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Studies on Tertiary Amine Oxides. XXXVIII.[1] Reaction of Quinoline 1-Oxide with N-Acylmethylpyridinium Salts in the Presence of Acylating Agents

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Quinoline 1-oxide (I) was found to react readily with N-acylmethylpyridinium salts (II) in the presence of acetic anhydride to give N-(α-acyl-2-quinolylmethyl)pyridinium salts (III) in good yields, but no reaction was observed without acetic anhydride. Treatment of benzoyl-adduct of quinoline 1-oxide (Ia) with II in the presence of acetic anhydride also afforded III, but the yields of III were somewhat less compared with the former procedure.

In previous papers of this series[3] it has been shown that quinoline 1-oxides react with active methylene compounds in the presence of acetic anhydride and the corresponding 2-substituted quinolines are produced in good yields accompanied by deoxygenation of the N-oxide function. This reaction occurs smoothly with compounds of considerably high acidity such as ethyl cyanoacetate and diethyl malonate *etc.*, but no reaction was observed with somewhat less reactive ones such as acetone, acetophenone, and cyclohexanone. This difficulty, however, has been successfully overcome in some cases by modifying these ketones as an enamine or enol ether; for example, enamines of cyclohexanone,[4] 1-ethoxycyclohexene,[1] and 2-ethoxypropene[1] can readily enter into reaction with quinoline 1-oxides in the presence of an acylating agent. In order to further widen the scope of this type of reaction, we tried to enhance the reactivity of active methylene compound by introducing pyridinium residue as an activating group.

The present paper describes the reactions of acyl-adduct of quinoline 1-oxide with N-acylmethylpyridinium salts which are easily obtainable by the Ortoleva-King reaction,[5] of acetophenone or other aroyl methyl ketones.

At first, the reaction of quinoline 1-oxide (I) and N-phenacylpyridinium iodide (IIb) was examined in some detail. When a solution of I (0.01 mole), acetic anhydride (7 ml), and IIb (0.01 mole) in acetonitrile was heated under reflux for 3 hours, and then the reaction mixture was evaporated under reduced pressure followed by treatment with methanol and 20% sodium perchlorate solution, N-(α-benzoyl-2-quinolylmethyl)pyridinium perchlorate (IIIb) was obtained as yellow needles in 76% yield. On recrystallization from methanol it melted at 229—230°. The structure of IIIb was confirmed unequivocally by the following synthetic route; 2-phenacylquinoline[6] was brominated with bromine in dichloromethane[7]

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[1] Part XXXVII: M. Hamana and H. Noda, *Chem. Pharm. Bull.* (Tokyo), **18**, 26 (1970).

[2] Location: *a*) *Nanakuma, Fukuoka*; *b*) *Katakasu, Fukuoka.*

[3] *a*) M. Hamana and M. Yamazaki, *Chem. Pharm. Bull.* (Tokyo), **11**, 411 (1963); *b*) *Idem, ibid.*, **11**, 415 (1963).

[4] *a*) M. Hamana and H. Noda, *Chem. Pharm. Bull.* (Tokyo), **13**, 912 (1965); *b*) *Idem, ibid.*, **14**, 762 (1966); *c*) *Idem, ibid.*, **15**, 447 (1967).

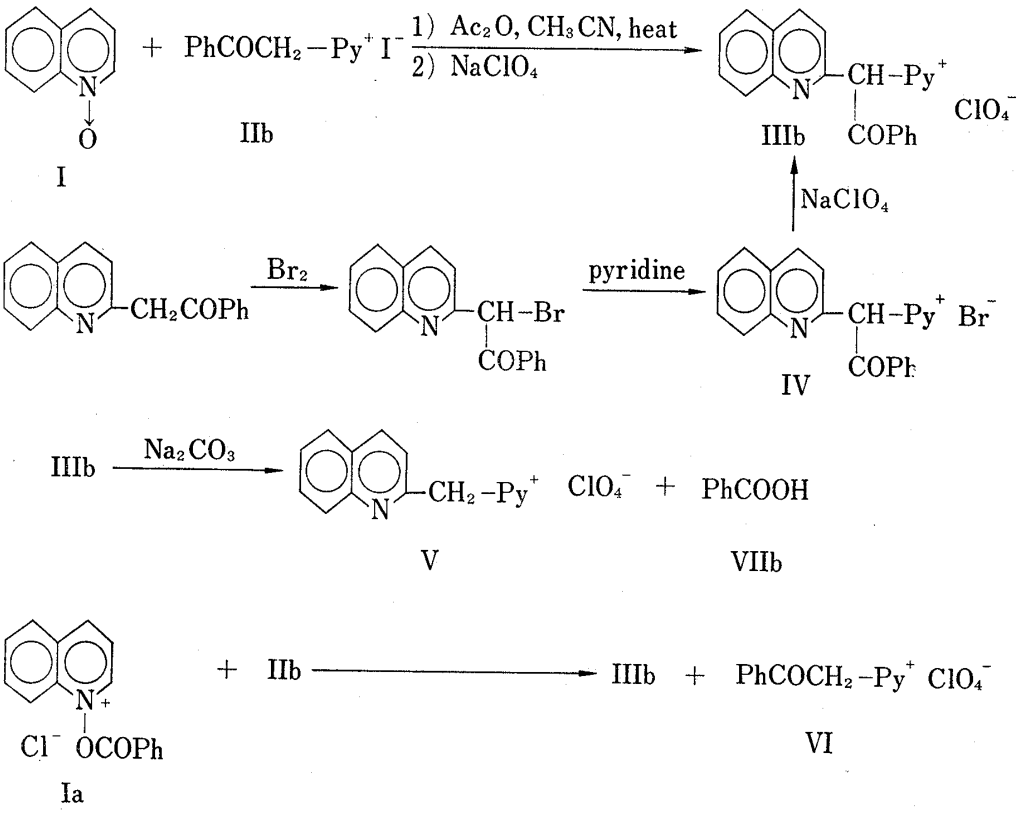
[5] *a*) F. Kröhnke, *Ber.*, **66**, 604 (1933); *b*) L.C. King, *J. Am. Chem. Soc.*, **66**, 894 (1944); *c*) J.L. Hartwell and S.R.L. Kornberg, *ibid.*, **68**, 868 (1946); *d*) L.C. King, M. McWhirter, and R.L. Rawland, *ibid.*, **70**, 239 (1948); *e*) F. Kröhnke, *Angew. Chem.*, **65**, 608 (1953).

[6] N.N. Goldberg and R. Levine, *J. Am. Chem. Soc.*, **74**, 5217 (1952).

[7] J.M. Smith, Jr., U.S. Pantent 2414389, June 9, (1945) [*C.A.*, **41**, 5904 (1947)].

followed by treatment with pyridine in benzene to give N-(α-benzoyl-2-quinolylmethyl)pyridinium bromide (IV), from which the corresponding perchlorate (IIIb) was obtained by means of sodium perchlorate. It was further noticed that when a suspension of IIIb in aqueous ethanol was heated with sodium carbonate solution on a water-bath, benzoyl group readily underwent hydrolytic cleavage and benzoic acid and N-(2-quinolylmethyl)pyridinium perchlorate (V)[8] were isolated on addition of perchloric acid.

Since I did not react with IIb without acetic anhydride and IIb was recovered as its perchlorate (VI) even when dibutylamine was added as a proton acceptor,[9] the role of acetic anhydride apparently essential for initiation of the reaction. Then, it was explored how the reaction would be affected by the nature of acylating agent. A similar reaction of benzoyl chloride-adduct of I (Ia), preliminary prepared from I and benzoyl chloride in acetonitrile, with IIb resulted in formation of IIIb in very poor yield of 2%. However, further addition of dibutylamine[9] or acetic anhydride[10] as a proton acceptor to the reaction medium caused to raise the yield of IIIb to 17 and 73%, respectively. Attempted reactions using tosyl chloride-adduct of I was curiously unsuccessful even in the presence of acetic anhydride.



reaction condition	yield of IIIb	and VI (%)
(1) CH_3CN, heat (2) $NaClO_4$	2	46
(1) $(n\text{-}Bu)_2NH$, CH_3CN, heat (2) $NaClO_4$	17	31
(1) Ac_2O, CH_3CN, heat (2) $NaClO_4$	73	—

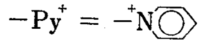


Chart 1

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8) a) L.C. King and S.V. Abrano, *J. Org. Chem.*, **23**, 1609 (1958); b) F. Kröhnke and K.F. Gross, *Chem. Ber.*, **92**, 22 (1959).

9) a) F. Kröhnke, *Ber.*, **70**, 546 (1937); b) *Idem, ibid.*, **73**, 310 (1940); c) E.D. Bergmann, H. Bendas, and Ch. Resnick, *J. Chem. Soc.*, **1953**, 2564.

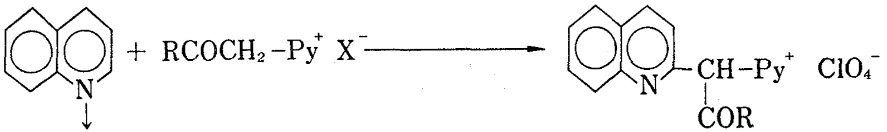
10) K. Dichore and F. Kröhnke, *Chem. Ber.*, **93**, 1072 (1960).

Subsequently, N-acetonylpyridinium chloride (IIa)[5a)] was shown to react with I or its benzoyl-adduct (Ia) in the same manner, giving N-(α-acetyl-2-quinolylmethyl)pyridinium perchlorate (IIIa) after treatment with sodium perchlorate. In this case, the direct treatment of I itself with IIa and an excess of acetic anhydride in acetonitrile (method A) gave the fairly better result (85%) compared with an alternative one (method B) which involved the addition of IIa and acetic anhydride to Ia (47%).

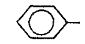
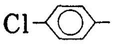
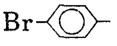
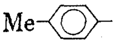
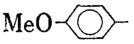
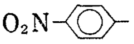
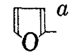
Further, the similar reactions were carried out with other nine kinds of N-aroylmethylpyridinium salts (IIc—k) using method A and B, and the corresponding N-(α-aroyl-2-quinolylmethyl)pyridinium compounds were successfully isolated as their perchlorates (IIIc—k) in good to excellent yields.

Method A seems to be generally superior to method B both in the yield of product and also as the practical procedure. The results are given in Table I, and some properties of III are shown in Table II.

Table I. Reaction of Quinoline 1-Oxide (I) with N-Acylmethylpyridinium Salts (II)



I II III

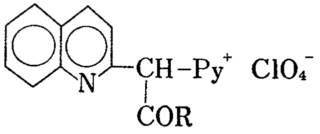
II	R	X	Method A I and II (mole)	 Reaction time (hr)	 Crude yield of III g (%)	Method B I and II (mole)	 Reaction time (hr)	 Crude yield of III g (%)
a	Me	Cl	0.01	5	3.10 (85)	0.01	5	1.70 (47)
b		I	0.01	3 5	3.20 (75) 3.25 (76)	0.01	5	3.10 (73)
c		I	0.005	3	2.18 (93)	0.005	3	1.87 (79)
d		I	0.005	3	2.03 (81)	0.005	3	1.99 (79)
e		I	0.005	3	1.40 (62)	0.005	3	1.12 (50)
f		I	0.005	3	1.33 (57)	0.005	3	0.86 (37)
g		I	0.005	3	1.67 (71)	0.005	3	1.65 (69)
h		I	0.005	3 5	1.60 (71) 1.75 (78)	0.005	3	1.38 (61)
i	 a)	I	0.005	5	1.80 (83)	0.005	5	1.52 (70)
j		I	0.005	6	1.72 (73)	0.005	6	1.00 (42)
k		I	0.005	6	1.79 (76)	0.005	6	1.70 (72)

a) N-(2-Furoylmethyl)pyridinium iodide(IIi) was synthesized from 2-acetylfuran (*cf.* Experimental).

For proof of the structures of the N-(α-acyl-2-quinolylmethyl)pyridinium compounds (III), they were subjected to alkaline hydrolysis to N-(2-quinolylmethyl)pyridinium perchlorate (V) and the corresponding carboxylic acids (VII) derived from the acyl moieties (Table III).

The infrared spectra of N-(α-acyl-2-quinolylmethyl)pyridinium perchlorate (IIIa—k) exhibited a strong absorption at 1630—1638 cm^{-1} indicative of a chelated carbonyl group (Table II). The ultraviolet spectra of IIIa and IIIb have a maximum at 400 and 403 mμ, respectively. From these observations it may be deduced that among three tautomeric

Table II. Properties of N-(α-Acyl-2-quinolylmethyl)pyridinium Perchlorates (III)



$\underset{\mid\atop COR}{CH}-Py^{+}\ ClO_4^{-}$

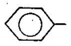
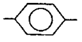
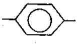
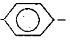
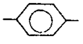
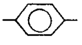
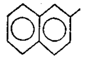
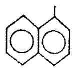
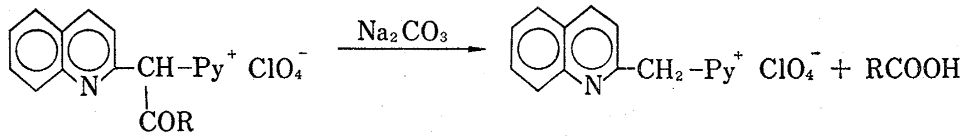
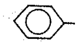
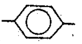
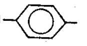
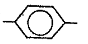
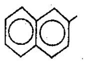
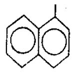
III	R	Appearance	mp (°C) (decomp.)	Formula	Analysis (%)						IR $\nu_{C=O}^{Nujol}$ (cm^{-1})
					Calcd.			Found			
					C	H	N	C	H	N	
a	Me	yellow needles	203—204	$C_{17}H_{15}O_4N_2Cl$	56.28	4.17	7.72	56.57	4.17	7.50	1638
b		yellow needles	229—230	$C_{22}H_{17}O_5N_2Cl$	62.19	4.03	6.60	62.13	3.90	6.74	1631
c	Cl-	yellow prisms	220—221	$C_{22}H_{16}O_5N_2Cl_2 \cdot \frac{1}{2}H_2O$	56.47	3.66	5.99	56.50	3.54	5.64	1634
d	Br-	yellow prisms	207—208	$C_{22}H_{16}O_5N_2BrCl$	52.45	3.20	5.56	52.26	3.17	5.23	1632
e	Me-	yellow needles	179—180	$C_{23}H_{19}O_5N_2Cl \cdot \frac{1}{2}H_2O$	61.66	4.50	6.25	61.93	4.48	6.22	1632
f	MeO-	yellow needles	148—150	$C_{23}H_{19}O_6N_2Cl \cdot \frac{1}{2}H_2O$	59.54	4.35	6.04	59.62	4.20	6.11	1632
g	O_2N-	yellow plates	(260—261)	$C_{22}H_{16}O_7N_3Cl$	56.25	3.43	8.95	55.87	3.58	9.09	1632
h		yellow needles	200—202	$C_{20}H_{15}O_5N_2SCl \cdot H_2O$	53.50	3.82	6.24	53.69	3.83	5.86	1630
i		yellow needles	(244—245)	$C_{20}H_{15}O_6N_2Cl \cdot H_2O$	55.48	3.96	6.47	55.25	4.02	6.61	1637
j		yellow plates	204—205	$C_{26}H_{19}O_5N_2Cl$	65.75	4.03	5.90	65.46	4.39	6.31	1635
k		yellow needles	(274—275)	$C_{26}H_{19}O_5N_2Cl$	65.75	4.03	5.90	65.76	3.84	5.94	1634

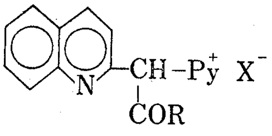
Table III. Alkaline Hydrolysis of N-(α-Acyl-2-quinolylmethyl)-pyridinium Perchlorates (III)

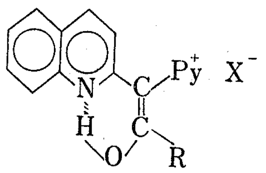

III V VII

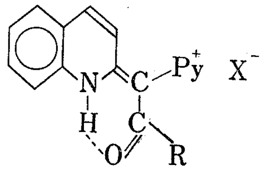
	R	VII			Yield of V (%)
		Appearance	mp (°C)	Yield (%)	
a	Me	—	—	—	63
b		colorless plates	121—122	25	93
c	Cl-	colorless plates	234—235	20	70
d	Br-	colorless plates	250—251	75	47
e	Me-	colorless needles	176—178	60	62
f	MeO-	colorless plates	181—182	66	56
g	O_2N-	colorless plates	233—235	90	87
h		colorless plates	126—127	47	69
i		colorless plates	129—131	71	63
j		colorless plates	182—183	64	81
k	 a)	colorless plates	157—158	75	9

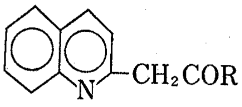
a) 10% NaOH was used in place of Na_2CO_3 solution.

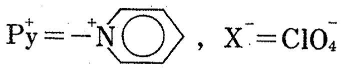
structures of III (III–A, III–B, and III–C), the chelated enaminic form, III–C is the predominant one quite similarly to the cases of quinaldyl ketones (VIII), the structure of which will be discussed in the following paper.


III – A


III – B


III – C


VIII



Experimental[11]

N-(α-Benzoyl-2-quinolylmethyl)pyridinium Perchlorate (IIIb)——Method A: A mixture of quinoline-1-oxide (I) (1.45 g), Ac_2O (7 ml) and N-phenacylpyridinium iodide (IIb) (3.3 g) in CH_3CN (50 ml) was refluxed for 3 hr. The solvent was removed *in vacuo* and the residue was dissolved in MeOH (50 ml), to which was

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[11] All melting points are uncorrected.

added a solution of $NaClO_4 \cdot H_2O$ (2 g) in H_2O (30 ml), and the whole was cooled for several hours in an ice–bath. The resultant precipitates were filtered and washed with $CHCl_3$ to give 3.2 g (75%) of crude IIIb (mp 212—214°). Recrystallization from MeOH afforded pure IIIb, yellow needles, mp 229—230°, which was identified by admixture with a specimen synthesized as described below. UV $\lambda_{max}^{95\%\ EtOH}$ mμ (log ε): 228 (4.45), 260 (3.94; shoulder), 291 (3.92), 390 (3.83; shoulder), 403 (3.88), 425 (3.81).

Method B: To a solution of I (1.45 g) in CH_3CN (50 ml), PhCOCl (1.7 g) was added under ice-cooling. After standing for 30 min at room temperature, IIb (3.3 g) and Ac_2O (5 ml) were added and the mixture was refluxed for 5 hr. Processing as the foregoing experiment gave 3.1 g of IIIb (73%).

Synthesis of IIIb from 2-Phenacylquinoline——To a refluxing solution of 2-phenacylquinoline⁶⁾ (1.2 g) in CH_2Cl_2 (30 ml), a solution of Br_2 (0.8 g) in CH_2Cl_2 (10 ml) was added dropwise over 20 min, and refluxing was continued further 10 min.⁸⁾ After cooling the reaction mixture was washed with H_2O, the organic layer was dried over Na_2SO_4 and evaporated. The residue was dissolved in benzene (30 ml), to which was added pyridine (0.5 g), and heated under reflux for 2 hr. The resultant precipitates were recrystallized from EtOH gave 0.96 g of N-(α-benzoyl-2-quinolylmethyl)pyridinium bromide (IV), yellow prisms, mp 215—216°. *Anal.* Calcd. for $C_{22}H_{17}ON_2Br \cdot H_2O$: C, 62.43; H, 4.52; N, 6.62. Found: C, 62.51; H, 4.34; N, 6.70. IR $\nu_{C=O}^{Nujol}$: 1631 cm^{-1}. Perchlorate (IIIb): Yellow needles, mp 228—229°. *Anal.* Calcd. for $C_{22}H_{17}O_5N_2Cl$: C, 62.19; H, 4.03; N, 6.60. Found: C, 62.43; H, 4.30; N, 6.88.

Reaction of Benzoyl Chloride-Adduct of Quinoline 1-Oxide (Ia) with IIb——a) To a solution of I (0.36 g) in CH_3CN (30 ml), PhCOCl (0.4 g) was added under ice-cooling. After standing 30 min at room temperature, IIb (0.81 g) was added and the mixture was refluxed for 3 hr. The solvent was evaporated under reduced pressure and the residue was dissolved in MeOH, to which was added a solution of $NaClO_4 \cdot H_2O$ (0.5 g) in H_2O (5 ml), and the whole was kept standing in a refrigerator overnight. Recrystallization of the resultant precipitates from MeOH gave 0.34 g (46%) of N-phenacylpyridinium perchlorate (VI), colorless leaflets, mp 188—189°. The materials from the methanolic mother liquor were recrystallized from EtOH to yield 0.02 g (2%) of IIIb.

b) To a solution of Ia prepared from 0.7 g of I and 0.8 g of PhCOCl in CH_3CN (50 ml) as described above, IIb (1.62 g) and dibutylamine (0.8 g) were added, and the mixture was refluxed for 3 hr. On similar working up, 0.46 g (31%) of VI and 0.36 g (17%) of IIIb were obtained.

N-(α-Acetyl-2-quinolylmethyl)pyridinium Perchlorate (IIIa)——Method A: A solution of I (1.45 g), N-acetonylpyridinium chloride⁵ᵃ⁾ (IIa) (1.7 g) and Ac_2O (5 ml) in CH_3CN (30 ml) was heated under reflux for 5 hr, and processed as described in the case of IIIb to give 3.10 g of crude IIIa, which was purified on recrystallization from MeOH to yellow needles of mp 203—204°. UV $\lambda_{max}^{95\%\ EtOH}$ mμ (log ε): 232 (4.50), 262 (3.87), 287 (3.79), 316 (3.48), 380 (3.32; shoulder), 400 (3.42), 422 (3.36). *Anal.* Calcd. for $C_{17}H_{15}O_4N_2Cl$: C, 56.28; H, 4.17; N, 7.72. Found: C, 56.57; H, 4.17; N, 7.50.

Method B: To a solution of Ia prepared from I (1.45 g) and PhCOCl (1.7 g) in CH_3CN (30 ml), were added IIa (1.7 g) and Ac_2O (5 ml). After refluxing for 5 hr, the reaction mixture was processed similarly to yield 1.7 g of IIIa.

N-(α-Acyl-2-quinolylmethyl)pyridinium Perchlorate (IIIc—k)——Method A: A solution of (0.7 g), Ac_2O (3 ml) and N-acylmethylpyridinium iodide (IIc—k) (0.005 mole) in CH_3CN (30—60 ml) was refluxed for 3—6 hr. After evaporation of the solvent *in vacuo*, the residue was dissolved in a mixture of MeOH (30 ml) and $CHCl_3$ (10 ml) to which was added a solution of $NaClO_4 \cdot H_2O$ (1 g) in H_2O (20 ml). The whole was kept standing in a refrigerator overnight to deposite precipitates, which were collected and washed with $CHCl_3$ to afford crude, yellow crystals of IIIc—k. Purification was effected by recrystallization from MeOH.

Method B: A solution of Ia in CH_3CN was prepared by adding PhCOCl (0.8 g) to a solution of I (0.7 g) in CH_3CN (30—60 ml), followed by being kept for 30 min at room temperature. To this solution were added IIc—k (0.005 mole) and Ac_2O (3 ml), and the solution was refluxed for 3—6 hr and processed similarly.

Alkaline Hydrolysis of III——Reaction of IIIa: To a solution of IIIa (0.36 g) in H_2O (10 ml)–EtOH (5 ml) was added 20% Na_2CO_3 (3 ml), and the solution was warmed on a water-bath for 15 min. After neutralization with 60% $HClO_4$, the mixture was kept standing in a refrigerator overnight. The resultant precipitates were collected and recrystallized from EtOH to give 0.2 g (63%) of N-(2-quinolylmethyl)-pyridinium perchlorate (V), colorless needles, mp 185—187°. It was identified by admixture with an authentic sample. *Anal.* Calcd. for $C_{15}H_{13}O_4N_2Cl$: C, 56.17; H, 4.08; N, 8.73. Found: C, 56.19; H, 3.92; N, 9.04.

Reaction of IIIb: To a suspension of IIIb (0.42 g) in H_2O (20 ml)–EtOH (10 ml) was added 20% Na_2CO_3 (4 ml), and the whole was warmed on a water-bath for 15 min. The reaction mixture was neutralized with 60% $HClO_4$ and extracted with ether. Evaporation of ether left a solid, which was recrystallized from H_2O to yield 0.03 g of benzoic acid (25%). The aqueous layer was kept standing in a refrigerator overnight and the resultant precipitates were recrystallized from EtOH to give 0.3 g of V.

Reaction of IIIc—k: A mixture of IIIc—j (0.001 mole), H_2O (20 ml), EtOH (10 ml), and 20% Na_2CO_3 (4 ml) was warmed on a water-bath for 15 min. The reaction mixtures were worked up as described above to afford V and the corresponding carboxylic acids (VII) which were recrystallized from water or aqueous EtOH and identified by elemental analyses and admixture with the corresponding authentic samples. The hydrolysis of IIIk was carried using 10% NaOH in place of Na_2CO_3 solution.

N-(2-Furoylmethyl)pyridinium Iodide (IIi)——A mixture of 2-acetylfuran (11 g), pyridine (40 g), and iodine (25 g) was heated on a water-bath for 1 hr. The resultant precipitates were collected, washed with acetone and cold aqueous EtOH, treated with charcoal in aqueous EtOH and recrystallized from the same solvent to afford 18.6 g (59%) of IIi, pale yellow plates, mp 188—189° (decomp.). *Anal.* Calcd. for $C_{11}H_{10}O_2NI$: C, 41.93; H, 3.20; N, 4.45. Found: C, 42.18; H, 3.18; N, 4.64. Perchlorate: Colorless needles, mp 179—180°. *Anal.* Calcd. for $C_{11}H_{10}O_6NCl$: C, 45.92; H, 3.50; N, 4.87. Found: C, 46.04; H, 3.35; N, 5.10.

Alkaline Hydrolysis of IIi——To a solution of IIi (0.95 g) in H_2O (20 ml)–EtOH (10 ml) was added 20% Na_2CO_3 (7 ml) and the mixture was warmed on a water-bath for 15 min. After treatment with charcoal, the solution was acidified with 10% HCl and extracted with ether. Evaporation of ether yielded 0.24 g (72%) of 2-furoic acid, colorless needles, mp 129—130°.

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