO)_2O$	180	$AlCl_3$	5	4.1	91.0
	C_6H_5COCl[4]	180	$AlCl_3$	2	9.3	90.0
V	$(C_6H_5CO)_2O$	180	H_2SO_4	3	25.5	8.5
	$(C_6H_5CO)_2O$	180	$AlCl_3$	3	2.7	62.0
	C_6H_5COCl[4]	180	$AlCl_3$	2	3.3	85.0

The results of the reaction of II with various acid anhydrides are shown in Table III. The reaction of II with acid anhydride had been partially reported by Muchowski, *et al.*[5] (No. 7 and 12). In the case of benzoylation, experiment No. 3 and 6 (sulfuric acid catalyst) showed excellent results, *i.e.*, it gave 4-benzoyl compound (VII) in almost quantitative yield which is far better than that of Muchowski, *et al.*[5] The reaction with benzoyl chloride (No. 8) gave two kinds of products [VII and 5-benzoyl compound (VIII)], but that of benzoic anhydride only gave VII. Comparison of No. 1 and 4, No. 2 and 5, and No. 3 and 6, shows that these benzoylation would not be much effected by the reaction temperature and, in general, it seems that the prolonged reaction time gave good results.

In the case of acetylation of II, No. 11 is the reexamination of the report by Muchowski, *et al.*[5] and would be the best reaction condition which gives far better yield than that with acetyl chloride (No. 9).

Propionylation of II also showed that the reaction using propionic anhydride (No. 14 and 15) gave only 4-substituted compound (VII) in a good yield.

The results of the reaction of III with acid anhydrides are shown in Table IV. In spite of our effort, the yield of products when using acid anhydrides did not improve compared to that with acid chlorides. The reactions of No. 9 in Table I, No. 6 in Table III, and No. 7 in

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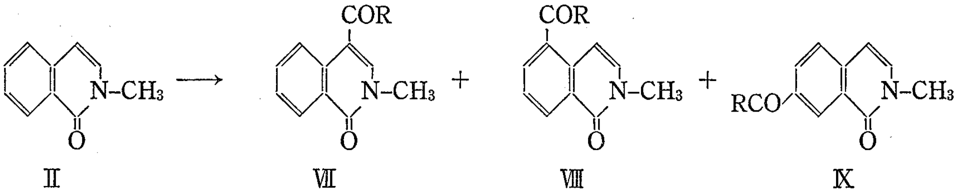
5) D.E. Horning, G. Lacasse, and J.M. Muchowski, *Can. J. Chem.*, 49, 2787 (1971).

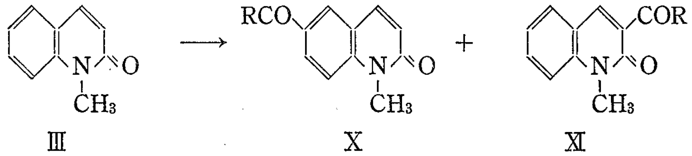
Table III. Reaction Conditions and Yields



Expt. No.	R-	Reagent	Temp. (°C)	Catalyst	Period (days)	Yield (%) VII	VIII	IX	Recovery
1	C_6H_5	$(RCO)_2O$	120	$AlCl_3$	9	52.0	—	—	43.3
2	C_6H_5	$(RCO)_2O$	120	H_2SO_4	2	67.3	—	—	10.0
3	C_6H_5	$(RCO)_2O$	120	H_2SO_4	5	96.4	—	—	—
4	C_6H_5	$(RCO)_2O$	180	$AlCl_3$	5	65.1	—	—	—
5	C_6H_5	$(RCO)_2O$	180	H_2SO_4	2	69.0	—	—	—
6	C_6H_5	$(RCO)_2O$	180	H_2SO_4	5	94.6	—	—	—
7[a]	C_6H_5	$(RCO)_2O$	200	H_2SO_4	5/3	57.5	?	?	—
8[b]	C_6H_5	RCOCl	120	$AlCl_3$	7	21.6	19.5	—	—
9[c]	CH_3	RCOCl	50	$AlCl_3$	2	40.4	—	6.9	35.8
10	CH_3	$(RCO)_2O$	140	$AlCl_3$	3	22.4	—	—	40.1
11	CH_3	$(RCO)_2O$	140	H_2SO_4	1/24	75.6	—	—	—
12[d]	CH_3	$(RCO)_2O$	140	H_2SO_4	1/24	72.0	—	—	—
13[c]	C_2H_5	RCOCl	80	$AlCl_3$	15/24	6.3	2.1	0.9	—
14	C_2H_5	$(RCO)_2O$	180	$AlCl_3$	3	58.0	—	—	—
15	C_2H_5	$(RCO)_2O$	180	H_2SO_4	3/24	54.5	—	—	—

a) From the report by Muchowski, *et al.*[5] who confirmed the structure of product only 4-benzoyl compound.
b) The best condition in which benzoyl chloride was used as a reagent.[4]
c) H. Tomisawa and R. Fujita, *Chem. Pharm. Bull.* (Tokyo), **21**, 2585 (1973).
d) D.E. Horning, G. Lacasse, and J.M. Muchowski, *Can. J. Chem.*, **49**, 2787 (1971).

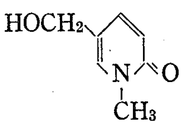
Table IV. Reaction Conditions and Yields



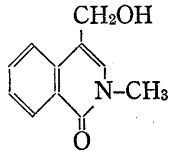
Expt. No.	R-	Reagent	Temp. (°C)	Catalyst	Period (days)	Yield (%) X	XI	Recovery
1	C_6H_5	$(RCO)_2O$	120	$AlCl_3$	9	—	—	81.0
2	C_6H_5	$(RCO)_2O$	120	$AlCl_3$	12	0.4	0.2	57.3
3	C_6H_5	$(RCO)_2O$	120	H_2SO_4	5	5.2	3.6	75.0
4	C_6H_5	$(RCO)_2O$	120	H_2SO_4	9	1.9	—	53.6
5	C_6H_5	$(RCO)_2O$	180	$AlCl_3$	5	—	—	26.2
6	C_6H_5	$(RCO)_2O$	180	$AlCl_3$	9	—	—	35.7
7	C_6H_5	$(RCO)_2O$	180	H_2SO_4	5	24.0	—	10.0
8[a]	C_6H_5	RCOCl	120	$AlCl_3$	2	28.3	2.3	13.8
9[b]	CH_3	$(RCO)_2O$	130	$AlCl_3$	7	16.6	—	—
10	CH_3	$(RCO)_2O$	130	H_2SO_4	3	3.2	—	31.1
11[b]	CH_3	RCOCl	50	$AlCl_3$	14	37.5	—	—
12	C_2H_5	$(RCO)_2O$	180	$AlCl_3$	3	—	—	98.4
13	C_2H_5	$(RCO)_2O$	180	H_2SO_4	3	16.1	—	—
14[b]	C_2H_5	RCOCl	80	$AlCl_3$	14	6.5	25.8	—

a) H. Tomisawa, R. Fujita, H. Hongo, and H. Kato, *Chem. Pharm. Bull.* (Tokyo), **22**, 2091 (1974).
b) H. Tomisawa, M. Watanabe, R. Fujita, and H. Hongo, *Chem. Pharm. Bull.* (Tokyo), **18**, 919 (1970).

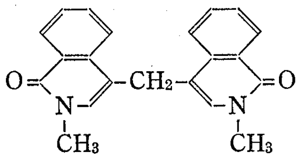
Table V. Conditions and Yields of Reaction of I, II, and III with HCHO and HCl



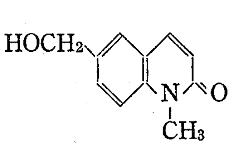
XII



XIII



XIV



XV

Compound No.	Temp. (°C)	Period (hr)	Product (Yield %)
I[a]	100	3	XII(46)
II[b]	100	3.5	XIII(27), XIV[c](32)
II[d]	100	2	XIV(97)
III[a]	100	5.5	XV(15.2), Recovery of III(48)

a) H. Tomisawa, Y. Kobayashi, H. Hongo, and R. Fujita, *Chem. Pharm. Bull.* (Tokyo), **18**, 932 (1970).
b) H. Tomisawa, K. Saito, H. Hongo, and R. Fujita, *Chem. Pharm. Bull.* (Tokyo), **18**, 937 (1970).
c) This compound was also synthesized from II, XIII, and HCl in 77% yield.[b]
d) EtOH was used as a solvent.[b]

Table IV were carried out under the same reaction condition, but the total yield of the products were 77.6, 94.6, and 24%, respectively. These results would depend on the reactivity of III which is the lowest in the electrophilic substitution reaction among I, II, and III, as shown clearly in Table V.

The Friedel-Crafts reaction of I and II with acid anhydride gave the products in a good yield, but the reaction of III with acid chloride gave a little better result than that with acid anhydride.

Experimental[6]

Reaction of 1-Methyl-2(1*H*)-pyridone (I) and Benzoic Anhydride——a) Benzoic Anhydride and H_2SO_4: A mixture of 1 g of I, 4.1 g of benzoic anhydride, and 3 drops of conc. H_2SO_4, mixed under anhydrous condition, was heated in an oil bath of 180° for 5 days. The reaction mixture was poured into ice water, basified with NaOH solution, and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over $MgSO_4$, evaporated, and the residue was passed through a column of silica gel. The column eluted with benzene-$(CH_3)_2CO$ (10: 1) gave three fractions. The first fraction was recrystallized from benzene to 1.067 g (36.7%) of 3,5-dibenzoyl-1-methyl-2(1*H*)-pyridone (VI)[4] as pale brown pillars, mp 158—160°. The second was recrystallized from benzene to 0.745 g (38.2%) of 5-benzoyl-2(1*H*)-pyridone (IV)[4] as a colorless crystalline powder, mp 178—179°. The third was recrystallized from benzene to 0.053 g (2.7%) of 3-benzoyl-2(1*H*)-pyridone (V)[4] as pale brown pillars, mp 115—116°.

b) Benzoic Anhydride and $AlCl_3$: A mixture of 12.3 g of benzoic anhydride and 5.4 g of $AlCl_3$ was warmed until $AlCl_3$ was completely dissolved in benzoic anhydride. The warmed mixture was cooled in ice water, added dropwise with 3 g of I, and the mixture was heated in an oil bath of 180° for 5 days. The reaction mixture was treated as in the foregoing case (a) and the product was separated by column chromatography over silica gel. The column afforded 0.14 g (1.6%) of VI, 1.64 g (27.1%) of IV, and 0.621 g (10.2%) of V.

Reaction of 2-Methyl-1(2*H*)-isoquinolone (II) and Acid Anhydride——a) Benzoic Anhydride and H_2SO_4: A mixture of 1 g of II, 4.2 g of benzoic anhydride, and 3 drops of conc. H_2SO_4 was heated in an oil bath at 120° for 5 days. The reaction mixture was treated as in the case of pyridone (a). The column eluted with benzene-$(CH_3)_2CO$ (10: 1) afforded 1.62 g (96.4%) of 4-benzoyl-2-methyl-1(2*H*)-isoquinolone[4,5] as colorless needles, mp 130—131°.

b) Propionic Anhydride and $AlCl_3$: A mixture of 1.3 g of $AlCl_3$ and 1.3 g of propionic anhydride was warmed until $AlCl_3$ was completely dissolved in propionic anhydride. The warmed mixture was cooled in ice water, 0.5 g of II was added, and the mixture was heated in an oil bath of 180° for 3 days and treated as in the case of pyridone (a). The column eluted with benzene-$(CH_3)_2CO$ (60: 1) afforded 0.373 g (58.0%) of 2-methyl-4-propionyl-1(2*H*)-isoquinolone[6] as pale yellow needles, mp 162—164°.

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[6] All melting points are uncorrected, and undepressed on admixture with authentic samples.

c) Propionic Anhydride and H_2SO_4: A mixture of 0.5 g of II, 1.3 g of propionic anhydride, and 2 drops of conc. H_2SO_4 was heated in an oil bath at 180° for 3 hr, and treated as in the foregoing case (b) to yield 0.35 g (54.5%) of 4-propionylisoquinolone.

d) Acetic Anhydride and H_2SO_4: A mixture of 0.5 g of II, 1 g of acetic anhydride, and 3 drops of H_2SO_4 was heated in an oil bath at 140° for 1 hr, and treated as in the foregoing cases. The $CHCl_3$ extract was recrystallized from benzene to 0.475 g (75.6%) of 4-acetyl-2-methyl-1(2*H*)-isoquinolone7) as pale yellow needles, mp 133—135°.

Reaction of 1-Methyl-2(1*H*)-quinolone (III) and Acid Anhydride——a) Benzoic Anhydride and H_2SO_4: A mixture of 0.5 g of III, 2.1 g of benzoic anhydride and 2 drops of conc. H_2SO_4 was heated in an oil bath at 180° for 5 days, and treated as in the case of pyridone (a). The fraction eluted with benzene–$(CH_3)_2CO$ (13: 1) was recrystallized from benzene to 0.202 g (24.0%) of 6-benzoyl-1-methyl-2(1*H*)-quinolone4) as a pale yellow crystalline powder, mp 126—128°.

b) Propionic Anhydride and H_2SO_4: A mixture of 1 g of III, 2.5 g of propionic anhydride, and 5 drops of conc. H_2SO_4 was heated in an oil bath at 180° for 3 days, and treated as in the foregoing case. The product was separated by column chromatography over silica gel. The fraction eluted with benzene–$(CH_3)_2CO$ (20: 1) afforded 0.311 g (16.1%) of 1-methyl-6-propionyl-2(1*H*)-quinolone,7) mp 172—174°.

Synthesis of 3,5-Dibenzoyl-1-methyl-2(1*H*)-pyridone (VI)——a) Under the same condition as for the pyridone in (a), a mixture of 0.5 g of IV, 1.06 g of benzoic anhydride, and 2 drops of conc. H_2SO_4 was reacted and treated to yield 0.304 g (41.1%) of VI.

b) To a mixture of 1.06 g of benzoic anhydride and 0.45 g of $AlCl_3$, 0.5 g of IV was added. This mixture was treated under the same condition as for the pyridone in (b) to yield 0.03 g (4.1%) of VI and 0.455 g (91.0%) of the recovered IV.

c) A mixture of 0.2 g of V, 0.4 g of benzoic anhydride, and 1 drop of conc. H_2SO_4 was heated in an oil bath at 180° for 3 days. The reaction mixture was treated as in the foregoing cases to yield 0.076 g (25.5%) of VI and the recovery of 0.017 g (8.5%) of V.

d) A mixture of 0.5 g of V, 1.1 g of benzoic anhydride, and 0.45 g of $AlCl_3$ was treated in the same way as in the foregoing (c) to yield 0.02 g (2.7%) of VI and 0.31 g (62.0%) of V.

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7) H. Tomisawa and R. Fujita, *Chem. Pharm. Bull.* (Tokyo), **21**, 2585 (1973).