understood in terms of its component rate constants, which are of more fundamental significance than the experimentally visible k.

The inset in Figure 2 shows the pH dependence of a large KSIE for another reaction involving nucleophilic addition to a moderately electrophilic center: the exchange of methoxide between methyl borate and methanol.[17] In this case also, the largest KSIE, which is between the regions of lyonium and lyate catalysis, appears where k is less pH dependent.

In 49.5% D_2O, the value of k, 7.7×10^{-8} s^{-1}, is 18% lower than the mean of the rate constants in H_2O and in D_2O, all at pL 2.5. This negative deviation from linearity of the Gross-Butler plot is not unexpected, since the transition state involves more than one transient proton.[18]

Experimental Section

Materials. 3,4-(Methylenedioxy)-β-nitrostyrene (S) was prepared according to Lange and Hambourger[19] and recrystallized from ethanol. Deuterium oxide (Aldrich Chemical Co. Gold Label, 99.8 atom % deuterium) was used without further purification.

Procedure. Kinetic runs were started by adding 1 mL of a 3×10^{-5} M solution of S in reagent-grade CH_3OH (containing 10^{-3} M hydrochloric acid to inhibit solvolysis) to the H_2O or D_2O buffer and diluting to 100 mL or equivalent proportions. The volumetric flask was sealed with Parafilm before it was placed in the thermostat. Fast runs were performed in the temperature-controlled compartment of a Beckman Model DU spectrophotometer. The nitrostyrene concentration was followed at its absorption maximum, 372 nm.

The pH meter was calibrated by adding measured quantities (up to 0.36 mL) of 0.11 M sodium hydroxide to 25 mL of boiled H_2O or D_2O, under a stream of nitrogen, in a Pyrex three-necked flask previously treated with boiling nitric acid. The glass electrode was introduced and a reading taken for each increment of sodium hydroxide. The measured pH for 10^{-4} to 10^{-3} M sodium hydroxide solutions was within 0.07 pH unit of the correct value, 14.00 + log [OH^-]. In D_2O, the measured pD (0.4 + pH meter reading)[18] differed from the calculated value of 14.88 + log [OD^-] by 0.07 unit (average of four determinations). These observations confirmed the relationship between pH meter reading and hydroxide ion concentration in the buffer solutions.

Acknowledgment. I appreciate the advice and encouragement of Dr. Thomas H. Cromartie.

Registry No. S, 1485-00-3; D_2D, 7789-20-0; D, 7782-39-0; D_2SO4, 13813-19-9; DCl, 7698-05-7; OH, 14280-30-9; acetate, 71-50-1; phthalate, 3198-29-6; phosphate, 14265-44-2; borate, 14213-97-9.

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Decarboxylative Ipso Halogenation of Mercury(II) Pyridinecarboxylates. Facile Formation of 3-Iodo- and 3-Bromopyridines[1]

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Treatment of mercury(II) nicotinate with iodine and bromine in nitrobenzene at 180–185 °C for 2 h afforded 3-iodo- and 3-bromopyridines in 44% and 27% yields, respectively, without any regioisomers and dihalopyridines. From mercury(II) picolinate only 2–3% of 2-bromopyridine was obtained under similar reaction conditions, while the reaction using mercury(II) isonicotinate did not give any products. When a mixture of nicotinic acid and HgO was used in place of mercury(II) nicotinate, the halodecarboxylation occurred with similar ease. An ionic pathway involving the initial attack of electrophilic Hg(II) species on the ring-C bearing carboxyl group to afford a 3-pyridylmercury(II) compound and the subsequent replacement of the Hg(II) moiety by electrophilic iodine and bromine was proposed for this reaction.

Electrophilic halogenation of pyridine itself with halogens is known to be difficult because of the electron-deficient nature of the pyridine ring.[2] Very high temperature and/or strong acidic conditions are generally required for the reaction, and in most cases the desired 3-halopyridines are formed in low yields and are accompanied by considerable amounts of 3,5-dihalopyridines.[2,3] During the study of developing a facile method for halopyridines we found that the treatment of mercury(II) nicotinate, out of various metal salts of pyridinecarboxylic acids, with iodine and bromine in nitrobenzene afforded 3-iodo- and 3-bromopyridines, respectively, in moderate yields under comparatively mild conditions without the formation of any of regioisomers and dihalopyridines. A similar reaction also proceeded by using nicotinic acid, HgO, and halogen. We report here the details of this decarboxylative ipso halogenation and discuss its probable reaction scheme briefly.

(1) Presented in part at the 13th Congress of Heterocyclic Chemistry, Shizuoka, Japan, 1980.
(2) See, for example: (a) "Rodd's Chemistry of Carbon Compounds", 2nd ed.; Coffey, S., Ed.; Elsevier: Amsterdam, 1976; Vol. IV, Part F, p 84. (b) Acheson, R. M. "An Introduction to the Chemistry of Heterocyclic Compounds", 3rd ed.; Wiley: New York, 1976; pp 236–239.
(3) Recently, a facile method for bromination and chlorination of pyridine by using pyridine–$PdCl_2$ complex was reported, although we could not reproduce the experimental data: Paraskewas, S. *Synthesis* **1980**, 378.

Results and Discussion

Reaction of Mercury(II) and Thallium(I) Pyridinecarboxylates with Halogens. Various metal salts of picolinic, nicotinic, and isonicotinic acids and nicotinic acid

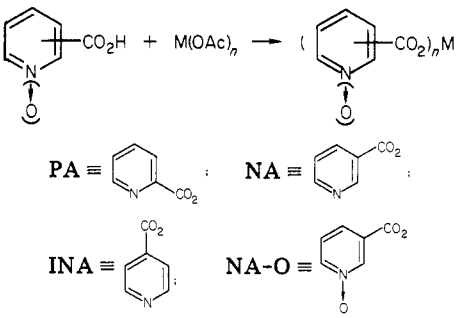
0022-3263/83/1948-3297$01.50/0

Table I. Hg(II), Tl(I), and Tl(III) Salts of Pyridinecarboxylic Acids and Their Oxides

metal carboxylate[a]	yield, %	mp (dec), °C
$Hg(PA)_2$	72	257
$Hg(NA)_2$[b]	99	273-277
$Hg(INA)_2 \cdot 4H_2O$	89	>295
$Hg(NA\text{-}O)_2$	46	>295
Tl(PA)	94	204-205
Tl(NA)	95	210-211
Tl(INA)	95	218-219
$Tl(NA)_3$[c]	100	253-256

[a] See eq 1 for abbreviations. Satisfactory analytical data (±0.4% for C, H, and N) were reported for all new compounds listed in the table except $Hg(NA)_2$ and $Tl(NA)_3$. [b] Anal. Calcd for $C_{12}H_8O_4N_2Hg$: C, 32.40; H, 1.81; N, 6.30. Found: C, 32.07; H, 2.13; N, 5.85. [c] Anal. Calcd for $C_{18}H_{12}O_6N_3Tl$: C, 37.88; H, 2.12; N, 7.36. Found: C, 37.77; H, 2.19; N, 6.95.

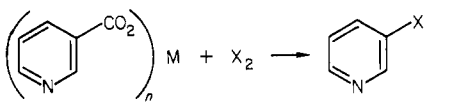
N-oxide were prepared in good yields by treating metal acetates with free acids in aqueous alkaline solution or in refluxing benzene. Data on the Hg(II), Tl(I), and Tl(III) salts are summarized in Table I (eq 1). When these metal salts (1 equiv) were heated with excess I_2 or Br_2 (3 equiv) in nitrobenzene, appreciable amounts of halopyridines were obtained only from Hg(II) and Tl(I) nicotinates. For example, the yields (GLC) of 3-bromopyridine (1; X = Br)



(1)

M = Hg, Tl; n = 1-3;

from Hg(II) and Tl(I) salts were 20% and 8%, respectively, at 165 °C for 2 h, and the yield of 3-iodopyridine (1; X = I) from the Hg(II) salt was 44% at 180–185 °C for 2 h (eq 2). It was confirmed separately that 1 (X = I or Br) is



(2)

1

M = Hg (n = 2), Tl (n = 1); X = Br, I

stable and remained unreacted under the reaction conditions. The reaction of mercury(II) picolinate with Br_2

Table II. Halopyridine from the Metal Salt of Pyridinecarboxylic Acid[a]

metal salt (1 mmol)	halogen (3 mmol)	reaction temp, °C	reaction time, h	product	yield, %
$Hg(NA)_2$	I_2	125	2	1 (X = I)	0
$Hg(NA)_2$	I_2	165	2	1 (X = I)	6
$Hg(NA)_2$	I_2	165	5	1 (X = I)	15
$Hg(NA)_2$	I_2	180-185	2	1 (X = I)	44
$Hg(NA)_2$	I_2	180-185	17	1 (X = I)	48
Tl(NA)	I_2	180-185	2	1 (X = I)	9[b]
$Hg(NA)_2$	Br_2	125	2	1 (X = Br)	12
$Hg(NA)_2$	Br_2	165	2	1 (X = Br)	20
$Hg(NA)_2$	Br_2	180-185	2	1 (X = Br)	27
$Hg(NA)_2$	Br_2	180-185	5	1 (X = Br)	23
$Hg(NA)_2$	Br_2[c]	30-35	5	1 (X = Br)	0
$Hg(NA)_2$	Br_2[d]	160-170	1	1 (X = Br)	22
$Hg(NA)_2$	NBS[e]	160	2	1 (X = Br)	9
Tl(NA)	Br_2	165	2	1 (X = Br)	8[b]
$Tl(NA)_3$	Br_2	150-160	1	1 (X = Br)	2[b]
$Hg(PA)_2$	Br_2	120	3	2-PyBr[f]	3
$Hg(PA)_2$	Br_2	155-160	2	2-PyBr	2[g]
$Hg(PA)_2$	Br_2	155-165	18	2-PyBr	0[h]

[a] Nitrobenzene (10 mL) was used as the solvent. [b] Small amounts of halonitrobenzenes were formed. [c] Irradiation with a high-pressure mercury lamp (Ushio UM-103). [d] $(PhCO)_2O_2$ (0.2 mmol) was added. [e] *N*-Bromosuccinimide. [f] 2-Bromopyridine. [g] Other product 2,2′-dipyridyl (2%). [h] Other products 2,2′- (2%) and 4,4′-dipyridyl (3%).

Table III. Halopyridine and Aryl Halide from Carboxylic Acid and Halogen in the Presence of Metal Salt[a]

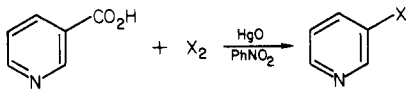
carboxylic acid (2 mmol)	halogen (3 mmol)	reaction temp, °C	reaction time, h	product	yield, %
nicotinic	I_2	160	2	1 (X = I)	6
nicotinic	I_2	160	5	1 (X = I)	12
nicotinic	I_2	180-185	2	1 (X = I)	34
nicotinic	I_2	180-185	5	1 (X = I)	42
nicotinic	I_2	180-185	15	1 (X = I)	50
nicotinic	Br_2	165	2	1 (X = Br)	21
nicotinic	Br_2	180-185	2	1 (X = Br)	18
nicotinic	Br_2[b]	180-185	2	1 (X = Br)	6
nicotinic[c]	Br_2	160	2	1 (X = Br)	15
p-nitrobenzoic	I_2	180-185	2	2 (X = I, Y = NO_2)	61
p-chlorobenzoic	I_2	180-185	2	2 (X = I, Y = Cl)	51
benzoic	I_2	180-185	2	2 (X = I, Y = H)	58
p-methylbenzoic	I_2	180-185	2	2 (X = I, Y = CH_3)	75
p-chlorobenzoic	Br_2	180-185	2	2 (X = Br, Y = Cl)	22
benzoic	Br_2	180-185	2	2 (X = Br, Y = H)	21

[a] Nitrobenzene (10 mL) as solvent and HgO(yellow) (1 mmol) were used. [b] Br_2 (10 mmol) was used. [c] HgO(red) (1 mmol) was used.

at 155–160 °C for 2 h, on the other hand, gave only 2% of 2-bromopyridine along with 2,2′-dipyridyl (2%). The formation of minute amounts of these products has already been known in the Hunsdiecker reaction of the corresponding Ag(I) salt.[4] From the reaction of mercury(II) isonicotinate with Br_2, however, no 4-bromopyridine and 4,4′-dipyridyl were produced either at 150 °C for 20 h or at 180 °C for 2 h. In the halodecarboxylation of aliphatic and aromatic acids via their Hg(II) salts, the fact is known that the acids which give less soluble Hg(II) salts under the reaction conditions degrade less easily to organic halides.[5] However, in our case all reaction mixtures containing the Hg(II) salts of the isomeric acids became homogeneous on heating, and therefore such a difference in reactivities of the Hg(II) salts may not be attributed to their solubilities. Several data are shown in Table II.

Although the light-assisted bromodecarboxylation of aromatic acids was recently reported,[6] the irradiation with a high-pressure mercury lamp had no effect on the reaction of mercury(II) nicotinate in nitrobenzene or CCl_4, and no products were formed at 30–35 °C. The addition of benzoyl peroxide to the reaction mixture did not show any influence on the product yield. Replacement of nitrobenzene by other solvents caused a sharp decrease in the yield; i.e., in the 2-h reaction of mercury(II) nicotinate with Br_2, 1 (R = Br) was formed in only 9% and 3% yields in *o*-dichlorobenzene (at 160 °C) and acetonitrile (at 82 °C), respectively, and no reaction occurred in *trans*-decaline, CCl_4, 1,1,2,2-tetrachloroethane, 1,4-dioxane, pyridine, *N*,*N*-dimethylformamide, and nitromethane. Further, some other metal [Na(I), Ag(I), Tl(III), or Pb(IV)] nicotinates and the Hg(II) salt of nicotinic acid *N*-oxide [Hg(NA–O)$_2$] did not afford any appreciable amounts of the expected bromides (at 160–170 °C for 1–2 h).

Formation of 3-Halopyridines from Nicotinic Acid, Mercury(II) Oxide, and Halogens. It was revealed by Bunce[5] that there is no significant difference in product distribution between the Hunsdiecker reaction using either the Ag(I) or Hg(II) salts of some aliphatic acids and the modified procedure (the Cristol–Firth method)[7] using the acids and HgO. Therefore, we examined the formation of 3-halopyridines by the modified procedure. When nicotinic acid (2 equiv) was treated with 1 equiv of HgO (yellow or red) and excess halogen (3 equiv) in nitrobenzene under similar reaction conditions as above, halodecarboxylation was found to occur with similar ease (eq 3). Typical data



(3)

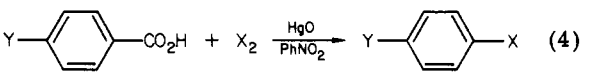
1

X = I, Br

obtained by using HgO(yellow) are shown in Table III. Both the red and the yellow forms of HgO appeared to be almost equally effective, as already cited by Davis et al.[8] and Bunce[5] in the cases of aromatic and aliphatic acids. Out of the metal oxides and acetates that were tested as replacements for HgO, only Tl_2O and $Hg(OAc)_2$ were slightly effective [1 (X = Br) was formed in 7% and 4% yields, respectively], and the reaction using each of the following oxides and acetate gave no products at 160 °C for 2 h: Ag_2O, Cu_2O, PbO, CoO, CdO, Fe_2O_3, and AgOAc.

Attempts to bromodecarboxylate the *N*-oxides of three isomeric pyridinecarboxylic acids by this modified procedure were also unsuccessful.

In view of the lack of information on the iododecarboxylation of aromatic acids by the Cristol–Firth procedure, we examined the reaction of some aromatic acids with HgO(yellow) and I_2 as well as Br_2 at ca. 180 °C for 2 h in nitrobenzene (eq 4). The obtained data are



(4)

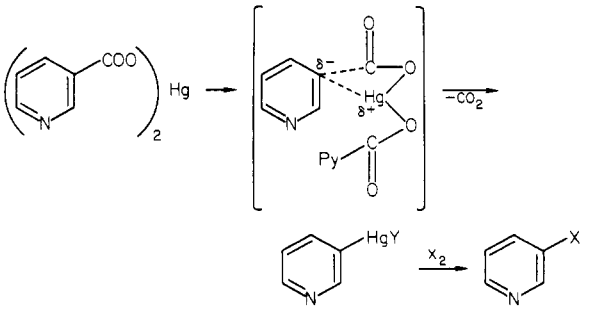
2

X = I, Br; Y = NO_2, Cl, H, CH_3

included in Table III. Thus it was revealed that the Cristol–Firth method is also applicable to the formation of aryl iodides [2 X = I)] from the corresponding acids, including the acids bearing an electron-donating group, in contrast to the Hunsdiecker reaction of the Ag(I) salts.

Ionic Pathway for the Decarboxylative Ipso Halogenation in Pyridinecarboxylates. For the Hunsdiecker reaction of aliphatic acids, the mechanism involving the intermediacy of acyl hypohalite (RCOOX) and its radical decomposition with decarboxylation to yield alkyl halide have been established with some certainty. In addition, Bunce[5] has confirmed that the Cristol–Firth reaction proceeds via the pathway involving the initial formation of the Hg(II) salt of the acid, followed by its degradation according to the pattern of the Hunsdiecker reaction.

As described above, all products obtained from mercury(II) picolinate can be rationalized by this mechanism. In the reaction of the nicotinate, however, the following findings appear to be inconsistent with the radical pathway. (1) No byproducts, including those arising from radicals, were found. (2) Irradiation by UV light or the addition of a peroxide had no effect. (3) Nicotinic acid was considerably reactive, whereas both picolinic and isonicotinic acids were far less reactive. In connection with this, a completely different trend was observed in the Hunsdiecker reaction where the decarboxylation rate decreases in the order picolinic > isonicotinic > nicotinic acid,[4] reflecting the stability order of isomeric pyridyl radicals (2- ≫ 3- > 4-).[9] Therefore, the most reactive feature of mercury(II) nicotinate can be rationalized by assuming an ionic pathway, in which an intramolecular electrophilic attack of the Hg(II) species on the ipso position to afford 3-pyridylmercury(II) compound is rate-determining, and the subsequent replacement of the Hg(II) moiety by electrophilic halogen leads to 3-halopyridine (eq 5). It has been known that the Hg(II), Pb(IV), and As(III) salts of certain carboxylates bearing strong electron-withdrawing groups were thermally de-



(5)

Y = OCO(3-Py) and 3-Py

(4) Kuffner, F.; Russo, C. *Monatsh. Chem.* **1954**, *85*, 1097.
(5) Bunce, N. J. *J. Org. Chem.* **1972**, *37*, 664.
(6) Meyers, A. I.; Fleming, M. P. *J. Org. Chem.* **1979**, *44*, 3405.
(7) Cristol, S. J.; Firth, W. C., Jr. *J. Org. Chem.* **1961**, *26*, 280.
(8) Davis, J. A.; Herynk, J.; Carroll, S.; Bunds, J.; Johnson, D. *J. Org. Chem.* **1965**, *30*, 415.
(9) Reference 2a, p 130.

carboxylated to afford the corresponding organometallic compounds.[10] The conversion of organomercury(II) and some other organometallic compounds into alkyl, alkenyl, and aryl halides by treatment with halogen has been well-known.[11] In fact, the halodemercuration step was evidenced by separate experiments using 3-pyridylmercury(II) chloride and bis(3-pyridyl)mercury; i.e., when these compounds were heated with I_2 or Br_2 in nitrobenzene, high yields of 3-halopyridines were obtained (see Experimental Section). To obtain some information on the electrophilic nature of the reaction, we determined the relative rates in iododecarboxylation of three para-substituted benzoic acids by the competition method (see Experimental Section). The observed substituent effect (CH_3/Cl/NO_2 ratio of ca. 19:5:1) appears to support the presumed ionic pathway involving a rate-determining electrophilic attack.

Experimental Section

IR spectra were recorded with a Hitachi EPI-S2 spectrometer in paraffin and hexachlorobutadiene mulls and in KBr disks. GLC analyses were carried out on a Shimadzu 4CMPF apparatus by using EGSS-X (15%)–Chromosorb W (1 or 3 m) and silicone QF-1 (30%)–Chromosorb W (1 m) columns (N_2 as carrier gas). Commercially available organic and inorganic compounds were used without further purification. The *N*-oxides of isonicotinic (mp 274–275 °C; lit.[12] mp 271 °C), nicotinic (mp 265–267 °C; lit.[13] mp 255–256 °C), and picolinic acids (mp 167–169 °C; lit.[14] mp 162–163 °C) were prepared by the reported method by treatment of the corresponding acid or methyl ester with H_2O_2 in AcOH. 2-Bromopyridine *N*-oxide (mp 65–66 °C; lit.[15] mp 64 °C) and 3-bromopyridine *N*-oxide [bp 123–125 °C (2 torr); lit.[16] bp 97–99 °C (0.5 torr)] were prepared by the oxidation of the corresponding bromopyridine with H_2O_2 in AcOH in a reported way. 3-Iodopyridine was prepared by the Sandmeyer reaction of 3-aminopyridine; mp 53–54 °C (lit.[17] mp 50 °C). 3,5-Dibromopyridine was prepared by treating a mixture of pyridine and thionyl chloride with bromine in a reported way;[18] mp 113 °C (lit.[18] mp 110–111 °C). 3-Pyridylmercury(II) chloride[19] and bis(3-pyridyl)mercury[20] were prepared by the reported method from direct reaction of pyridine with mercury(II) acetate. Typical experimental procedures are given below.

Preparation of the Mercury(II) Salt of Pyridinecarboxylic Acid (Table I). To an aqueous solution (20 mL) of mercury(II) acetate (1.91 g, 6 mmol) was added an alkaline solution (NaOH, 0.40 g, 10 mmol, H_2O 30 mL) of picolinic acid (1.23 g, 10 mmol) dropwise at room temperature, and the instantaneously precipitated white solid [$Hg(PA)_2$] was filtered off, washed with water and then ether, and dried over silica gel under vacuum: 1.60 g (3.6 mmol, 72%); mp 257 °C. Other salts were similarly prepared. In the case of mercury(II) isonicotinate [$Hg(INA)_2$] it was revealed by IR (hexachlorobutadiene mull) and combustion analysis that it has water of crystallization (4 mol/mol of the compound).

Preparation of Thallium(I) and -(III) Salts of Pyridinecarboxylic Acid (Table I). A heterogeneous mixture of nicotinic acid (1.23 g, 10 mmol) and thallium(I) acetate (2.63 g, 10 mmol) in benzene (40 mL) was heated under reflux for 1.5 h with stirring, and then acetic acid formed and benzene were distilled off. The residual white solids [Tl(NA)] were washed with benzene and dried under vacuum: 3.08 g (0.95 mmol, 95%); mp 210–211 °C. Other salts were similarly prepared except thallium(III) nicotinate [$Tl(NA)_3$], in the case of which more benzene [100 mL for 2.5 mmol of $Tl(OAc)_3$] was necessary to obtain an analytically pure compound.

Reaction of Mercury(II) Nicotinate [$Hg(NA)_2$] with Iodine in Nitrobenzene. A mixture of $Hg(NA)_2$ (0.444 g, 1 mmol) and iodine (0.762 g, 3 mmol) in nitrobenzene (10 mL) was heated at 180–185 °C for 2 h with stirring. After being cooled, the resulting solution was added to aqueous NaOH, and the precipitates formed were filtered off. The filtrate was added to aqueous NaCl and then extracted with CCl_4. The extract was washed with water and dried over Na_2SO_4. GLC analyses of the extract with 3-bromopyridine as an internal standard revealed the presence of 3-iodopyridine (1; X = I) as the sole product, 0.88 mmol (44% yield based on the Hg(II) salt charged).

The reactions of halogens with other metal carboxylates were similarly carried out (Table II).

Reaction of Nicotinic Acid with Iodine in the Presence of Mercury(II) Oxide in Nitrobenzene. A mixture of nicotinic acid (0.246 g, 2 mmol), mercury(II) oxide (yellow) (0.216 g, 1 mmol), iodine (0.762 g, 3 mmol), and nitrobenzene (10 mL) was heated at 180–185 °C for 5 h with stirring. After the workup as described above, GLC analysis of the organic extract revealed the presence of 3-iodopyridine (1; X = I) as the sole product (3-bromopyridine as internal standard), 0.84 mmol (42% yield based on nicotinic acid charged).

For the isolation of 1 (X = I) a reaction on a scale 5 times greater was carried out at 180–185 °C for 2 h. After being cooled, the resulted solution was washed with a small amount of aqueous NaOH and then with aqueous HCl. The aqueous acidic extract was then carefully neutralized with aqueous NaOH to give white precipitates. The combined mixture of the precipitates and aqueous solution was extracted with $CHCl_3$ which was then washed with brine and dried over $MgSO_4$. Evaporation of the $CHCl_3$ left a white solid of 1 (X = I): 0.65 g (31.7% isolated crude yield); 0.45 g (22%) after recrystallization; mp 52 °C.

The reactions of halogens with other acids including para-substituted benzoic acids in the presence of metal salts were similarly carried out (Table III).

Reaction of 3-Pyridylmercury(II) Chloride and Bis(3-pyridyl)mercury with Halogens in Nitrobenzene. A mixture of 3-pyridylmercury(II) chloride (0.314 g, 1 mmol) and bromine (0.32 g, 1 mmol) in nitrobenzene (10 mL) was stirred at 120 °C for 2 h during which period a heterogeneous solution turned to a clear red solution. GLC analyses of the organic extract after the workup procedure described above revealed the presence of 3-bromopyridine (1; X = Br) as a sole product, none of 2- and 4-bromopyridines, dibromopyridine, and 3,3′-dipyridyl being produced; 0.862 mmol (86.2% yield based on the Hg(II) compound charged). Similar reaction with iodine at 123–128 °C for 2 h afforded 3-iodopyridine (1; X = I) in a yield of 75%.

Bis(3-pyridyl)mercury (0.5 mmol) was similarly treated with bromine and iodine (2 mmol) in nitrobenzene (10 mL) at 120 °C for 2 h to give (1; X = Br) and (1; X = I) in a yield of 99% and 83%, respectively.

Competitive Reaction in Iododecarboxylation of Three Para-Substituted Benzoic Acids. A mixture of *p*-chlorobenzoic acid (0.313 g, 2 mmol), *p*-methylbenzoic acid (0.272 g, 2 mmol), and iodine (0.254 g, 1 mmol) was heated at 180 °C in nitrobenzene (20 mL) in the presence of mercury(II) oxide (yellow) (0.432 g, 2 mmol). The red color of iodine disappeared after 2 min, and a slightly heterogeneous pale yellow solution was obtained. After 30 min of stirring, the reaction mixture was cooled rapidly and worked up as described above. GLC analysis of the organic extract revealed the presence of *p*-methyliodobenzene (2; X = I, Y = CH_3) and *p*-chloroiodobenzene (2; X = I, Y = Cl), the molar ratio of which being ca. 4.1:1 and the total yield of both products being at most 5–10% (iodobenzene as internal standard).

A similar reaction using *p*-nitrobenzoic acid (2 mmol), *p*-chlorobenzoic acid (1 mmol), iodine (1 mmol), HgO(yellow) (1.5 mmol), and nitrobenzene (20 mL) was carried out at 180 °C for

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30 min. The color of iodine disappeared after 5 min, and a heterogeneous pale yellow solution was obtained. The molar ratio of two products, *p*-chloroiodobenzene and *p*-nitroiodobenzene, was ca. 4.5:1 by GLC analysis after a correction for the concentration of the acids.

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Registry No. 1 (X = I), 1120-90-7; 1 (X = Br), 626-55-1; 2 (X = I; Y = NO_2), 636-98-6; 2 (X = I; Y = Cl), 637-87-6; 2 (X = I; Y = H), 591-50-4; 2 (X = I; Y = CH_3), 624-31-7; 2 (X = Br; Y = Cl), 106-39-8; 2 (X = Br; Y = H), 108-86-1; $Hg(PA)_2$, 86668-72-6; $Hg(NA)_2$, 41408-73-5; $Hg(INA)_2$, 41408-74-6; $Hg(NA\text{-}O)_2$, 86668-73-7; Tl(PA), 86668-74-8; Tl(NA), 86668-75-9; Tl(INA), 86668-76-0; $Tl(NA)_3$, 86668-77-1; HgO, 21908-53-2; nicotinic acid, 59-67-6; *p*-nitrobenzoic acid, 62-23-7; *p*-chlorobenzoic acid, 74-11-3; *p*-methylbenzoic acid, 99-94-5; benzoic acid, 65-85-0; 3-pyridinylmercury(II) chloride, 5428-90-0; bis(3-pyridyl)mercury, 20738-78-7.

A Chemical Model for the Mechanism of Vitamin K Epoxide Reductase[1]

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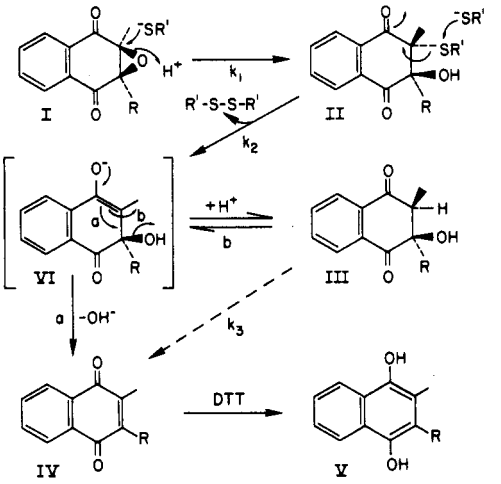
The reactions of vitamin K_1 epoxide and 2,3-dimethylnaphthoquinone epoxide with dithiothreitol and mercaptoethanol have been studied as a potential model for the mechanism of the enzyme vitamin K epoxide reductase. The reaction proceeds with thiol addition to open the oxirane ring, yielding preferentially the 2-thio-3-hydroxy adduct in the case of vitamin K_1 epoxide. Reaction with a second thiol group results in reductive cleavage of this adduct and elimination of water to yield the quinones. All steps are catalyzed by triethylamine. Evidence for a hydroxy-substituted 2,3-dihydronaphthoquinone enolate intermediate in the second step is found in the observation of the corresponding keto compounds as equilibrated side products in the reaction with dithiothreitol. With this reagent, intramolecular reaction to form the cyclic disulfide permits cleavage of the thiol adduct under mild conditions where protonation of the enolate is rapid relative to elimination of the hydroxyl. Isolation and characterization of the intermediates and their conversion to the quinones are described.

Vitamin K epoxide reductase is a key enzyme in the function of vitamin K to promote coagulation factor biosynthesis.[3-6] Vitamin K 2,3-epoxide is formed as a product of the vitamin K dependent microsomal carboxylation of peptide-bound glutamyl residues.[7-10] Vitamin K epoxide reductase is necessary to convert the epoxide back to quinone to permit continued carboxylation at physiologic concentrations of the vitamin. The clinically significant coumarin anticoagulants block this cycle by inhibiting the epoxide reductase.[11-14]

A mechanism for vitamin K epoxide reductase has recently been proposed, and a chemical model for the reaction of the epoxide with a reduced active site disulfide has been demonstrated.[15] Scheme I illustrates the proposed pathway of vitamin K epoxide reduction by thiols under alkaline conditions. Silverman[15] examined the reaction of dimethylnaphthoquinone epoxide (Ib) with ethanethiol and triethylamine and demonstrated the formation of the thiol adduct (II″b). This was converted to dimethylnaphthoquinone (IVb) by treatment with sodium ethanethiolate. The enolate (VI) was postulated as an intermediate in this reaction. We have now found evidence

Scheme I. Proposed Pathway of Vitamin K Epoxide Reduction[a]



[a] Ia-Va, R = phytyl. Ib-Vb, R = methyl. IIa,b, R′ = $CH_2(CHOH)_2CH_2SH$. II′b, R′ = CH_2CH_2OH. II″b, R = CH_2CH_3. Stereochemistry is shown to indicate the relationship between structures. All materials were racemic mixtures. The dashed line indicates the macroscopic rate constant.

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