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Studies on Organosulfur Compounds. XIII.[1] The Substituent Effect on the Acid Dissociation of Thioanilides and on the Rate of Oxidation by Hydrogen Peroxide[2]

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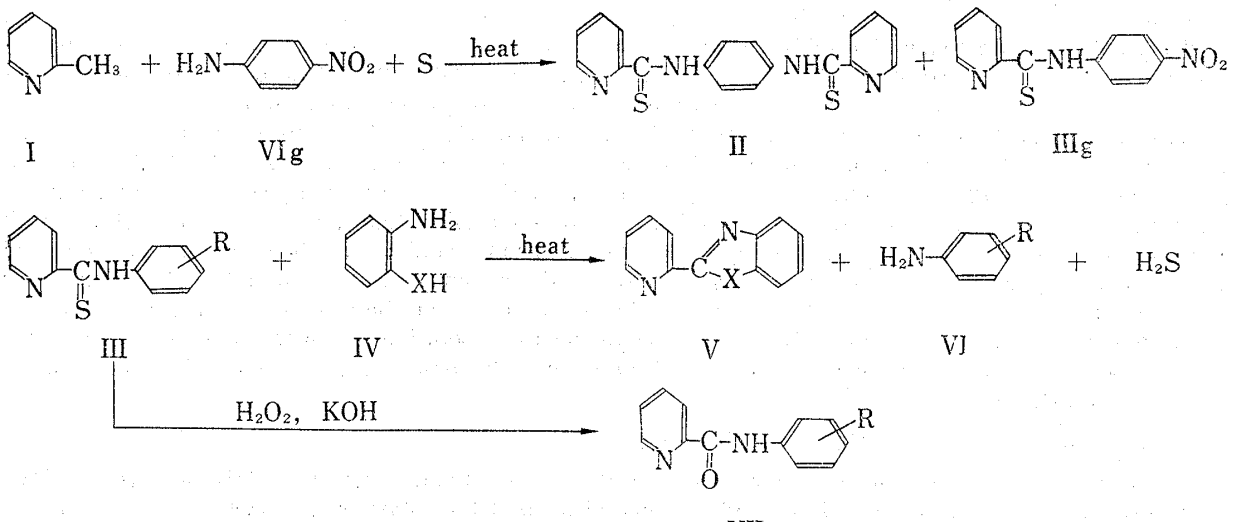
2-Thiopicolinoanilide and its *meta*- and *para*-substituted derivatives were synthesized. These thioanilides were converted readily to the corresponding O-amides by hydrogen peroxide in alkaline solution. The oxidations of the thiopicolinoanilides by use of a large excess of hydrogen peroxide were kinetically carried out and the activation energies were determined. The small increase in the rates is attributed primarily to the electron-attracting effect of the substituents. On the other hand, these acid dissociation constants were measured in 20% ethanol–water at 20° by spectrophotometry and fitted the Hammett equation with the use of σ ($\rho=1.4$), but the *p*-carboethoxy group deviates from the straight line because of its much lower pK_a (8.42) value. In the reaction between 2-thiopicolinoanilides and *o*-aminophenol, the yield of 2-(2-pyridyl)benzoxazole increased with increasing electron–attracting effect of the substituent in the order of the observed acidity of thioanilides.

Since the reaction of thioanilide-type compounds with aromatic primary amines easily affords amidine compounds by dehydrosulfuration,[4] reactions between 2-thiopicolinoanilides and *ortho*-substituted bifunctional compounds (*o*-aminophenol, *o*-phenylenediamine) were



R = a: H, b: *p*-CH_3, c: *p*-OCH_3, d: *p*-OC_2H_5, e: *p*-Cl, f: *p*-$COOC_2H_5$, g: *p*-NO_2, h: *m*-CH_3, i: *m*-Cl, j: *m*-CF_3, k: *m*-$COOC_2H_5$

X = x: NH, y: O

Chart 1

1) Part XII: T. Hisano, M. Ichikawa, A. Nakagawa, and M. Tsuji, *Chem. Pharm. Bull.* (Tokyo), **23**, 1910 (1975).
2) A part of this work was presented at the Kyushu Local Meeting of the Pharmaceutical Society of Japan, Nagasaki, July 1975.
3) Location: *Oe-honmachi, Kumamoto, 862, Japan.*
4) P.E. Miller, G.L. Oliver, J.R. Dann, and J.W. Gates, Jr., *J. Org. Chem.*, **22**, 664 (1957); H. Saikachi and T. Hisano, *Yakugaku Zasshi*, **81**, 64 (1961); T. Hisano, *Yakugaku Zasshi*, **81**, 69 (1961).

carried out and it was found that cyclization occurred by liberation of hydrogen sulfide and aniline group, resulting in the formation of imidazole and oxazole rings.[5] Liberation of the anilide group from thiopicolino-anilides thereby suggested the effect of a substituent group in the anilide on the rate of cyclization. This finding led us to examine the contributory factors of these substituents. We have synthesized and purified representative homologs in several series of thioanilides: thioquinald-,[6] 4-thiopicolino-, and 2-thiopicolino-anilides having a substituent group in the aniline ring. The present paper reports the preparation of these compounds and the substituent effects on their acid dissociation constants, on the hydrogen peroxide oxidation of 2-thiopicolino-anilides to the O-amides, and on the oxazole cyclization with *o*-aminophenol.

Experimental

Preparation of Thioanilides——Thioanilides were prepared by the methods already described (Table I) except for 2-thiopicolino-*p*-nitroanilide (IIIg) which was prepared by the following procedure.

A mixture of 0.25 mol of I, 0.25 mol of VIg, and 0.62 mol of sulfur was heated in an oil bath at 185° for 5 hr. After the reaction was over, the reaction mixture was allowed to stand at room temperature. The resulting solid was extracted with EtOH (500 ml) under refluxing for 30 min and the extract was concentrated to separate a crystalline mass, which extracted with 10% KOH in a water bath and the alkaline solution was neutralized with dil. HCl. The precipitated crystals were collected by suction, washed with H_2O, dried, and recrystallized from EtOH, giving IIIg (mp 138—139°) as orange yellow needles in 12% yield. *Anal.* Calcd. for $C_{12}H_9O_2N_3S$: C, 55.59; H, 3.50; N, 16.21. Found: C, 55.70; H, 3.22; N, 16.06. Mol. wt. Calcd.: 259. Found: 259 (by mass analysis).

The above insoluble solid in hot EtOH was extracted with 10% KOH in a water bath and the alkaline solution was neutralized with dil. HCl. The precipitated crystals were collected by suction, washed with H_2O, dried, and recrystallized from a large amount of EtOH, giving N,N′-di(2-thiopicolinoyl)-*p*-phenylene diamine (mp 220—221.5°) as light yellow needles in 40% yield (based on amount of *p*-nitroaniline started). *Anal.* Calcd. for $C_{18}H_{14}N_4S_2$: C, 61.69; H, 4.03; N, 15.99. Found: C, 61.48; H, 4.18; N, 15.87. Mol. wt. Calcd.: 350. Found: 350 (by mass analysis).

Spectrophotometric Evaluation of Dissociation Constants——The acid dissociation constants of thioanilides were evaluated spectrophotometrically using a Hitachi EPS-3T at 20°±1 according to the previous report.[7] A Hitachi-Horiba Model F-5 type pH meter was used for pH measurements.

Stock solutions of these compounds (2×10^{-4} M for IX, X, and XI; 2.5×10^{-4} M for the rest) were prepared by dissolving a weighed sample of each thioanilide in 500 ml of EtOH and diluting to 1000 ml with H_2O. Spectra solutions (4×10^{-5} M for IX, X, and XI; 5×10^{-5} M for the rest) were then prepared by diluting one part of the stock solution with four parts of buffer solution containing 12.5% EtOH, respectively. In all cases, the alcohol content of the spectra solution was 20%. The thioanilide was dissolved in a buffered acid solution to ensure that all the solute was in the undissociated form and in a solution of 0.1 N NaOH in order to give complete dissociation of the solute. Other solutions were made in buffers whose pH were near to the pK_a of the compound. By measuring the absorbance of the above solutions (with the same total concentration of the solute) at the wavelength of maximum absorbance of the dissociated form, the pK_a was calculated by use of equation (1)[7-9]

$$pK_a = pH - \log (D_{[H^+]} - D_A)/(D_B - D_{[H^+]}) \qquad (1)$$

where $D_{[H^+]}$ is the absorbance of the buffered solution at a given pH and D_A and D_B are the absorbance of the solutions of the completely undissociated and dissociated form of the solute, respectively. In the range of pH 9 to 12, a mixture of 0.05 M $Na_2B_4O_7$ and 0.1 N NaOH was used as a buffer solution, while for pH<9 a mixture of 0.05 M $Na_2B_4O_7$ and 0.1 N HCl was adopted.[10]

The pK_a values reported in Table II are the average of at least four determinations. The measurement is accurate to within 1%.

5) T. Hisano and M. Ichikawa, *Yakugaku Zasshi*, **91**, 727 (1971).
6) T. Hisano and M. Ichikawa, *Chem. Pharm. Bull.* (Tokyo), **22**, 2051 (1974).
7) T. Hisano and M. Ichikawa, *Chem. Pharm. Bull.* (Tokyo), **22**, 1923 (1974).
8) E. Pelizzetti and C. Verdi, *J. Chem. Soc.* (Perkin II), **1973**, 808; J.P. Idoux, U.S. Cantwell, J. Hinton, S.O. Nelson, and P. Hollier, *J. Org. Chem.*, **39**, 3946 (1974).
9) H.H. Jaffe and M. Orchin, "Theory and Application of Ultra Violet Spectroscopy," John Wiley & Sons, Inc., New York, 1966, p. 560.
10) L. Meites, "Handbook of Analytical Chemistry," McGraw-Hill, London, 1963, section 11-7.

Kinetic Measurement——The rate of oxidation of 2-thiopicolinoanilides (III) by use of a large excess (20 times in the molarity) of H_2O_2 was followed by spectrophotometry. Since thiopicolino–anilides shown in Table I are only slightly soluble in H_2O, reaction mixtures always contained 20% EtOH to assist dissolution. Stock solution (0.06 M) of III were made up in 1 N KOH ethanol–aq. (1: 1) soln. Hydrogen peroxide stock solution (3%) was prepared just before use by diluting commercial hydrogen peroxide (30%) with H_2O.

a) Preparation of Sample: In a typical rate run, a 20 ml glass-stoppered volumetric flask was immersed in a thermostatted water bath and cooled to within a few degrees of the reaction temperature. A 1.5 ml aliquot of the 2-thiopicolinoanilide stock solution was pipetted into the flask and then a thermometer was inserted into the solution. After the temperature of the thioanilide solution had been adjusted to within $\pm 0.5°$ of a desired temperature, the reaction was initiated by the addition of a 2 ml aliquot of the hydrogen peroxide stock solution which had been cooled to 5° so that the reaction temperatures of 17, 27, and 37° could be attained by a rise in temperature upon the addition in each case. After the desired interval, during which the temperature variation was held to $\pm 0.5°$ or better, the reaction was quenched by adding as rapidly as possible 2 ml of 0.5 N HCl (cooled to below 5°) to adjust to pH 6—8 and then 0.1 g of MnO_2 to decompose the remaining H_2O_2 below 5° in an ice bath. After 3 min with shaking occasionally, during which time the remaining H_2O_2 was decomposed, the reaction mixture was extracted two times with 7 ml each of $CHCl_3$. The extract was collected and evaporated *in vacuo* below 40°. The residue was dissolved in 2 ml of EtOH and submitted to the following analysis. It was necessary to repeat the above operation for each point of the rate plots.

b) Thin–Layer Chromatographic Analysis and Measurement of Absorption Spectrum of the Remaining 2-Thiopicolinoanilide: Thin–layer chromatography prepared in this laboratory was applied to the separation and detection of 2-thiopicolinoanilides. Silica–layer G-10 (Nakarai Chemicals, LTD.) containing 10% $CaSO_4$ was evenly mixed with a slight excess of 2 volumes of H_2O by vigorous shaking and made into a thin–layer. A 0.01 ml aliquot of the sample was applied to the starting line of this plate, in which the 0.01 ml was conveniently divided in five parts on the starting line to improve tailing of the spots. The plate was developed by ascending technique with a solvent system of petr. benzin–benzene–$CHCl_3$ (3: 1: 1) until the solvent front migrates to about 10 cm at 20°. After development, the plate was air dried, and the yellow spot of 2-thiopicolinoanilide at *Rf* value, 0.80—0.85, was eluted with 6 ml of EtOH at about 50°. The ultraviolet spectrum of the eluate was measured on a Hitachi EPS-3T and concentrations of 2-thiopicolinoanilides were determined from a calibration curve with considerable accuracy, ranging in concentration from 2.0 to 7.0×10^{-5} M. The oxidations were followed over 3 to 5 minutes periods at temperatures of 17.0, 27.0, and 37.0°, providing coverage of 30 to 70% of the reactions. Logarithmic plots of the decrease rate of thioanilides against time gave a straight line, from which the rates of the oxidations of thioanilides were calculated.

c) Oxidation Products: To a solution of 0.01 mol of III in 100 ml of 5% KOH ethanol–aq. (1: 1) soln. 60 ml of 3% H_2O_2 aq. soln. was added dropwise at room temperature with stirring. After 1 hr reaction period crystals separated from the reaction solution were collected by suction and purified by recrystallization, giving products (VII) in 90% yield as collected in Table III.

Reaction between 2-Thiopicolinoanilides (III) and *o*-Aminophenol——The procedure was similar to that previously described.[5]

Without a solvent, 0.01 mol of III was fused with 0.01 mol of *o*-aminophenol at 150° for 10 hr. After the reaction was over, the reaction mixture was allowed to stand at room temperature. The resulting solid was dissolved with 20 ml of $CHCl_3$ at room temperature with shaking for 5 min, and then applied to the top of a column packed with 70 g of Al_2O_3 (300 mesh). From the first effluent fraction with 150 ml of $CHCl_3$, 2-(2-pyridyl)benzoxazole was obtained. The solvent was evaporated completely *in vacuo* and the residue was recrystallized from 25% aq. EtOH, giving 2-(2-pyridyl)benzoxazole (mp 107°)[5] as colorless needles.

In order to observe the progress of the formation of oxazole ring at regular intervals, after application to the above column the obtained residue was treated with 3 N NaOH at 60° for 3 min. The insoluble product was collected by suction and purified in the same manner as above. All of reactions showed the heighest yield at 10 hr reaction period.

Results and Discussion

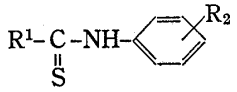
The compounds investigated, their melting points, and analytical data are listed in Table I.

The Substituent Effect on Acid Dissociation

Little is known on acidic properties of thioamide structures attached to a heterocycle such as pyridine, quinoline, or thiazole, although there is a report on the determination of acidities of aromatic thioamide series by potentiometric titration in dimethyl sulfoxide–water.[11]

11) W. Walter, H.W. Meyer, and A. Lehmann, *Liebigs Ann. Chem.*, **1974**, 765.

Table I. Structures and Analytical Data of the Thioanilides

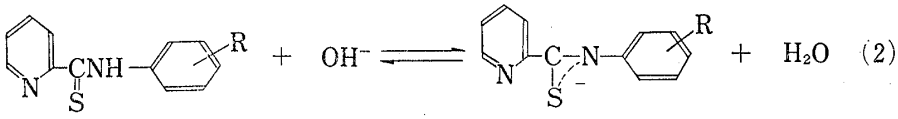


Compd. No.	R^1	R^2	mp (lit.) (°C)	Appearance (recryst. solvent)	Analysis (%) Calcd. (Found) C	H	N
IIIa	2-pyridyl	H	54 (54)[a]				
IIIb	2-pyridyl	*p*-CH_3	102 (101.5—102.5)[b]				
IIIc	2-pyridyl	*p*-OCH_3	101—103 (102—103)[a]				
IIId	2-pyridyl	*p*-OC_2H_5	82 (81—82.5)[a]				
IIIe	2-pyridyl	*p*-Cl	85—87 (87)[c]				
IIIf	2-pyridyl	*p*-$COOC_2H_5$	97 (96—97)[b]				
IIIg	2-pyridyl	*p*-NO_2	138—139	orange yellow needles (EtOH)	55.59 (55.70)	3.50 (3.22)	16.21 (16.06)
IIIh	2-pyridyl	*m*-CH_3	79 (79—80)[d]				
IIIi	2-pyridyl	*m*-Cl	99 (96—98)[d]	orange yellow prisms (EtOH)	57.95 (57.90)	3.65 (3.51)	11.26 (11.35)
IIIj	2-pyridyl	*m*-CF_3	96 (92—94)[d]	orange yellow prisms (EtOH)	55.31 (55.20)	3.21 (3.32)	9.92 (9.76)
IIIk	2-pyridyl	*m*-$COOC_2H_5$	155 (155—157)[e]				
VIII	4-pyridyl	H	180 (180—182)[b]				
IX	2-quinolyl	H	109 (109—110)[f]				
X	2-quinolyl	*m*-CH_3	117 (116—117)[g]				
XI	2-benzothiazolyl	H	156 (155—156)[h]				

a) H. Saikachi, T. Hisano, and S. Yoshina, *Yakugaku Zasshi*, **74**, 1318 (1954)
b) H. Saikachi and T. Hisano, *Chem. Pharm. Bull.* (Tokyo), **7**, 349, 716 (1959)
c) T. Hisano and Y. Yabuta, *Chem. Pharm. Bull.* (Tokyo), **22**, 316 (1974)
d) T. Hisano and Y. Yabuta, *Chem. Pharm. Bull.* (Tokyo), **21**, 511 (1973)
e) T. Hisano and M. Tamayama, *Yakugaku Zasshi*, **93**, 1356 (1973)
f) H. Saikachi and T. Hisano, *Chem. Pharm. Bull.* (Tokyo), **8**, 51 (1960)
g) T. Hisano and M. Ichikawa, *Chem. Pharm. Bull.* (Tokyo), **22**, 2051 (1974)
h) H. Saikachi and T. Hisano, *Yakugaku Zasshi*, **79**, 1305 (1959)

In order to examine the influence of a substituent group of the thioanilides on the acidities, we have, therefore, designed to measure their acid dissociation constants by spectrophotometry, using ethanol to assist dissolution. The ultraviolet absorption spectra of 2-thiopicolinoanilide (IIIa) in ethanol–aqueous buffers (1:5) of various pH are shown in Fig. 1. The spectra in the pH 9.28 to 9.70 pass through one isosbestic point (*ca.* 240 mμ). The same behavior was observed with other thioanilides in such limited pH ranges. The pK_a, λ_{max}, and log ε values of the undissociated form of the thioanilides are listed in Table II.

Figure 2 shows that the pK_a data for 2-thiopicolinoanilides substituted in the aniline ring fit the Hammett equation (3) where K_H is the equilibrium constant of unsubstituted 2-thiopicolinoanilide (IIIa) in the reaction (2).



(2)

$$\log K/K_H = \rho\sigma \qquad (3)$$

The slope of the linear plot is 1.4. Only the point for 2-thiopicolino-*p*-carboethoxyanilide (IIIf) deviates considerably from the straight line in Fig. 2 because of its much lower pK_a (8.42). The pK_a of 4′-nitro-2-thiopicolinoanilide (IIIg) was not possible to be determined under this condition owing to its low solubility in ethanol–aqueous solutions, although the

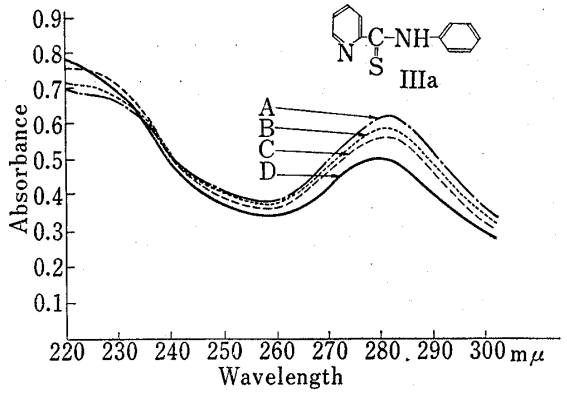


Fig. 1. Absorption Spectra of Compound(IIIa) at Different pH Values [IIIa] 5.0×10^{-5}M; 20°. pH: A, 9.28; B, 9.49; C, 9.70; D, *ca.* 12

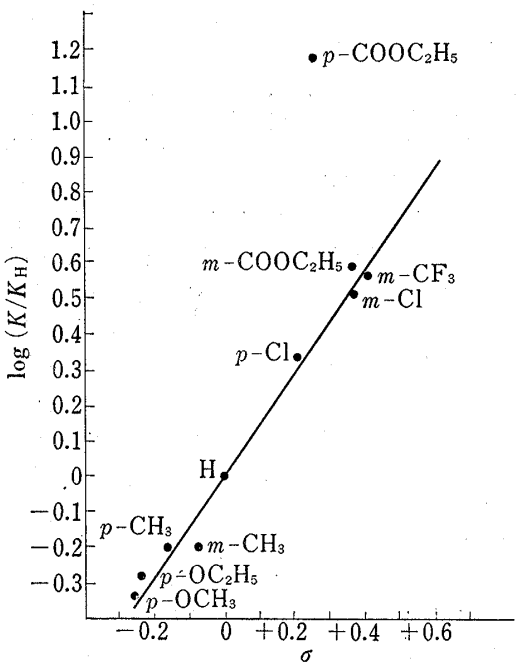
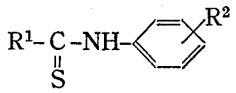


Fig. 2. log (K/K_H) as a Function of Substituent Effect for the Substituted 2-Thiopicolinoanilides (III)

TABLE II. Dissociation Constants and Spectrophotometric Data of the Thioanilides at 20° ±1



Compd. No.	R^1	R^2	λ_{max} (mμ)	log ε_{max}	p$Ka^{a)}$
IIIa	2-pyridyl	H	281	4.08	9.67
IIIb	2-pyridyl	*p*-CH_3	283	4.10	9.89
IIIc	2-pyridyl	*p*-OCH_3	284	4.09	10.00
IIId	2-pyridyl	*p*-OC_2H_5	284	4.09	9.96
IIIe	2-pyridyl	*p*-Cl	283	4.04	9.34
IIIf	2-pyridyl	*p*-$COOC_2H_5$	283	4.18	8.42[b)]
IIIh	2-pyridyl	*m*-CH_3	282	4.05	9.87
IIIi	2-pyridyl	*m*-Cl	282	4.09	9.17
IIIj	2-pyridyl	*m*-CF_3	282	4.04	9.10
IIIk	2-pyridyl	*m*-$COOC_2H_5$	282	4.12	9.08[b)]
VIII	4-pyridyl	H	283	4.16	9.97
IX	2-quinolyl	H	320	4.10	10.20
X	2-quinolyl	*m*-CH_3	322	4.10	10.54
XI	2-benzothiazolyl	H	327	4.15	9.03

a) in 20% ethanol–water
b) The ester is stable against hydrolysis to the corresponding acid[5] under the condition used.

nitro group could be of benefit in increasing the acidity. The results indicate that the dissociation occurs at the acidic site (–CS–NH–) of these compounds and the withdrawing power of substituent groups in the anilide, such as carboethoxy, trifluoromethyl, and nitro group, increases the acidity.

On the other hand, in comparison with other heterocycle groups (VIII—XI), 2-benzothiazolyl group (XI) showed a much lower pK_a value (9.03) and 2-pyridyl (IIIa) a lower value

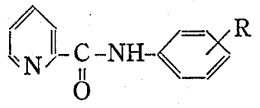
(9.67) than 4-pyridyl (VIII). This result appears to fall in line with the scope of charge density of pyridine nucleus.[12]

Oxidation of 2-Thiopicolinoanilides in Alkaline Solution by Hydrogen Peroxide

Although catalyzed hydrolysis of thioamide in moderately concentrated aqueous mineral acid has led initially to both benzamide and thiobenzoic acid,[13] 2-thiopicolinoanilides are stable against hydrolysis in both acidic and alkaline media. However, 2-thiopicolinoanilides in alkaline solution are fairly readily oxidized with hydrogen peroxide at room temperature to afford the corresponding 2-picolinanilides.

It has been reported that oxidations of some Bis(chlorobenzyl) sulfide by hydrogen peroxide in isopropyl alcohol lead to sulfone through a sulfoxide intermediate, following the second order rate law.[14] The oxidation of 2-thiopicolinoanilides by hydrogen peroxide is also expected to follow the bimolecular reaction kinetics. However, our work was conducted with a large excess of hydrogen peroxide in 1N potassium hydroxide ethanol–aqueous (1: 1) solution to observe the pseudo-first-order rate in hope that the results would be useful in clarifying the effect of a substituent group in the aniline ring on the thioamide group. The oxidations were carried out at temperatures of 17.0, 27.0, and 37.0° in 300 seconds and the remaining 2-thiopicolinoanilides were measured by spectrophotometry after isolation by the thin-layer chromatography, in which the thioanilides (III) were always determined as a yellow spot at *Rf* value, 0.80—0.85, while the oxidation products, 2-picolinanilides (VII), were viewed at *Rf* value, 0.14—0.15, under ultraviolet light. The oxidation products (VII) were prepared in a large scale reaction as described in Experimental and compound (VIIa) was identical in

TABLE III. Chemical Properties of 2-Picolinanilides(VII)



Compd.	R	mp (°C)	Appearance (recryst. solvent)	Formula	Analysis (%) Calcd. (Found) C	H	N
VIIa	H	75—76.5[a]	colorless needles (petr. benzine)	$C_{12}H_{10}ON_2$	72.73 (72.70)	5.05 (4.91)	14.14 (14.32)
VIIb	*p*-CH_3	105—106	colorless needles (pert. benzine)	$C_{13}H_{12}ON_2$	73.58 (73.69)	5.66 (5.62)	13.20 (13.44)
VIIc	*p*-OCH_3	93—94.5	colorless needles (petr. benzine)	$C_{13}H_{12}O_2N_2$	68.42 (68.23)	5.26 (5.32)	12.28 (12.26)
VIId	*p*-OC_2H_5	118—120	colorless needles (benzene-petr. benzine)	$C_{14}H_{14}O_2N_2$	69.41 (69.58)	5.82 (5.97)	11.56 (11.60)
VIIe	*p*-Cl	138.5—140	colorless plates (benzene-petr. benzine)	$C_{12}H_9ON_2Cl$	61.95 (62.19)	3.90 (4.04)	12.04 (11.80)
VIIg	*p*-NO_2	236.5	light yellow needles (benzene)	$C_{12}H_9O_3N_3$	59.25 (59.44)	3.70 (3.72)	17.28 (17.39)
VIIi	*m*-Cl	91—92.5	colorless needles (petr. benznie)	$C_{12}H_9ON_2Cl$	61.95 (62.05)	3.90 (3.95)	12.04 (11.74)
VIIj	*m*-CF_3	107—108.5	colorless plates (petr. benzine)	$C_{13}H_9ON_2F_3$	58.64 (58.89)	3.38 (3.36)	10.52 (10.68)

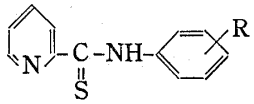
a) reported,[14] 72—74°

12) H.C. Brown, D.H. McDaniel, and O. Hafliger, "Determination of Organic Structures by Physical Methods," Vol. 1, Academic Press, New York, 1955, p. 597.
13) A.J. Hall and D.P.N. Satchell, *J. Chem. Soc.* (Perkin II), **1974**, 1077.
14) C.G. Overberger and R.W. Cummins, *J. Am. Chem. Soc.*, **75**, 4250, 4783 (1953).

all respects with 2-picolinanilide prepared from picolinic acid according to Engler.[15] The structural assignment of VII (similar to that of VIIa) is based on the satisfactory elemental analysis and the infrared spectrum [1650—1700 cm^{-1} (C=O)]. These results are shown in Table III.

Arrhenius plots by use of the rate data determined at temperatures of 17.0, 27.0, and 37.0° gave a straight line, from which activation energies were calculated. The rate constants at the three temperatures and activation energies are collected in Table IV.

Table IV. Rate Constants and Activation Energies(E) for the Oxidation of 2-Thiopicolinoanilides in Alkaline Solution by Hydrogen Peroxide



Compound No.	R	Rate constants, k_1(sec.$^{-1}$) 17°	27°	37°	Rel. rate (37°)	E (kcal·mol^{-1})
IIIa	H	2.83	5.75	12.83	1.00	12.4
IIIb	*p*-CH_3	2.84	4.45	11.60	0.91	12.5
IIIe	*p*-Cl	3.57	5.29	14.55	1.13	11.9
IIIg	*p*-NO_2	4.12	7.88	17.16	1.34	11.3
IIIi	*m*-Cl	3.45	7.05	14.25	1.11	12.4

Changes in the electron-attracting group from Cl to NO_2 have little further effect upon the relative rate, the effect increasing in the order (37°): *p*-CH_3 (0.91)<H (1.00)<*m*-Cl (1.11)< *p*-Cl (1.13)<*p*-NO_2 (1.34), accompanied by a small difference in the activation energies. No completely satisfactory quantitative explanation for these low values has been given, but this would be suggested by the fact that the effects are not so strong (ρ: 1.4) for the acidic dissociations as implied by Fig. 2 and the thione group is in the more distant position from such a substituent.

Substituent Effects on the Oxazole Cyclization with *o*-Aminophenol

Substituent effects in the reaction between 2-thiopicolinoanilides (III) and *o*-aminophenol as an *ortho*-substituted bifunctional compound have been examined; some data are shown in Fig. 3. The yield of 2-(2-pyridyl)benzoxazole increases with increasing electron-attracting power of a substituent group in the anilide. The available evidence indicates that the yield increases moderately in the order of the observed acidity of thioanilides. The *p*-carboethoxy group expectedly showed a much increasing effect. However, when 2-thiopicolino-*p*-nitro-anilide (IIIg) was used, the benzoxazole was barely obtained in 40% yield for five hours and the elongation of the reaction time did not lead to the increase of product. It

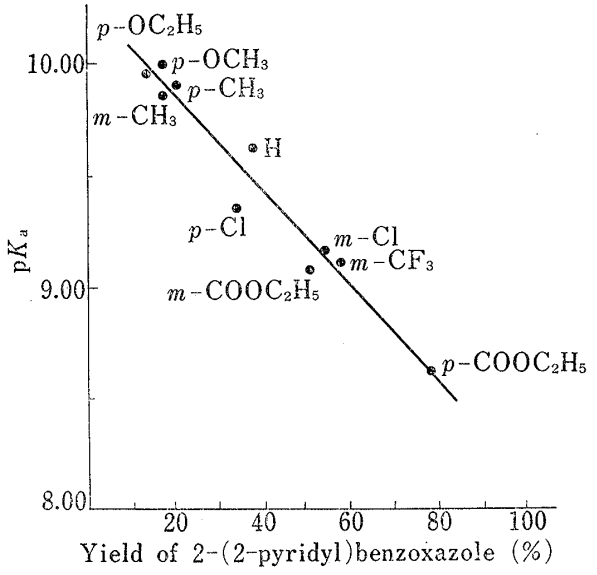


Fig. 3. Correlation between the Acidity of Thioanilides and the Yield of 2-(2-Pyridyl)benzoxazole in the Reaction of 2-Thiopicolinoanilides with *o*-Aminophenol

15) C. Engler, *Chem. Ber.*, **27**, 1786 (1894).

appears that the evolution of hydrogen sulfide in this reaction disturbs the effect of the *p*-nitro group.

In one interpretation, since the rates of oxidations of thione groups in 2-thiopicolinoanilides vary much less with structure, substituent effects must be attributed primarily to a contribution with making the electron deficient center in the anilide for the liberation of aniline group in the transition state, in which the liberation of aniline ring would be in the rate determining step. It appears possible that the observed pK_a values of thioanilides are important in understanding the effect of substituents on the orientation taken by entering substituents in this selected area.

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