Kinetic Study of the Acid-Catalyzed Chromium(VI) Oxidation of the Methyl Group. Oxidation of 3-Picoline 1-Oxide and 4-Nitro-3-picoline 1-Oxide

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The acid-catalyzed Cr^{VI} oxidation of 3-picoline 1-oxide (PNO) and 4-nitro-3-picoline 1-oxide (NPNO) has been studied kinetically in aqueous sulfuric acid solution. The rate law is first order with respect to both Cr^{VI} and the substrate; the logarithm of the experimental second-order rate constant increases linearly with the H_0 function up to a sulfuric acid concentration of 10 M and becomes acidity independent at higher acid concentrations. The observed kinetics are consistent with a rate-limiting attack by the chromacidium ion, $H_3CrO_4^+$. The constant for the protolytic equilibrium $H_3CrO_4^+ \rightleftharpoons H_3CrO_4 + H^+$ amounts to $K_1 = 2.4 \times 10^5\ M$; the second-order rate constants for the oxidation by the chromacidium ion are $k_2 = 1.75 \times 10^{-2}\ M^{-1}\ sec^{-1}$ for PNO and $k_2 = 4.9 \times 10^{-3}\ M^{-1}\ sec^{-1}$ for NPNO at 45°. The activation parameters measured at a sulfuric acid concentration of 10.6 M are $\Delta H^{\ddagger} = 11.7$ kcal/mol and $\Delta S^{\ddagger} = -33.1$ eu for PNO and $\Delta H^{\ddagger} = 13.5$ kcal/mol and $\Delta S^{\ddagger} = -30.2$ eu for NPNO.

The acid-catalyzed Cr^{VI} oxidation of methyl arenes yields the corresponding aryl carboxylic acids.[1] In spite of its synthetic significance this reaction has been studied kinetically to a lesser extent than the Cr^{VI} oxidation of other functional groups for which the kinetics are well established.[2] Moreover, most of the previous work has been carried out with acetic acid as a solvent, due to the fact that most arenes are only weakly soluble in aqueous systems. In the similar case of diphenylmethane, a substrate which has been studied extensively, the rate law $v = kh_0[Cr^{VI}]$[diphenylmethane] has been reported for the acetic acid system.[3] This study is concerned with the kinetics of the Cr^{VI} oxidation of a methyl group in the α position to a heterocyclic ring with aqueous sulfuric acid as a solvent. The title compounds are particularly suitable as substrates since they exhibit excellent solubilities in aqueous sulfuric acid and do not decompose even at high acid concentrations. The oxidation leads almost exclusively to the corresponding nicotinic acid *N*-oxides without major complications by side reactions. Furthermore, the use of two substrates of similar structure but with different reactivities toward Cr^{VI} should allow one to discriminate between the effects which are caused by the oxidant and those which are specific for the respective substrate.

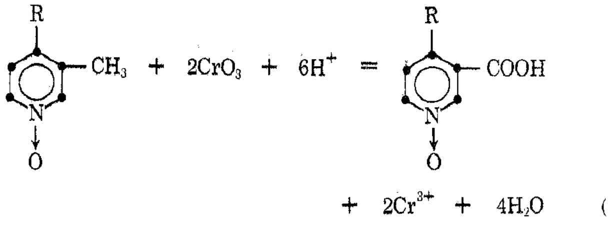
Experimental Section

Chemicals.—Sulfuric acid (Baker) and chromium trioxide (Matheson) were both reagent grade. PNO was synthesized by oxidation of 3-picoline with hydrogen peroxide in acetic acid solution. The product had mp 31–35°. NPNO was obtained by nitration of PNO and purified by recrystallization from toluene. The pure material had mp 137–138°. Nicotinic acid 1-oxide (Aldrich) had mp 258–259° and was used without further purification.

Kinetic Procedure.—The kinetic runs were carried out in a thermostat with a temperature constancy of ±0.1°. Fifty milliliters of a solution of picoline oxide in sulfuric acid of known acidity was mixed with an equal volume of a solution of chromium trioxide in sulfuric acid. In order to minimize heat effects during the mixing, both solutions always had identical acidities. Suitable aliquots were withdrawn at different times and the Cr^{VI} concentration was determined by iodometric titration. If possible, the reaction was monitored to more than 90% completion.

Results

The stoichiometry of the reaction is given by eq 1.



(1)

RPNO = R = H: PNO (3-picoline 1-oxide)
R = NO_2: NPNO (4-nitro-3-picoline 1-oxide)

Oxidation of the aromatic ring is expected to be slow compared to the attack on the methyl group. This is verified by the observation that, with identical reaction conditions, nicotinic acid 1-oxide is oxidized at a rate which is negligible in comparison with the oxidation rate of 3-picoline 1-oxide. It is therefore possible to follow the reaction by the decay of the analytical Cr^{VI} concentration. In order to simplify the kinetic analysis the reaction conditions are always chosen so that $[H^+] \gg [RPNO] \gg [Cr^{VI}]_0$. For $[H_2SO_4] \leq 14\ M$ the kinetics are pseudo first order with respect to Cr^{VI}. The rate constants obtained from the slopes of log $[Cr^{VI}]$ *vs.* time plots are summarized in Table I.

TABLE I[a]
EFFECT OF REACTANT CONCENTRATION ON THE PSEUDO-FIRST-ORDER RATE CONSTANTS

Substrate	$[Cr^{VI}]_0 \times 10^2\ M$	$[RPNO] \times 10^1\ M$	$k_I \times 10^3\ sec^{-1}$	$k_{II} \times 10^2\ M^{-1}\ sec^{-1}$
PNO	0.41	2.50	4.32	1.73
	1.25	2.50	4.15	1.66
	2.50	2.50	3.92	1.57
	2.50	5.00	8.90	1.78
	2.50	1.00	1.58	1.58
	2.50	0.60	0.98	1.63
NPNO	0.40	2.50	1.12	0.448
	1.26	2.50	1.17	0.469
	2.50	2.50	1.21	0.484
	2.50	4.00	1.90	0.475
	2.50	1.00	0.48	0.48
	2.50	0.50	0.23	0.46

[a] $[H_2SO_4] = 10.6\ M$; $T = 45°$.

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(1) D. G. Lee, "Oxidation, Techniques and Applications in Organic Synthesis," Vol. I, R. L. Augustine, Ed., Marcel Dekker, New York, N. Y., 1969.

(2) K. B. Wiberg, "Oxidation in Organic Chemistry," Part A, K. B. Wiberg, Ed., Academic Press, New York and London, 1965.

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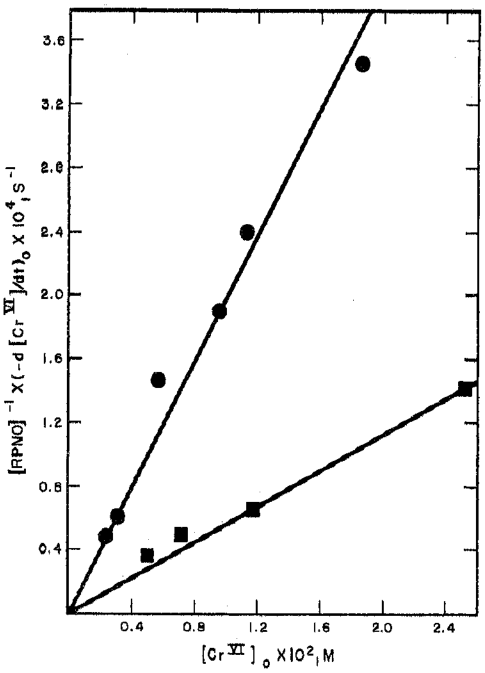

Figure 1.—Estimation of k_{II} from the initial reaction rates: $[H_2SO_4] = 17.7\ M$, $T = 45°$; ●, PNO; ■, NPNO.

Table I shows that for identical reaction conditions PNO is oxidized faster than NPNO. No effect of the initial $[Cr^{VI}]$ on the rate constants is apparent for $4 \times 10^{-3}\ M < [Cr^{VI}]_0 < 2.5 \times 10^{-2}\ M$, indicating that the formation of dimeric Cr^{VI} species is kinetically not important. For $5 \times 10^{-2}\ M < [RPNO] < 5 \times 10^{-1}\ M$ the relation $k_{II} = k_I/[RPNO]$ is obeyed. Therefore, the experimental rate law for $[H_2SO_4] \leq 14\ M$ and constant acidity is given by eq 2.

$$\text{Rate} = k_{II}[Cr^{VI}][RPNO] \qquad (2)$$

For $[H_2SO_4] > 14\ M$ the log $[Cr^{VI}]$ *vs.* time plots are no longer linear. However, evaluation of the reaction order from the initial slopes of the concentration–time curves yields again an order of unity for both Cr^{VI} and the substrate. This indicates that the rate law given by eq 2 is obeyed throughout the entire acidity range examined; however, for $[H_2SO_4] > 14\ M$ its validity is restricted to the initial stage of the reaction. Since a deviation from the uncomplicated pseudo-first-order kinetics occurs only at high acidity, it is probably caused by a species which becomes protonated at $[H_2SO_4] > 14\ M$. Figure 1 shows plots of the reduced initial rates, $[RPNO]^{-1} \times (-d[Cr^{VI}]/dt)_0$, *vs.* $[Cr^{VI}]_0$ for $[H_2SO_4] = 17.7\ M$. The slopes of the straight lines yield second-order rate constants of $2.0 \times 10^{-2}\ M^{-1}\ sec^{-1}$ for PNO and $0.57 \times 10^{-2}\ M^{-1}\ sec^{-1}$ for NPNO. Table II shows the effect of acidity on the rate constants. Up to $[H_2SO_4] = 10\ M$ a strong increase of the rate constants with increasing acid concentration is observed; at acid concentrations higher than that the rate constants become acidity independent.

In Figure 2, log k_{II} is plotted *vs.* the H_0 acidity function.[4] For acidities lower than $H_0 = -5$ these plots are linear with slopes close to unity. At $H_0 = -5.5$ the rate constants for both PNO and NPNO level off; the average plateau values amount to $k_{II} = 1.75 \times 10^{-2}\ M^{-1}\ sec^{-1}$ for PNO and to $k_{II} = 4.9 \times 10^{-3}\ M^{-1}\ sec^{-1}$ for NPNO.

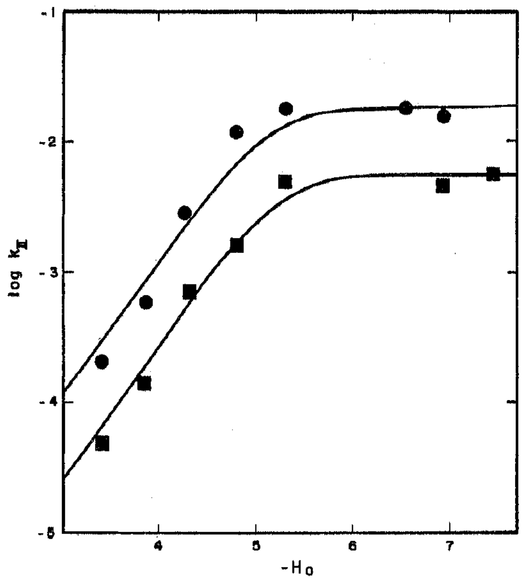

Figure 2.—Acidity dependence of k_{II}. Plot of k_{II} *vs.* H_0: ●, PNO; ■, NPNO.

TABLE II[a]
EFFECT OF ACIDITY ON THE SECOND-ORDER RATE CONSTANTS

$[H_2SO_4]$, M	k_{II}, $M^{-1}\ sec^{-1}$ PNO	k_{II}, $M^{-1}\ sec^{-1}$ NPNO
7.1	1.95×10^{-4}	4.95×10^{-5}
8.0	5.80×10^{-4}	1.51×10^{-4}
8.9	2.75×10^{-3}	7.05×10^{-4}
9.7	1.16×10^{-2}	1.59×10^{-3}
10.6	1.70×10^{-2}	4.69×10^{-3}
12.4	1.75×10^{-2}	
13.3	1.61×10^{-2}	4.40×10^{-3}
14.2		5.70×10^{-3}
17.7[b]	2.0×10^{-3}	5.7×10^{-3}

[a] $[Cr^{VI}]_0 = 1.25 \times 10^{2}\ M$; $[RPNO] = 0.250\ M$; $T = 45°$. [b] The rate constants for this acidity are obtained from the initial reaction rates.

The temperature dependence of the rate constants follows the Arrhenius equation. The rate constants measured at different temperatures are listed in Table III together with the graphically determined activation energies and frequency factors. From these the apparent activation enthalpies and entropies are calculated. For PNO the values $\Delta H^{\ddagger} = 11.7$ kcal/mol and $\Delta S^{\ddagger} = -33.1$ eu are obtained; the corresponding values for NPNO are $\Delta H^{\ddagger} = 13.5$ kcal/mol and $\Delta S^{\ddagger} = -30.2$ eu.

TABLE III[a]
EFFECT OF TEMPERATURE ON THE
PSEUDO-FIRST-ORDER RATE CONSTANTS

Temp, °C	k_I, sec^{-1} PNO	k_I, sec^{-1} NPNO
25	1.03×10^{-3}	
35	2.11×10^{-3}	4.48×10^{-4}
45	3.92×10^{-3}	1.21×10^{-3}
55	7.12×10^{-3}	1.77×10^{-3}
65		3.46×10^{-3}
E	12.3 kcal/mol	14.1 kcal/mol
log A	6.08, sec^{-1}	6.66, sec^{-1}

[a] $[Cr^{VI}]_0 = 2.5 \times 10^{-2}\ M$; $[RPNO] = 0.250\ M$; $[H_2SO_4] = 10.6\ M$.

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(4) M. A. Paul and F. A. Long, *Chem. Rev.*, **57**, 1 (1957).

Discussion

The reaction is first order with respect to Cr^{VI}, which suggests that the oxidizing agent is a monomeric Cr^{VI} species. Since the rate constants are independent of the total Cr^{VI} concentration, the equilibrium concentration of dimeric Cr^{VI} has to be very small. This may be accounted for by the high sulfuric acid concentration present, which favors the formation of sulfatochromate instead of dichromate species.[5]

The shape of the acidity profile shown in Figure 2 indicates the existence of a kinetically important protolytic equilibrium with a pK within the acidity range examined. Alternatively, this may involve the ionization of either a Cr^{VI} species or the substrates. For PNO pK = 1.08 has been reported[6] and a comparable value should be reasonable for NPNO, which means that both substrates are completely protonated throughout the entire acidity range. Since a further protonation of the picoline 1-oxides appears to be unlikely, the shape of the observed acidity profile is probably caused by the protonation of a Cr^{VI} species. This is also supported by the fact that the plateau values of the rate constants are attained at the same acidity regardless whether PNO or NPNO is the substrate which is oxidized.

The acid chromate ion, $HCrO_4^-$, has been reported to oxidize the side chain of alkyl benzenes at elevated temperatures and $5.4 < pH < 7.0$.[7] However, within the acidity range of this study, oxidation by the acid chromate ion can be ruled out, since with $K = 1.68$ for the dissociation of chromic acid at 45° as extrapolated from the data of Tong and Johnson,[8] the equilibrium concentration of the acid chromate ion is negligible. Therefore, the protolytic equilibrium, which is kinetically important, is evidently established between chromic acid, H_2CrO_4, and the chromacidium ion, $H_3CrO_4^+$, with both species probably existing as complexes with sulfuric acid. If the equilibrium constant is defined by eq 3, the analytical Cr^{VI} concentration may be expressed according to eq 4, provided that chromic acid and the chromacidium ion are the only species present.

$$K_1 = [H_2CrO_4]h_0/[H_3CrO_4^+] \tag{3}$$

$$[Cr^{VI}] = [H_3CrO_4^+](1 + K_1/h_0) \tag{4}$$

With $H_3CrO_4^+$ as the oxidizing agent, the true rate law is given by eq 5. From eq 4 one obtains the rate law in terms of the analytical $[Cr^{VI}]$ according to eq 6.

$$\text{Rate} = k_2[H_3CrO_4^+][RPNO] \tag{5}$$

$$\text{Rate} = k_2[Cr^{VI}][RPNO]/(1 + K_1/h_0) \tag{6}$$

From eq 2 and 6 the acidity dependence of the experimental rate constants, k_{II}, is obtained. By means of eq 7 the true rate constants k_2 and the equilibrium constant K_1 may be graphically evaluated.

$$1/k_{II} = 1/k_2 + K_1/k_2h_0 \tag{7}$$

The plot of eq 7 using the k_{II} values from Table II is shown in Figure 3. Straight lines are obtained with slopes of 1.27×10^7 M^2 sec for PNO and of 5.1×10^7 M^2 sec for NPNO. The ordinate intercepts are too small to be evaluated with any degree of accuracy. However, since, for $K_1/h_0 \ll 1$, the experimental rate constants k_{II} become identical with the true rate constants k_2, one may use the plateau values of k_{II} from Figure 2 to obtain an estimate for K_1. Multiplying the plateau values $k_{II} = 1.75 \times 10^{-2}$ M^{-1} sec^{-1} for PNO and $k_{II} = 4.9 \times 10^{-3}$ M^{-1} sec^{-1} for NPNO by the respective slopes of the Figure 3 plots gives $K_1 = 2.2 \times 10^5$ M in the case of PNO and $K_1 = 2.5 \times 10^5$ M in the case of NPNO. The fact that, for both substrates, the equilibrium constants are virtually identical confirms the validity of the proposed mechanism. Independent evidence for the oxidation by a protonated Cr^{VI} species may be derived from the acidity profile obtained with 2-propanol as a substrate.[9] In this case a maximum, rather than a plateau, is observed which is attributed to the existence of two different protolytic equilibria with constants of 2.16×10^5 and 1.51×10^4 M, respectively. The first value agrees with the results of this study and therefore represents the ionization of the Cr^{VI} species; consequently, the second one should be ascribed to the protonation of 2-propanol.

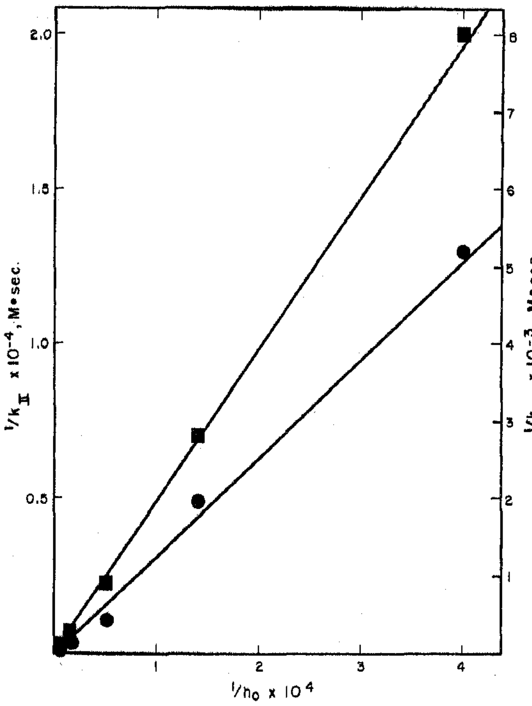

Figure 3.—Acidity dependence of k_{II}. Plot of $1/k_{II}$ vs. $1/h_0$: ●, right-hand scale, PNO; ■, left-hand scale, NPNO.

It should be mentioned that, in the case of the Cr^{VI} oxidation of a series of aliphatic dicarboxylic acids in acetic acid, the plateau values of the individual rate constants are attained at acidities which differ with each substrate, suggesting a kinetic effect caused by the protonation of the substrate rather than the Cr^{VI}.[10] However, it has been shown earlier that in sulfuric acid solution, at very high acidities, the rate constants decrease from these plateau values, again indicating that two independent protolytic equilibria are operative.[11] For $K_1/h_0 \gg 1$, *i.e.*, for low acidities, the rate ex-

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[6] H. H. Jaffé and G. O. Doak, *ibid.*, **77**, 4441 (1955).

[7] D. G. Lee and U. A. Spitzer, *Can. J. Chem.*, **49**, 2763 (1971).

[8] J. Y. P. Tong and R. L. Johnson, *Inorg. Chem.*, **5**, 1902 (1966).

[9] P. Zuman, *Collect. Czech. Chem. Commun.*, **32**, 1610 (1967).

[10] F. Mareš and J. Roček, *ibid.*, **26**, 2389 (1961).

[11] H. G. S. Snethlage, *Recl. Trav. Chim. Pays-Bas*, **54**, 651 (1935); **56**, 873 (1937); **59**, 111 (1940); **60**, 877 (1941).

pression, eq 6, may be written as $v = (k_2/K_1)h_0[\mathrm{Cr^{VI}}][\mathrm{RPNO}]$, which agrees with the rate law reported for the oxidation of diphenylmethane in acetic acid.[3] This indicates that the kinetic behavior is essentially the same in both the aqueous sulfuric and the acetic acid system. However, since the value of K_1 presumably depends on the nature of the anions present,[5] the equilibrium constants are not expected to be identical for the two solvent systems.

Registry No.—$\mathrm{Cr^{VI}}$, 18540-29-9; PNO, 2398-81-4; NPNO, 1078-05-3.

The Effect of Solvent and Cation on the Reaction of Organometallic Derivatives of Indole with Methyl Iodide[1]

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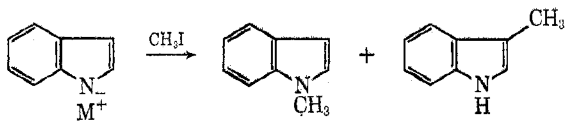
The alkali metal salts of indole behave as typical ambident anions in their reactions with methyl iodide. Indolylmagnesium halides reveal their ambident character only in HMPT which breaks up the tight N–Mg association *via* a 2:1 complex. This observation can be used to reveal structural effects on the reactions of indole Grignard reagents as illustrated by the variation of the C- to N-methylation ratio with the halogen atom of the Grignard reagent.

The rate and position of reaction of ambident anions is markedly affected by a variety of structural and experimental variables.[3,4] Among heterocyclic compounds this phenomenon is most obvious in the chemistry of alkali metal and Grignard derivatives of pyrrole[5] and indole[6] which may react with electrophiles at either carbon or nitrogen. As part of the study of the structure of these derivatives by nmr,[7-9] detailed information on their reactivity as ambident anions was desired. Since such data was already available in the pyrrole series,[5] an examination of the related indole derivatives was undertaken.[1]

The reaction selected for investigation, the methylation of indole salts (eq 1), was known for both the sodium[10] and Grignard[11] derivatives, which yield primarily the N- and C-methylated products 2 and 3, respectively. A methyl halide was chosen rather than an allyl or benzyl halide, since the latter reagents increase the tendency toward reaction at the less electronegative atom of an ambident system[4,12] thereby leading, particularly with the Grignard derivatives, to essentially exclusive C-alkylation.[13,14] By using methyl iodide, however, some reaction on nitrogen was anticipated with the Grignard reagent,[11] thus permitting an examination of C- *vs.* N-alkylation as a function of structural and media effects for both the Grignard and alkali metal derivatives of indole. The results of this study, as summarized in Tables I–III,



(1)

1 2 3

TABLE I

EFFECT OF CATION AND SOLVENT ON THE REACTION OF INDOLE SALTS WITH METHYL IODIDE (EQ 1)

Cation	Per cent of methylation on carbon[a] THF	Et$_2$O	Toluene
K	2		13
Na	12	35	60
Li	44	85	91
MgBr	100		100

[a] ±4% calculated as $[\mathbf{3}/(\mathbf{2}+\mathbf{3})] \times 100$; in several experiments traces (<4%) of 1,3-dimethylindole were also found and counted as C-methylation product **3**.

TABLE II

EFFECT OF SOLVENT COMPOSITION ON REACTION OF INDOLYLMAGNESIUM BROMIDE WITH METHYL IODIDE

Equiv of $\frac{\mathrm{HMPT}}{\mathrm{InMgBr}}$	Vol % HMPT in THF	Per cent of methylation on carbon[a]
0	0	100
1	12.5	100
2	25	97
2.5	22	62
2.8	22	36
3.1	24	30
3.4	22	9
3.9	30	5
4.4	33	0
6.4	50	0
10.3	100	0

[a] See footnote to Table I.

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(1) Taken in part from the Ph.D. Dissertation of J. F. Sebastian, University of California, Riverside, 1965.

(2) To whom inquiries should be directed at the first address.

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