682. *Stability of* N-*Heterocyclic Oxime Derivatives. Part I. Decomposition of* N-*Methylpyridinium* 3- *and* 4-O-*Acetylaldoxime Iodides in Aqueous Solution*

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The kinetics of the decomposition of *N*-methylpyridinium 3- and 4-*O*-acetylaldoxime iodides have been studied in the pH range 4·75—9·5. In the reaction with hydroxyl ions the acetylaldoximes yield the corresponding nitriles as well as the parent oxime. Both rates of reaction are first-order with respect to the activity of the hydroxyl ion and of the acetylaldoxime compound. The ratio nitrile : oxime is different for the two compounds studied. The nitrile formation has the higher energy of activation.

The hydrolysis by water, however, yields oximes only, and the reaction rate follows the second-order law.

For some time, oximes have been known to be reactivators of cholinesterase inhibited by organophosphorus compounds. The reactions between strong nucleophilic reagents such as hydroxamic acid, and oximes, and organophosphorus compounds have been studied in order to elucidate the mechanism of this reactivation.[1-7] It has been shown that the reaction between organophosphorus compounds and oximes occurs in two steps. The first step is generally considered to be a displacement reaction, involving a nucleophilic attack of the reagent on the phosphorus atom (S_N2 mechanism),[6] yielding a phosphylated [8] oxime. The second step is a decomposition of this compound to the corresponding organophosphorus acid and the original oxime or reaction products thereof, depending on the oxime used. The kinetic study of the second step is complicated by the relative rates of the two steps, and difficulties in the preparation of the pure phosphylated oxime.

To obtain information on analogous decomposition reactions, studies of the stability of acetylated oximes were started.

Unsymmetrical oximes and oxime derivatives may exist in *syn*- and *anti*-configurations. Ginsburg and Wilson [9] prepared the 2-, 3-, and 4-pyridinal doximesand *N*-methylpyridinium 3-, and 4-*O*-acetylaldoxime iodides. They assigned the tertiary pyridine oximes, *O*-acetyloximes, and the quarternary *O*-acetyloximes the *syn*-configuration. They claimed, however, to have isolated the quarternary oximes in both isomeric forms. The compounds which were assigned the *syn*-configuration were later studied by Poziomek *et al.*,[10,11] who proved them to be the hydroxy-amine intermediates of the oxime formation. They also succeeded in preparing the true *anti*-form of 4-pyridinaldoxime and *N*-methylpyridinium 4-aldoxime iodide, and therefore assigned to the earlier prepared "*anti*" forms the *syn*-configuration.

Experimental

Materials.—3- and 4-Pyridinaldoxime (PA), and 3- and 4-cyanopyridine (PC) were commercial samples, obtained from Dr. F. Raschig G.m.b.H, Ludwigshafen a. R., and purified by recrystallisation from ethanol–water; *syn*-3-PA, m. p. 151°, and *syn*-4-PA, m. p. 132°.

syn-*N*-Methylpyridinium 3- and 4-*O*-acetylaldoxime iodides (PAM-*O*-Ac) were prepared by

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[1] B. E. Hackley, jun., R. Plaringer, M. Stolberg, and T. Wagner-Jauregg, *J. Amer. Chem. Soc.*, 1955, **77**, 3651.

[2] A. L. Green and B. Saville, *J.*, 1956, 3887.

[3] A. L. Green, G. L. Sainsbury, B. Saville, and M. Stansfield, *J.*, 1958, 1583.

[4] B. E. Hackley, jun., G. M. Steinberg, and J. C. Lamb, *Arch. Biochem. Biophys.*, 1959, **80**, 211.

[5] F. Hobbiger, *Brit. J. Pharmacol.*, 1956, **11**, 295.

[6] L. Larsson, *Svensk. kem. Tidskr.*, 1958, **70**, 405.

[7] G. Aksnes, *Acta Chem. Scand.*, 1960, **14**, 1515.

[8] R. F. Hudson and L. Keay, *J.*, 1960, 1859. (See nomenclature therein.)

[9] S. Ginsburg and I. B. Wilson, *J. Amer. Chem. Soc.*, 1957, **79**, 481.

[10] E. J. Poziomek, D. N. Kramer, W. A. Mosher, and H. O. Michel, *J. Amer. Chem. Soc.*, 1961, **83**, 3916.

[11] E. J. Poziomek, D. N. Kramer, B. W. Fromm, and W. A. Mosher, *J. Org. Chem.*, 1961, **26**, 423.

acylation of 3- and 4-PA (treatment with acetic anhydride) and subsequently quaternised with an excess of methyl iodide in acetone;[9] 3-PAM-*O*-Ac, m. p. 165° and 4-PAM-*O*-Ac, m. p. 156°.

syn-*N*-Methylpyridinium 3- and 4-aldoxime iodides (PAM) were prepared from *syn*-3- and -4-PA by quaternisation with methyl iodide in acetone.[9, 10]

N-Methylpyridinium 3- and 4-nitrile iodides (PCM) were prepared from 3- and 4-PC by quaternisation with methyl iodide in acetone; 3-PCM, m. p. 198° and 4-PCM, m. p. 197°.

Potassium chloride, potassium bromide, and sodium nitrate were AnalaR grade.

Kinetic Measurements.—The rates of reactions were studied by means of an automatic recording titrator. The instrument was a Radiometer Titrator type TTT 1, connected to a Scale Expander type PHA 630 T, Titrigraph type SBR2, and Auto-Burette type ABU1. The electrodes were a Radiometer G 202 b glass electrode and a Radiometer K 401 calomel electrode. The Auto-Burette had a capacity of 2·5 ml. and was filled with 0·1N-sodium hydroxide. The initial volume of the reaction mixture was 250 ml., and the mixture was obtained by mixing the prediluted and preheated reactants at 25 or 35°.

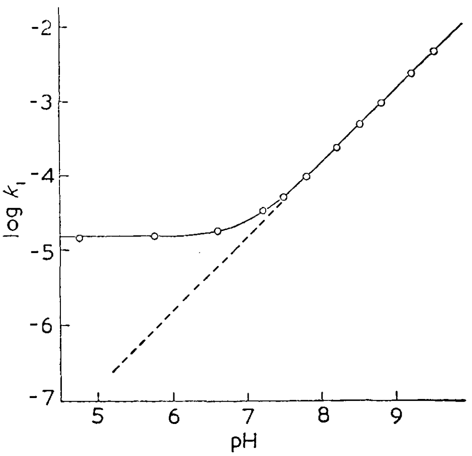

FIGURE 1. The logarithm of the first-order rate constant versus pH of the reaction mixture

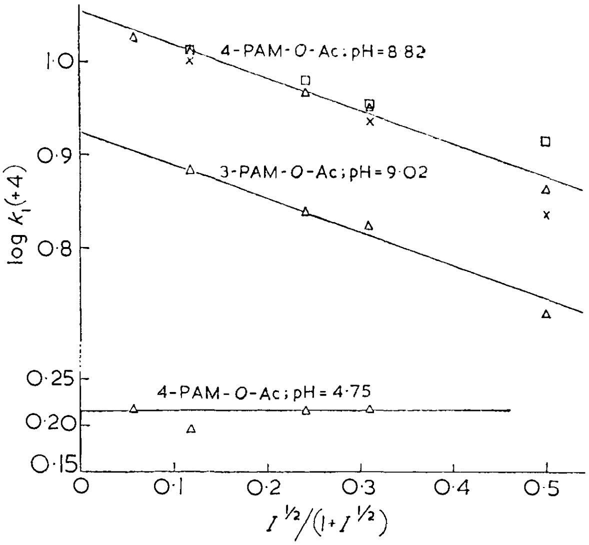

FIGURE 2. The logarithm of the first-order rate constant at 25° against $I^{\frac{1}{2}}/(1 + I^{\frac{1}{2}})$ for the decomposition of 3- and 4-PAM-*O*-Ac at different pH values in the presence of various salts: KCl, △; $NaNO_3$, □; KBr, ×. *I* is the total ionic concentration.

The temperature of the jacketed reaction vessel was kept constant within ±0·03° by a circulating water-bath. During the reaction, the fluctuation of pH was generally less than ±0·005 pH units. Deviations in pH caused by stirring the reaction mixture were taken into account. This effect, probably due to disturbance of the diffusion potential of the calomel electrode, was dependent on the salt concentration, and amounted to 0·03 pH units for the lowest ionic concentration.

The pH-meter was standardised before each run against 0·01 mole $l.^{-1}$ sodium tetraborate and 0·05 mole $l.^{-1}$ potassium hydrogen phthalate. The pH values of the standard buffer solutions and the ionic product of water, pK_w, at different temperatures were taken from Larsson.[12]

Dissociation Constants.—These were determined by potentiometric titration of the oximes (0·005 mole $l.^{-1}$) with 0·1N-sodium hydroxide at 25 and 35°. The p*K* values were calculated according to the Henderson–Hasselbalk equation from the pH value at the half-neutralisation point: 3-PAM, $pK^{25} = 9{\cdot}04$, $pK^{35} = 8{\cdot}94$; 4-PAM, $pK^{25} = 8{\cdot}36$, $pK^{35} = 8{\cdot}25$.

[12] L. Larsson, *Acta Chem. Scand.*, 1957, **11**, 1131.

Analysis of the End-products.—The qualitative composition of the end-products was determined by infrared spectroscopy. The aqueous solution of a completed kinetic run of 4-PAM-*O*-Ac at pH 9·0 and 35° was adjusted to pH 5·5 and freeze-dried. A sample of the yellow residue was mulled with Nujol, and its infrared spectrum was recorded over the range 4000—400 cm.$^{-1}$ on a Perkin-Elmer Infracord 337. The spectrum was compared with the spectra of samples of 4-PAM, 4-PCM, and sodium acetate, and the reaction products were identified as a mixture of these compounds. The absorption band at 2242 cm.$^{-1}$, assigned as the C≡N stretch of 4-PCM, was very evident. The same method was used for the determination of the end-products of the corresponding reaction with 3-PAM-*O*-Ac. In addition to the absorption bands of 3-PAM and sodium acetate, a band at 2246 cm.$^{-1}$, assigned as the C≡N stretch frequency of 3-PCM, was positively identified.

The quantitative composition of the reaction products was determined by u.v. spectroscopy using a Beckman DU spectrophotometer. Solutions of 3- and 4-PAM (5×10^{-5} mole l.$^{-1}$ in 0·1N-NaOH) were prepared and their spectra recorded at 25° (Figures 3 and 4). The absorption bands at 290 and 337 mμ followed Beer's law and were suitable for the quantitative determinations of the oximes. The spectra of solutions of 3- and 4-PCM (5×10^{-5} mole l.$^{-1}$ in 0·1N-NaOH) were recorded after the solution had stood for 30 min. (Figures 3 and 4). The absorption bands at 348 and 262 mμ followed Beer's law and were suitable for the quantitative determination of the nitriles. The quantitative composition of the reaction products of the completed kinetic runs (initial concentration 5×10^{-4} mole l.$^{-1}$ PAM-*O*-Ac) was determined by comparing the light absorption of a sample, diluted ten times with 0·1N-sodium hydroxide, with standard curves. The standard curves were obtained by using composite solutions of PAM and PCM having constant total concentration (5×10^{-5} mole l.$^{-1}$ in 0·1N-NaOH).

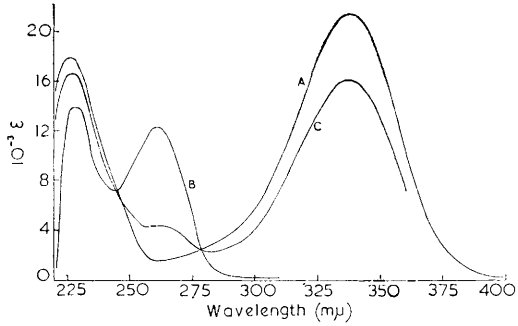

FIGURE 3. Spectra of: (A) 4-PAM, (B) 4-PCM, and (C) end-products of a run of 4-PAM-*O*-Ac at pH 9·0, [KCl] = 0·01 mole l.$^{-1}$, T = 25°, in 0·1N-NaOH. The concentrations were 5×10^{-5} mole l.$^{-1}$, T = 25°.

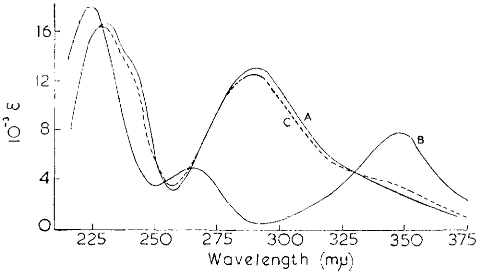

FIGURE 4. Spectra of: (A) 3-PAM, (B) 3-PCM, and (C) end-products of a run of 3-PAM-*O*-Ac at pH 9·0, [KCl] = 0·01 mole l.$^{-1}$, T = 25°, in 0·1N-NaOH.

The spectra of 3- and 4-PCM in 0·1N-sodium hydroxide are very different from their spectra in neutral solution, and are probably the spectra of their reaction products, rapidly formed in the strong alkaline solution. The spectrum of 4-PCM indicates that this is a mixture of the corresponding amide and *N*-methyl-4-pyridone, which have absorption bands at 226 and 262 mμ, respectively. Extraction of a sample of 4-PCM in 0·1N-sodium hydroxide with chloroform gave, after evaporation of the solvent, a dark oil identified as *N*-methyl-4-pyridone by comparison of its infrared spectrum with that of an authentic sample. The reaction products of 3-PCM were not determined.

RESULTS AND DISCUSSION

Using the titrator as a pH-stat for the reaction mixture, the alkali consumption recorded represents the acid production as a function of time. The curves were treated according to the method given by Guggenheim.[13] Straight lines were obtained, indicating that acid production is a pseudo-first-order reaction. This was established over the pH range 47·5—9·5. The initial concentration of the *O*-acetyl compound was generally 5×10^{-4} mole l.$^{-1}$, and that of the added salt 0·01 mole l.$^{-1}$. Owing to the low rate of reaction at

[13] E. A. Guggenheim, *Phil. Mag.*, 1926, **2**, 538.

TABLE 1

Experimental data for the decomposition of 4- and 3-PAM-*O*-Ac in 0·01 mole l.$^{-1}$ KCl at 25°

	4-PAM-*O*-Ac		3-PAM-*O*-Ac	
pH	$k_1 \times 10^5$ (sec.$^{-1}$)	log k_1	$k_1 \times 10^5$ (sec.$^{-1}$)	log k_1
9·50	480·0	0·680—3	—	—
9·20	241·0	0·381—3	114·0	0·056—3
8·80	97·5	0·988—4	46·0	0·662—4
8·50	49·0	0·690—4	23·0	0·361—4
8·20	24·7	0·392—4	11·2	0·049—4
7·80	9·88	0·994—5	4·58	0·660—5
7·50	5·30	0·724—5	2·57	0·410—5
7·20	3·70	0·570—5	1·05	0·200—5
6·60	1·85	0·267—5	0·852	0·930—6
5·75	1·65	0·217—5	0·604	0·780—6
4·75	1·55	0·190—5	0·671	0·826—6

pH < 6, the initial concentration was raised tenfold and the calculation of the first-order rate constant, k_1, made from the initial velocity. The pH dependence of the rate of decomposition at 25° can be seen from Figure 1 and Table 1.

The influence of different salts of various concentrations on the rate of reaction is a function of the pH value. In Figure 2 the logarithm of the first-order rate constant is plotted against an expression for the total ionic concentration, I, of the reaction mixture according to the theory of Debye and Hückel[14] (see equation 5).

Assuming the rate of acid production to be equal to that of the disappearance of the *O*-acetyloxime compound, (Ac), we have:

$$d[H^+]/dt = -d[Ac]/dt \qquad (1)$$

This rate will generally be influenced by hydroxyl ions, water molecules and hydronium ions. From Figure 1 it can be seen that, above pH 4·75, the acid catalysis is comparatively small and can be neglected. The decomposition rate, salt effects taken into account, may then be expressed by the Brönsted–Bjerrum equation:[15]

$$-\frac{d[Ac]}{dt} = k_2^{OH} \cdot \frac{f_{OH} \cdot f_{Ac}}{f_{OH^\ddagger}}[OH][Ac] + k_2^{H_2O}\frac{f_{H_2O} \cdot f_{Ac}}{f_{H_2O^\ddagger}}[H_2O][Ac] \qquad (2)$$

where k_2^{OH} and $k_2^{H_2O}$ represent second-order rate constants, and f the activity coefficient of the indicated species. In equation (2), the product f_{OH} . [OH] is related to the measured pH by:

$$f_{OH} \cdot [OH] = \frac{Kw}{\text{antilog}\ (-pH)} = a_{OH}.$$

The activity coefficient of water, f_{H_2O}, and the activity coefficient of the activated complex (zwitterion), $f_{OH^\ddagger}$, may be taken as unity. In addition, f_{Ac} is expected to be approximately equal to $f_{H_2O^\ddagger}$. Equation (2) may thus be written:

$$-\frac{d[Ac]}{dt} = (k_2^{OH} \cdot f_{Ac} \cdot a_{OH} + k_2^{H_2O} \cdot [H_2O]) \cdot [Ac], \qquad (3)$$

where a_{OH} is the activity of the hydroxyl ions. Our experimental data are consistent with equation (3) and therefore:

$$k_1 = k_2^{OH} \cdot f_{Ac} \cdot a_{OH} + k_2^{H_2O} \cdot [H_2O]. \qquad (4)$$

The activity coefficient of the PAM-*O*-Ac compound, f_{Ac}, can be expressed by the Debye–Hückel[14] equation, which at 25°, using the estimated value of 4·3 Å as mean distance of approach, reduces to:

$$-\log f_{Ac} = 0{\cdot}3582\ I^{\frac{1}{2}}/(1 + I^{\frac{1}{2}}), \qquad (5)$$

where I is the total ionic concentration.

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[14] J. Kielland, *J. Amer. Chem. Soc.*, 1937, **95**, 1675.

[15] J. N. Brönsted, *Z. phys. Chem.*, 1922, **102**, 169.

TABLE 2

The titrimetric second-order rate constants (l. mole^{-1} sec.$^{-1}$) at different temperatures

Compound	25°		35°	
	k_2^{OH}	$k_2^{H_2O}$	k_2^{OH}	$k_2^{H_2O}$
4-PAM-*O*-Ac	170·7	$2{\cdot}72 \times 10^{-7}$	325·0	$5{\cdot}62 \times 10^{-7}$
3-PAM-*O*-Ac	80·0	$1{\cdot}09 \times 10^{-7}$	143·5	$2{\cdot}27 \times 10^{-7}$

The values of k_2^{OH} and $k_2^{H_2O}$ calculated from equation (4) (cf. Table 1) are given in Table 2. If, in the kinetic runs, the hydrolysis of 3- and 4-PAM-*O*-Ac yields oximes and acetic acid only,[9] the consumption of sodium hydroxide, equal to the total acid production, H$^+$, can be calculated from:

$$H^+ = \mathrm{Ac}_{\mathrm{total}} \cdot \left(\frac{A}{1 + A} + \frac{B}{1 + B}\right) \qquad (6)$$

where $\mathrm{Ac}_{\mathrm{total}}$ = total amount of hydrolysed PAM-*O*-Ac,

$A = \mathrm{antilog}\,(-\mathrm{p}K_{\mathrm{oxime}} + \mathrm{pH} + \log f_{\mathrm{oxime}})$,

and $B = \mathrm{antilog}\,(-\mathrm{p}K_{\mathrm{AcOH}} + \mathrm{pH} - \log f_{\mathrm{AcO^-}})$

However, our measurements showed the acid production to be less than the amount calculated from equation (6). This led us to undertake a more detailed examination of the end-products of the reactions. Spectrophotometric measurements in the range 215—400 mμ in 0·1N-sodium hydroxide indicated that, in addition to oximes, nitriles were also formed (see Figures 3 and 4, and Scheme 1).

SCHEME 1

$$\text{Py}\,(+)\text{-}O\text{-acetylaldoxime} + \text{OH}^- \begin{array}{ll} \nearrow \text{Py}\,(+)\text{-oxime} & \text{Reaction (I)} \\ \searrow \text{Py}\,(+)\text{-nitrile} & \text{Reaction (II)} \end{array}$$

The quantitative composition of the end-products was taken from standard curves based on light absorption measurements of known solutions at suitable wavelengths. Table 3 clearly demonstrates that the water hydrolysis yields the oximes only, and that the ratio of nitrile to oxime in the alkaline hydrolysis is constant for different salt concentrations and pH values, but dependent on the temperature.

TABLE 3

End-products of the decomposition of 3- and 4-PAM-*O*-Ac in aqueous potassium chloride at 25° (*: 35°) and at different pH values

Compound	Nitrile (%)	Oxime (%)	pH	KCl (mole l.$^{-1}$)
4-PAM-*O*-Ac	26·2	73·8	(0·1N-NaOH)	—
	24·7	75·2	9·20	10^{-2}
	26·6	73·4	8·80	,,
	25·7	74·3	8·20	,,
	0	100·0	5·75	,,
	24·0	76·0	8·80	5×10^{-1}
	30·5 *	69·5 *	8·20	10^{-2}
3-PAM-*O*-Ac	5	95	(0·1N-NaOH)	—
	5	95	9·02	10^{-1}
	5 *	95 *	9·00	,,

In competing reactions of this type, [cf. reactions (I) and (II) Scheme 1], the ratio of the rate constant is equal to the ratio of reaction products formed, and independent of the stage of the reaction:

$$\frac{k_2^{II}}{k_2^{I}} = \frac{[\text{nitrile}]}{[\text{oxime}]}. \qquad (7)$$

Further we have:

$$k_2^{OH} = k_2^{I} + k_2^{II}. \qquad (8)$$

From equations (7) and (8), and the experimental data (Tables 2 and 3), the individual second-order constants, k_2^{I} and k_2^{II}, may be computed. In Table 4 the values of k_2^{I} and k_2^{II} at 25° and 35° are listed, in addition to other kinetic data. The energy of activation, E_a, and the pre-exponental factor, A, were calculated from the Arrhenius equation:

$$k_2 = A \exp(-E_a/\boldsymbol{R}T). \tag{9}$$

The entropy of activation was calculated according to the Eyring theory of activated intermediates.[16]

$$k_2 = \mathrm{e} \cdot \frac{kT}{h} \cdot \exp(-E_a/\boldsymbol{R}T) \,.\, \exp(\Delta S^{\ddagger}/\boldsymbol{R}). \tag{10}$$

The value of $\Delta S^{\ddagger} = -1{\cdot}5$ e.u. for the nitrile formation seems rather high. Reactions between oppositely charged ions are, however, known to have high entropies of activation. Another example of this is the elimination reaction of 2-phenylethyldimethylsulphonium bromide and sodium hydroxide in aqueous solution, where $\Delta S^{\ddagger}$ was found to be —4, 2 e.u.[17] A more detailed discussion of the kinetic data will be given in Part II.

TABLE 4

Kinetic data for the decomposition of 3- and 4-PAM-O-Ac in the reaction with hydroxyl ions and water molecules

Compound	Type of reaction	k_2 (l. mole^{-1} sec.$^{-1}$)		E_a (kcal. mole^{-1})	A (l. mole^{-1} sec.$^{-1}$)	$-\Delta S^{\ddagger}$ (e.u.)
		25°	35°			
4-PAM-*O*-Ac	I(OH)	128·0	226·0	10·4	$5{\cdot}2 \times 10^9$	16·1
	II(OH)	42·7	99·1	15·4	$7{\cdot}9 \times 10^{12}$	1·5
3-PAM-*O*-Ac	I(OH)	76·0	136·4	10·7	$5{\cdot}1 \times 10^9$	16·1
	II(OH)	4·0	—	—	—	—
4-PAM-*O*-Ac	I(H_2O)	$2{\cdot}72 \times 10^{-7}$	$5{\cdot}62 \times 10^{-7}$	13·2	$1{\cdot}4 \times 10^3$	46·1
3-PAM-*O*-Ac	I(H_2O)	$1{\cdot}09 \times 10^{-7}$	$2{\cdot}27 \times 10^{-7}$	13·4	$0{\cdot}78 \times 10^3$	47·3

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[16] H. Eyring, *J. Chem. Phys.*, 1935, **3**, 107; S. Glasstone, K. J. Laidler, and H. Eyring, " The Theory of Rate Processes," McGraw-Hill, New York, 1941, p. 199.

[17] W. H. Saunders, jun., C. B. Gibbons, and R. A. Williams, *J. Amer. Chem. Soc.*, 1958, **80**, 4099.