Anal. Calcd for $C_{12}H_{26}O_4N_2Cl_2$: C, 43.4; H, 7.8; N, 8.4. Found: C, 43.4; H, 7.8; N, 8.3.

When equilibrated at pH 7.5 as described for **24**, **26** afforded *cis*-decahydronaphthyridinedione **21** in 95% yield.

Ethyl 3-Amino-6-oxohexahydropyridine-4-propionate Hydrochloride (27).—Bislactam **10** (300 mg) was dissolved in 5 ml of 6 *N* hydrochloric acid and the solution heated under reflux for 24 hr. The same technique described previously for the synthesis of **23** was then followed and 225 mg (50%) of **27** was obtained: mp 134–136°; ir 1690 (CO), 1740 cm^{-1} (CO ester); nmr δ 1.4 (t, CH_2CH_3), 2.2 (b, C-5 H_2), 2.7 (m, $CH_2CH_2CO_2Et$), 3.7 (b, C-2 H_2), 4.4 (q, CH_2CH_3).

Anal. Calcd for $C_{10}H_{19}N_2O_3Cl$: C, 47.9; H, 7.6; N, 11.2. Found: C, 47.7; H, 7.6; N, 11.4.

***cis*-Decahydro-1,5-naphthyridine (28).**—*cis*-Decahydro-1,5-naphthyridine-2,6-dione (**21**) (1.7 g) was slowly added with constant stirring to a suspension of 3 g of lithium aluminum hydride in 200 ml of tetrahydrofuran. The resulting mixture was heated at reflux for 10 hr, and then 200 ml of water was added. The solution was adjusted to pH 12 with a concentrated sodium hydroxide solution and extracted with five 50-ml portions of chloroform. The extract was dried (Na_2SO_4), concentrated, and distilled giving 500 mg (50%) of **28**: bp 66° (0.25 mm) [lit.[11] bp 55° (0.1 mm)]; identical (ir, nmr, tlc) with a sample prepared by reduction of 1,5-naphthyridine.[11]

Anal. Calcd for $C_8H_{16}N_2$: C, 68.5; H, 11.5; N, 20.0. Found: C, 68.6; H, 11.5; N, 20.1.

***trans*-Decahydro-1,5-naphthyridine (29)** was obtained following the procedure described for the synthesis of **28**. From 560 mg of **24** was obtained 210 mg (45%) of **29**: mp 176–177° (lit.[11] mp 177–178°); identical (ir, tlc, melting points, nmr) with a sample prepared by reduction of 1,5-naphthyridine.[11]

Registry No.—**2**, 3469-64-5; **3**, 27017-56-7; **4**, 27017-57-8; **5**, 27017-58-9; **6**, 27017-59-0; **7**, 27017-60-3; **8**, 27017-61-4; **9**, 27017-62-5; **10**, 27022-27-1; **12**, 27017-63-6; **13**, 27017-64-7; **14**, 27017-65-8; **15**, 27017-66-9; **16**, 27017-67-0; **17**, 7689-62-5; **18**, 27017-69-2; **20**, 27017-70-5; **21**, 27022-28-2; **23**, 27022-29-3; **24**, 27022-30-6; **26**, 27022-31-7; **27**, 27017-71-6.

Further Evidence as to the Nature of the Transition State Leading to Decarboxylation of 2-Pyridinecarboxylic Acids. Electrical Effects in the Transition State

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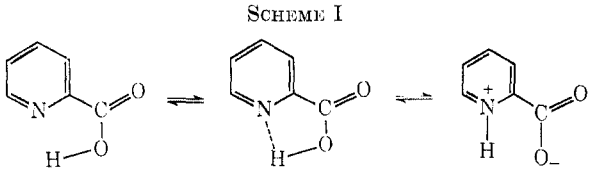
The rates of decarboxylation of 6-nitro-2-pyridinecarboxylic, 6-chloro-2-pyridinecarboxylic, 6-bromo-2-pyridinecarboxylic, 2-pyridinecarboxylic, 6-acetamido-2-pyridinecarboxylic, 6-methyl-2-pyridinecarboxylic, 6-methoxy-2-pyridinecarboxylic, and 6-amino-2-pyridinecarboxylic acids in 3-nitrotoluene were determined. The $\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$, and $\Delta S^{\ddagger}$ were then calculated. An examination of a linear free-energy plot of relative rates *vs.* the σ' constants suggested that the electron density on the ring nitrogen affects the $\Delta G^{\ddagger}$ of the reaction. The observation that 6-methoxy and 6-acetamido groups decrease the rate of decarboxylation by a factor of 4 and 10, respectively, as compared to 6-amino and 6-methyl groups was indicative of a steric effect by the larger substituents. A mechanism is suggested which is consistent with the available data.

Preliminary work has been done on the decarboxylation of 2-pyridinecarboxylic acid in various solvents.[1-4] All of these investigators have looked at the transition state and tried to deduce the structure of the intermediate leading to the transition state. Different methods must be used to study the distribution of reactant other than those used to deduce the structure of the transition state. Thus, we have not tried to postulate that either I or II is the principal reactant but assumed that both are present and that a rapid equilibrium exists between the two reactants (Scheme I).

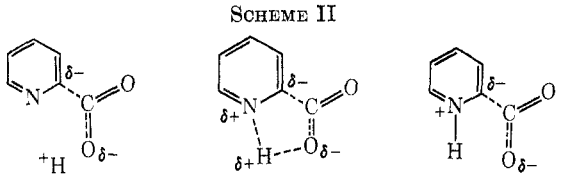
SCHEME I



I II

Irrespective of which reactant leads to which transition state, there are a total of three possible transition states, III, IV, or V (Scheme II). The electrical effects

SCHEME II



III IV V

in the three possible transition states are quite different. If transition states III or V lead predominantly to decarboxylation, one would predict that electron-withdrawing effects would stablize the transition state and lead to larger rate constants.

If transition state IV were the one leading to products, one would argue that there are opposing effects. In one case electron withdrawal should increase the rate constants and in the other case decrease the rate constants. On close examination of IV, it can be seen that two events are occurring: (1) NH bond formation, and (2) CC bond cleavage. With these two events three possibilities exist: (a) CC bond cleavage is leading NH bond formation resulting in a developing negative charge on C-2 in the transition state, (b) CC bond cleavage is lagging behind NH bond formation resulting in a developing positive charge on the ring nitrogen in the transition state, or (c) CC bond cleavage has progressed at an even rate with NH bond formation, resulting in no overall charge being developed on the ring in the

(1) L. W. Clark, *J. Phys. Chem.*, **66**, 125 (1962).
(2) L. W. Clark, *ibid.*, **69**, 2277 (1965).
(3) N. H. Cantwell and E. V. Brown, *J. Amer. Chem. Soc.*, **74**, 5967 (1952).
(4) N. H. Cantwell and E. V. Brown, *ibid.*, **75**, 4466 (1953).

transition state. Only if b exists will the information obtained in this study indicate that IV is the best representation of the transition state. Theoretically, there is a second possibility if b exists. If it were assumed that the transition state for decarboxylation was the formation of the zwitterion, which then rapidly decomposes, then the ring, in the transition state, would have a developing positive charge. This argument is dismissed for two reasons: (1) it is difficult to explain why an acid–base reaction should have a higher activation energy than a CC bond cleavage reaction, and (2) amino acids are known to exist as zwitterions, and they are quite stable.

Since the decarboxylation of 2-pyridinecarboxylic acid in various solvents has thrown little light on the nature of the transition state, the next step is to study the effects of substituents on the rate of decarboxylation. After eliminating a vicinal relationship between the substituent (R) and the carboxyl function (Y), the following cases should be considered: 4-R-2-Y, 5-R-2-Y, and 6-R-2-Y. In the first of a series of papers we have chosen to study the 6-substituted 2-pyridinecarboxylic acids.

If the electron density on the ring nitrogen is changed (without changing anything else) by substituents, one should see a rate change if the NH bond is forming in the transition state. It has already been shown that the electron density on the ring nitrogen can be controlled by ortho substituents. Ortho-substituted pyridines in which the ring nitrogen atom is not the reaction site show a linear relation with σ_p; however, the electrical effect exerted by ortho substitutents on reactions involving the lone-pair electrons on the ring nitrogen atom in pyridine is best represented by σ_I.[5] The σ' constants are almost the same as the σ_I constants, and it would be expected that much of the field effect present in the σ_I constants is eliminated in the σ' constants.[6]

To determine if sterically hindering the lone electron pair on the ring nitrogen would retard the rate of decarboxylation, we decided to look at 6-acetamido- and 6-methoxy-2-pyridinecarboxylic acids. The acetamido group was chosen because it was intuitively felt that it was large enough to prevent the NH bond from forming when one considers the volume swept out by rotation about its bonds. It is believed that this rotation must be considered, since an acid proton which starts to bond to the ring nitrogen would be pushed away by the rotation of the substituent. These rotations are many times faster than the rates of decarboxylation. The methoxyl group was chosen because it was felt that this group was large enough to prevent the NH bond from forming.

Results and Discussion

The 6-substituted 2-pyridinecarboxylic acids, 6-nitro-2-pyridinecarboxylic, 6-chloro-2-pyridinecarboxylic, 6-bromo-2-pyridinecarboxylic, 2-pyridinecarboxylic, 6-acetamido-2-pyridinecarboxylic, 6-methyl-2-pyridinecarboxylic, 6-methoxy-2-pyridinecarboxylic, and 6-amino-2-pyridinecarboxylic acids, were synthesized and their rates of decarboxylation in 3-nitrotoluene were determined in the manner described in the Experimental Section. The rate constants are in Table I, and the activation parameters are in Table II. The coefficient of variation for the data has been calculated in each case. This value is used as a measure of the relative variability of the data. In all cases it is less than 5%.

TABLE I

APPARENT FIRST-ORDER RATE CONSTANTS FOR THE DECARBOXYLATION OF 6-SUBSTITUTED 2-PYRIDINECARBOXYLIC ACIDS IN 3-NITROTOLUENE

Acid	Temp, °C	Rate constant × 10^4 sec^{-1}	Coefficient variation	Standard deviation
6-Nitro-2-pyridinecarboxylic acid	189.9	0.53	3.76	0.009
	195.0	0.78	1.26	0.003
	199.7	1.47	1.82	0.008
	200.0	1.33[a]		
	204.8	2.16	4.10	0.016
	210.1	2.99	2.02	0.010
6-Bromo-2-pyridinecarboxylic acid	190.2	1.25	0.56	0.002
	194.5	2.02	1.24	0.007
	200.0	2.97[a]		
	200.6	2.63	3.78	0.016
	205.0	4.83	3.47	0.023
	209.6	6.78	2.08	0.016
6-Chloro-2-pyridinecarboxylic acid	190.3	0.93	0.70	0.003
	194.6	1.74	2.24	0.013
	200.0	2.36[a]		
	200.4	2.12	4.04	0.026
	205.3	3.71	1.08	0.004
	210.9	6.39	2.17	0.012
2-Pyridinecarboxylic acid	158.5	0.57	3.51	0.006
	163.6	1.22	4.31	0.016
	169.8	1.92	1.21	0.007
	175.0	2.96	1.73	0.008
	179.5	4.49	1.14	0.008
	200.0	26.5[a]		
6-Acetamido-2-pyridinecarboxylic acid	185.2	0.79	0.44	0.001
	190.3	1.25	0.62	0.002
	194.5	1.89	1.50	0.006
	199.7	2.78	1.95	0.009
	200.0	3.01[a]		
	204.0	4.50	1.00	0.005
6-Methyl-2-pyridinecarboxylic acid	161.2	0.59	3.28	0.008
	164.6	0.76	1.66	0.005
	170.1	1.62	2.58	0.012
	174.8	2.31	1.54	0.008
	180.2	4.26	2.53	0.012
	200.0	28.8[a]		
6-Methoxy-2-pyridinecarboxylic acid	200.0	0.33[a]	3.91	0.009
	204.5	0.47	3.91	0.009
	210.6	1.23	3.95	0.012
	213.5	2.03	1.01	0.005
	218.2	2.60	0.89	0.003
	224.8	4.85	0.37	0.002
6-Amino-2-pyridinecarboxylic acid	195.0	0.70	1.53	0.004
	200.0	1.23[a]		
	200.2	1.21	0.80	0.003
	204.6	2.28	1.15	0.006
	209.8	3.32	0.45	0.002
	215.4	4.55	1.92	0.007

[a] Calculated from rate constants at other temperatures.

Hammett Plot.—Table II shows that, as the electron-withdrawing ability of the substituent increases, the activation energy ($\Delta G^{\ddagger}$) increases. The last three compounds in Table II do not fit into this generalization. They will be discussed later. Figure 1 shows

(5) M. Charton, *J. Amer. Chem. Soc.*, **86**, 2033 (1964).
(6) E. M. Kosower, "Physical Organic Chemistry," Wiley, New York, N. Y., 1968, p 49.

TABLE II

ACTIVATION PARAMETERS FOR THE DECARBOXYLATION OF 6-SUBSTITUTED 2-PYRIDINECARBOXYLIC ACIDS IN 3-NITROTOLUENE

Acid	$\Delta G_{200}^{\ddagger}$, kcal/mol	E_{act}, kcal/mol	$\Delta H_{200}^{\ddagger}$, kcal/mol	$\Delta S_{200}^{\ddagger}$, cal/deg/mol	Coefficient varation	Standard deviation
6-Nitro-2-pyridinecarboxylic acid	(36.53)[a]		(38.60)	(+4.38)		
	36.52	39.54	37.66	+2.39	0.98	0.088
6-Chloro-2-pyridinecarboxylic acid	(35.99)		(38.72)	(+5.78)		
	35.99	39.66	37.78	+3.79	1.47	0.123
6-Bromo-2-pyridinecarboxylic acid	(35.77)		(36.89)	(+2.37)		
	35.77	37.83	35.95	+0.39	1.27	0.103
2-Pyridinecarboxylic acid	(33.71)		(35.60)	(+3.99)		
	33.71	36.54	34.66	+2.00	1.14	0.098
6-Methyl-2-pyridinecarboxylic acid	(33.63)		(40.34)	(+14.18)		
	33.63	41.28	39.40	+12.19	0.77	0.068
6-Acetamido-2-pyridinecarboxylic acid	(35.76)		(38.36)	(+5.50)		
	35.76	39.30	37.42	+3.51	0.46	0.039
6-Amino-2-pyridinecarboxylic acid	(36.59)		(41.73)	(+10.85)		
	36.60	42.67	40.79	+8.86	1.45	0.124
6-Methoxy-2-pyridinecarboxylic acid	(37.84)		(51.84)	(+29.61)		
	37.83	52.87	51.90	+27.62	1.99	0.173

[a] The quantities in parentheses are based on first-order kinetics (*i.e.*, $\Delta H^{\ddagger} = E_{act} - RT$). The quantities not in parentheses are based on apparent first-order kinetics (*i.e.*, $\Delta H^{\ddagger} = E_{act} - 2RT$).

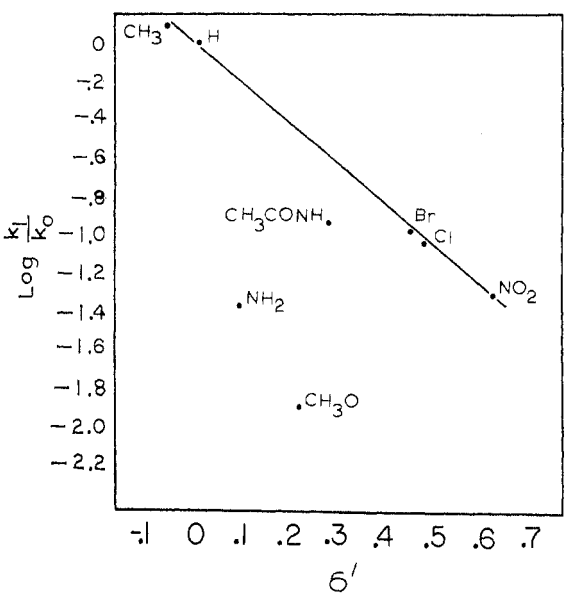


Figure 1.—A plot of σ' *vs.* log k_1/k_0 for the calculated rates of decarboxylation of 6-substituted 2-pyridinecarboxylic acids at 200°.

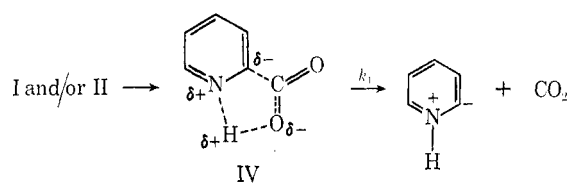
that a linear relation exists between the σ' values of CH_3, H, Br, Cl, and NO_2 and their relative rate constants. The slope of this line is −1.92. With a ρ value as large as this, it must indicate that a very large positive charge is developing in the transition state. This indicates that if IV is the transition state, then NH bond formation is slightly ahead of CC bond cleavage.

One of the results of a Hammett $\sigma\rho$ plot is that all compounds which fall on the plotted line must be decarboxylating by the same mechanism if the $\Delta S^{\ddagger}$ is relatively constant. We propose that 2-pyridinecarboxylic acid has the same transition state and feels the same electrical effects in the transition state as 6-methyl-, 6-chloro-, 6-bromo-, and 6-nitro-2-pyridinecarboxylic acids. The fact that the methyl group lies on the line may be fortuitous since the $\Delta S^{\ddagger}$ for this group is larger than for the other substituents. This proposed transition state is shown in Scheme III.

It must be pointed out that possibly these data could

SCHEME III

SUGGESTED INTERMEDIATES AND TRANSITION STATES FOR DECARBOXYLATION OF 2-PYRIDINECARBOXYLIC ACIDS



IV

be explained by kinetics of complex mechanisms involving equilibria. There are two reasons why the authors have not developed this idea further: (1) there are no data to support the idea that the equilibrium between the zwitterion and neutral molecule is affected by substitution on 2-pyridinecarboxylic acid in 3-nitrotoluene, and (2) if it can be assumed that the rate of approach to equilibrium is rapid as compared to the rate of decarboxylation, then the position of equilibrium between zwitterion and neutral molecule will have relatively no effect on which intermediate decarboxylates. However, further work is needed in these areas.

The 6-amino substituent does not fall on the straight line in Figure 1. Since the amino group is such a strong electron-releasing group by resonance, this could be used to explain its effect. However, if the effect of resonance could be simplified to only how much electron density the amino group donated to the ring nitrogen, then we would expect it to lie on the straight line similar to the methyl group. Since it does not, and the rate of decarboxylation of 6-amino-2-pyridinecarboxylic acid is slower than expected, resonance must have an opposing effect. At the present time this is not understood; however, it has already been pointed out that the 2-amino substituent does not correlate well with σ_I in the ionization of 2-substituted pyridines in water either.[5]

Sterically Hindered Decarboxylation.—Table II and Figure 1 show that 6-acetamido- and 6-methoxy-2-pyridinecarboxylic acids do not behave as the other substituted acids do. Taft has pointed out that failure of the Hammett equation for a particular substituent (or type of substituent) may result in a change in reac-

tion mechanism.[7] Both compounds have a much slower reaction rate than expected. Thus, the rotation of the substituent must be preventing the ring nitrogen and acid proton from interacting easily.

Kaneda and Hara have found that 2-pyridinecarboxylic acid and 2,6-pyridinedicarboxylic acid both decarboxylate at similar rates and the rate data do not fit equations for consecutive reactions.[8] Although they did not interpret it as such, this could be used as further evidence that transition state IV does lead to decarboxylation. An acid function at the 6 position would be expected to slow the rate of decarboxylation of the acid function at the 2 position as the 6-nitro group does, but, since there are two acid functions present in 2,6-pyridinedicarboxylic acid, either one can decarboxylate. Statistically then the rates of decarboxylation of 2-pyridinecarboxylic and 2,6-pyridinedicarboxylic acids could be equal. We would expect to observe no steric effect with the diacid since, when either proton was in the vicinity of the ring nitrogen, that particular acid function would decarboxylate.

Experimental Section

Starting material, unless otherwise specified, is 6-amino-2-methylpyridine purchased from Reilly Tar and Chemical Corp., Chicago, Ill. All of the compounds had satisfactory C, H, and N analyses and these are reported only for the new compounds. All melting points are uncorrected.

Preparation of 6-Nitro-2-pyridinecarboxylic Acid.—This compound was prepared as described in the literature[9] and has mp 168° (lit.[10] mp 168°).

Preparation of 6-Chloro-2-pyridinecarboxylic Acid.—This compound was prepared *via* diazotization[11] followed by oxidation[9] and has mp 190° (lit.[10] mp 190°).

Preparation of 6-Bromo-2-pyridinecarboxylic Acid.—This compound was prepared by M. B. Shambhu *via* diazotization[12] followed by oxidation[13] and had mp 189° (lit.[10] mp 189–190°).

Preparation of 2-Pyridinecarboxylic Acid.—This compound was prepared from 2-methylpyridine *via* oxidation[14] and had mp 131° (lit.[10] mp 132–133°).

Preparation of 6-Methyl-2-pyridinecarboxylic Acid.—This compound was prepared by Brown and Cantwell and is reported in the literature.[3] It had mp 128° (lit.[10] mp 129°).

Preparation of 6-Acetamido-2-pyridinecarboxylic Acid.—This compound was prepared by acetylation[15] followed by oxidation[16] and had mp 220–221° (lit.[10] mp 227–229°).

Preparation of 6-Methoxy-2-pyridinecarboxylic Acid.—This compound was prepared by M. B. Shambhu from 6-bromo-2-pyridinecarboxylic acid[17] and had mp 130°.

(7) R. W. Taft, in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, Chapter 13.

(8) T. Hara and A. Kaneda, *Sci. Eng. Rev. Doshisha Univ.*, **7** (4), 172 (1967).

(9) E. V. Brown, *J. Amer. Chem. Soc.*, **76**, 3167 (1954).

(10) E. P. Oliveto in "Heterocyclic Compounds," E. Klingsberg, Ed., Interscience, New York, N. Y., 1962, Chapter 10.

(11) E. V. Brown, *J. Amer. Chem. Soc.*, **79**, 3565 (1957).

(12) C. F. Allen and J. R. Thirtle, *Org. Syn.*, **26**, 16 (1946).

(13) H. Gilman and S. M. Spatz, *J. Org. Chem.*, **16**, 1485 (1951).

(14) G. Black, E. Depp, and B. B. Carson, *ibid.*, **14**, 14 (1949).

(15) S. M. McElvain, "The Characterization of Organic Compounds," Revised ed, Macmillan, New York, N. Y., 1964, pp 210–221.

(16) G. Ferrari and E. Marcon, *Farmaco, Ed. Sci.*, **14**, 594 (1959); *Chem. Abstr.*, **54**, 6709*a* (1960).

(17) R. Adams and T. Govindachari, *J. Amer. Chem. Soc.*, **69**, 1806 (1947).

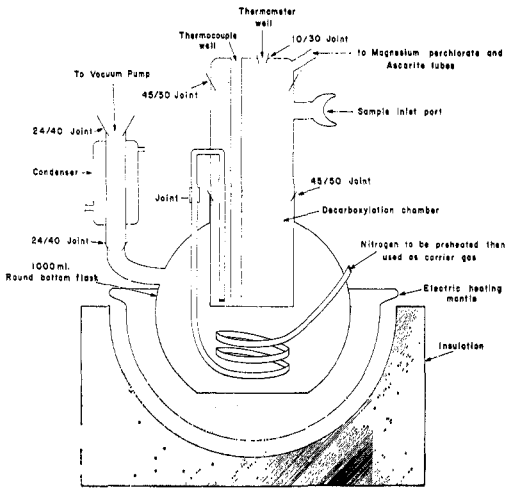


Figure 2.—A modified version of the decomposition apparatus described by E. G. Prout and F. C. Tomplins [*Trans. Faraday Soc.*, **40**, 488 (1944)] was used in this study. The round-bottomed flask contains any suitably boiling solvent, usually methyl salicylate, 1,4-dicyanobutane, or *p*-cymene.

Anal. Calcd for $C_7H_7O_3N$: C, 54.8; H, 4.6; N, 9.2. Found: C, 54.4; H, 4.5; N, 8.9.

Preparation of 6-Amino-2-pyridinecarboxylic Acid.—This compound was prepared from 6-acetamido-2-pyridinecarboxylic acid[16] and had mp 320° (lit.[10] mp 317–319°).

Procedure.—In each experiment 80 ml of 3-nitrotoluene were poured into the decarboxylation chamber (Figure 2). The heating mantle, vacuum pump, and carefully regulated stream of nitrogen carrier gas were turned on. The boiling point of the refluxing liquid was adjusted to the desired temperature by manipulation of the rheostat governing the heating mantle and manostat governing the pressure above the refluxing liquid. This took about 2.5 hr. When the thermometer and thermocouple both measured the desired temperature, the magnesium perchlorate drying tube and ascarite tubes connected to a three-way stopcock were arranged in two sets to alternate. The two ascarite tubes were filled with ascarite and weighed about 25 g each. Nitrogen was allowed to pass through each ascarite tube about 20 min, and then each ascarite tube was weighed on an analytical balance. Enough acid was weighed out in a glass boat to deliver about 0.0500 g of carbon dioxide. The boat and sample were then pushed into the sample inlet port and allowed to fall into the hot 3-nitrotoluene. The weighing of the first ascarite tube was always taken 10 min after the sample was dumped into the solvent. This was taken as zero time, and then the ascarite tubes were weighed alternately. The carbon dixoide absorbed every weighing was subtracted from that known to have been present in the acid at zero concentration. The logarithm of the decrease of carbon dioxide *vs.* time was plotted and a straight line was obtained. On the average, six readings were taken for each experiment and, in most cases, the reaction was allowed to proceed to greater than 50% completion. Reaction rates were taken for each acid over a 20° range at approximately 5° intervals.

Registry No.—6-Nitro-2-pyridinecarboxylic acid, 268-93-68-5; 6-bromo-2-pyridinecarboxylic acid, 21190-87-4; 6-chloro-2-pyridinecarboxylic acid, 4684-94-0; 2-pyridinecarboxylic acid, 98-98-6; 6-acetamido-2-pyridinecarboxylic acid, 26893-72-1; 6-methyl-2-pyridinecarboxylic acid, 934-60-1; 6-methoxy-2-pyridinecarboxylic acid, 26893-73-2; 6-amino-2-pyridinecarboxylic acid, 23628-31-1.