Reactivity of Thieno[2,3-*b*]pyridine towards Electrophilic Substitution

By **Sergio Alunni** and **Sergio Clementi,*** Istituto di Chimica Organica, Università di Perugia, 06100 Perugia, Italy
LeRoy H. Klemm, Department of Chemistry, University of Oregon, Eugene, Oregon 97403, U.S.A.

A kinetic study of hydrogen exchange and nitration in thieno[2,3-*b*]pyridine permitted evaluation of standard rate constants for reaction of the protonated species. Comparison of these results with reactivities of quinoline benzo[*b*]thiophen, and other heteroaromatic compounds is made in terms of electronic effects of the heteroatoms.

RECENTLY, there has been considerable interest in the measurement of reactivity towards electrophilic substitution of bicyclic aromatic compounds.[1-4] In particular, results for benzo[*b*]furan and benzo[*b*]thiophen in acylations and halogenations allowed quantitative evaluation of the ' annelation ' effect due to the fusion of a benzene ring to a five-membered heteroaromatic system. Reactivity is always decreased at the 2-position and increased at the 3-position for the bicyclic system, with respect to the monocyclic heteroaromatic system.[1] Results for the formylation of indoles are also consistent with these relationships.[2]

A kinetic study of deuteriation of pyrrolopyridines (or azaindoles)[4] showed that further deactivation results from the inclusion of a protonated aza-group in the six-membered ring. In connection with our previous studies on electrophilic substitution into bicyclic heteroaromatic systems[1,2,4] and on the chemistry of thienopyridines[5-7] we report here the first quantitative data on the reactivity of thieno[2,3-*b*]pyridine. This compound undergoes deuteriation,[5] nitration,[6] and halogenation[7] in the thiophen ring, mainly at the 3-position, but the available data are insufficient to permit an estimation of the relative reactivity of the thienopyridine molecule with respect to other heteroaromatic systems.

Two features make hydrogen exchange and nitration in sulphuric acid particularly suitable electrophilic reactions for studying heteroaromatic substrates, and both are due to the acidity dependence of the rate constants. (a) The slope of a plot of log k against acidity (' rate profile ') constitutes the best available criterion for establishing whether a protonated or a non-protonated species is undergoing reaction.[8,9] (b) For both reactions, kinetic rates can be obtained for substrates of widely differing reactivities by choosing the appropriate concentrations of sulphuric acid to use. Thus two measures of susceptibility to electrophilic attack are available for a wide variety of aromatic and heteroaromatic substrates, provided that experimental data can be evaluated for standard conditions.

Recently Katritzky and his co-workers developed a procedure for obtaining standard rate constants (k_0)

---

[1] S. Clementi, P. Linda, and G. Marino, *J. Chem. Soc.* (*B*), 1971, 79.

[2] S. Clementi, P. Linda, and G. Marino, *J.C.S. Chem. Comm.*, 1972, 427.

[3] A. R. Katritzky and C. D. Johnson, *Angew. Chem. Internat. Edn.*, 1967, **6**, 608.

[4] A. El-Anani, S. Clementi, A. R. Katritzky, and L. Yakhontov, *J.C.S. Perkin II*, 1973, 1072.

[5] L. H. Klemm, C. E. Klopfenstein, R. Zell, D. R. McCoy, and R. A. Klemm, *J. Org. Chem.*, 1969, **34**, 347.

[6] L. H. Klemm, R. Zell, I. T. Barnish, R. A. Klemm, C. E. Klopfenstein, and D. R. McCoy, *J. Heterocyclic Chem.*, 1970, **7**, 373.

[7] L. H. Klemm, R. E. Merrill, and F. H. W. Lee, *J. Heterocyclic Chem.*, 1974, **11**, 535, and previous papers of the series.

[8] A. El-Anani, J. Banger, G. Bianchi, S. Clementi, C. D. Johnson, and A. R. Katritzky, *J.C.S. Perkin II*, 1973, 1065.

[9] A. R. Katritzky, B. Terem, E. V. Scriven, S. Clementi, and H. O. Tarhan, *J.C.S. Perkin II*, 1975, 1600.

for acid-catalysed exchange reactions at pH 0 and T 100°.[8] Later a similar procedure was suggested for comparing nitration data (k_2^0) under the standard conditions of H_0 −6.6 and T 25°.[9] Accordingly the standard rate constants for >100 species were recorded.[8,9]

Our kinetic studies on deuteriation and nitration of thieno[2,3-*b*]pyridine were accomplished under experimental conditions previously used for similar compounds.[8,9] Hydrogen exchange was followed by n.m.r. spectrometry, by observing the disappearance of the signal relative to the exchanged proton, whereas nitration was followed by u.v. spectrophotometry, by observing the increase in absorption due to the 3-nitro-product. Control experiments on thieno[2,3-*b*]pyridine, as well as its deuteriated derivatives and the 3-nitro-product, showed an absence of side reactions which could interfere with the analytical methods used.

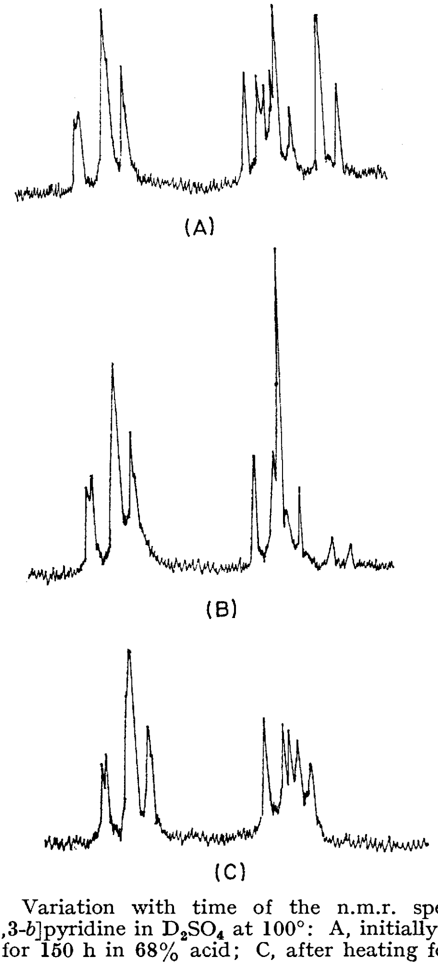


FIGURE 1 Variation with time of the n.m.r. spectrum of thieno[2,3-*b*]pyridine in D_2SO_4 at 100°: A, initially; B, after heating for 150 h in 68% acid; C, after heating for 30 h in 93% acid

RESULTS AND DISCUSSION

Hydrogen Exchange.—On heating at 100° in 61—85% D_2SO_4, thieno[2,3-*b*]pyridine underwent smooth exchange of 3-H. Further reaction was observed at the 2-position on protracted heating in 85—96% D_2SO_4. Figure 1A shows the initial n.m.r. spectrum of the substrate. In Figure 1B, exchange is almost complete at the 3-position, and in Figure 1C is almost complete at the 2-position also. The first-order rate constants are recorded in Table 1 and the rate profiles are plotted in Figure 2. Statistical analysis of these correlations gives linear regression slopes of 0.67 and 0.83 (at confidence levels >99.5% for both slopes and intercepts) for exchange at C-3 and -2, respectively. These large positive values clearly indicate a majority species reaction. Since the pK_a value for thieno[2,3-*b*]pyridine in water is 2.75,[10] and can be estimated as 2.35 in deuteriated media,[8] the exchange reaction must occur on the conjugate acid of the thienopyridine.

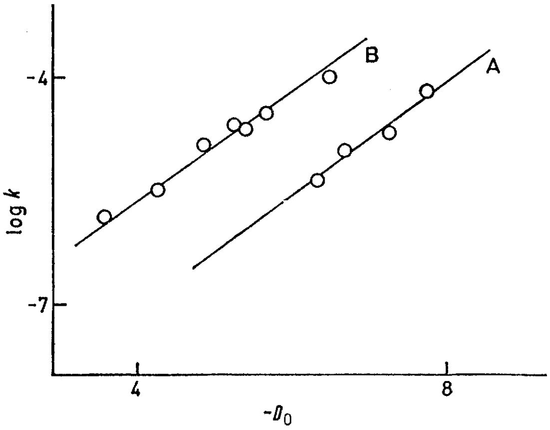


FIGURE 2 Rate profiles for deuteriodeprotonation of thieno-[2,3-*b*]pyridine at 100°: A, for 2-H; B, for 3-H

TABLE 1

Pseudo-first-order rate constants for hydrogen exchange of thieno[2,3-*b*]pyridine in deuteriosulphuric acid at 100°

D_2SO_4 (%)	$-D_0$ (100°)	$10^5k/s^{-1}$	$-\log k$
(i) Exchange of the 3-proton			
61.1	3.97	0.159	5.799
66.8	4.66	0.352	5.454
71.9	5.26	1.33	4.876
75.2	5.66	2.68	4.572
76.3	5.79	2.23	4.653
78.5	6.06	4.13	4.385
78.9	6.10	4.26	4.371
85.6	6.88	11.6	3.937
(ii) Exchange of the 2-proton			
84.1	6.72	0.378	5.422
87.5	7.09	1.31	4.883
92.4	7.63	2.08	4.681
96.2	8.14	7.22	4.142

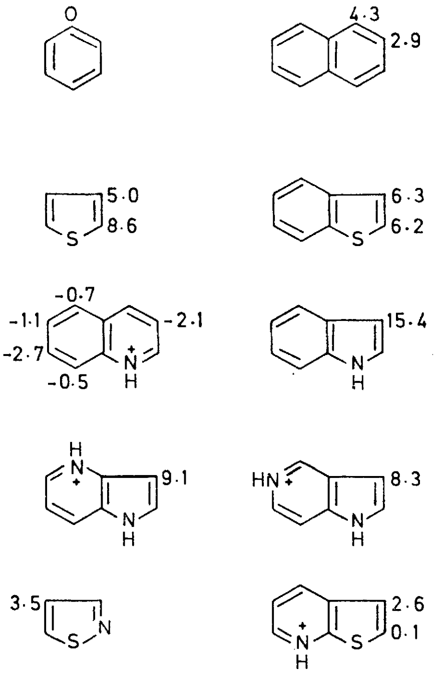
Application of the standard procedure [8] is very simple in this case, since it requires only the acidity extrapolations to D_0 0. The standard rate constants (log k_0) are then given by the intercepts, −8.45 (k_0 3.58 × 10^{-9}) and −10.93 (k_0 1.18 × 10^{-11}), respectively, for deuteriodeprotonation at positions 3 and 2.

Knowledge of the standard rates enables quantitative comparisons to be made between the reactivities of protonated thieno[2,3-*b*]pyridine and other aromatic

---

[10] L. H. Klemm and R. D. Jacquot, *J. Electroanalyt. Chem. Interfacial Electrochem.*, 1973, **45**, 181.

and heteroaromatic substrates. The difference between the logarithm of the standard rate constant of a substrate and that of benzene (log k_0 —11),[11] taken as the reference compound, gives the logarithm of the partial rate factor (log *f*) for the substrate. Values of log *f* for benzene (*f* taken as 1), for the 2- and 3-positions of thieno[2,3-*b*]pyridine, and for designated positions of various other substrates [4,8,11-15] are collected in Scheme 1.



Scheme 1

The data on reactivity of benzothiophen were not measured directly, because of the low solubility of this substrate in D_2SO_4. Instead, they were calculated by combining kinetic data available for protiodetritiation of benzothiophen in trifluoroacetic acid [16] with the suggested quantitative relationship between the two exchange reactions,[13] to give the estimated standard rates in D_2SO_4 of —4.7 for attack at C-3 and —4.8 for attack at C-2.

The decrease in reactivity due to the replacement of a CH group by a protonated aza-group is very large: thienopyridinium cation is nearly 4 log units less reactive than benzothiophen at position 3 and *ca.* 6 log units less reactive at position 2. The magnitude of this decrease is similar to that observed in other bicyclic systems: position 6 of quinolinium ion is 4 log units less reactive than position 2 of naphthalene and position 8 of quinolinium ion is 4.8 log units less reactive than position 1 of naphthalene. Neither the 6- nor the 8-position in quinoline can exhibit direct conjugative interaction with protonated nitrogen. In fact, when the position undergoing electrophilic attack is of conjugative type with the heteroatomic group, the decrease in reactivity is enhanced (*e.g.* C-7 of quinolinium ion is 5.6 log units less reactive than C-2 of naphthalene).

In bicyclic systems where five- and six-membered rings are fused no position in the six-membered ring is of the conjugative type with respect to position 3, while positions 4 and 6 can interact directly with position 2. Since most of these systems, including thienopyridine, react at C-3, comparison with other bicyclic systems is allowed only when positions of non-conjugative type are considered. Accordingly, ignoring inductive effects, one expects the isomeric azaindoles to exhibit the same reactivity. Effectively this is observed, for the range of reactivities is <1 log unit in the three cases investigated (see Scheme 1 and ref. 4). The higher reactivity (by 6 log units) of the azaindoles (as compared to thienopyridine) can be ascribed to the higher reactivity of pyrrole than thiophen.[17] However, the azaindoles are 6—7 log units less reactive than indole. Hence, deactivation by the protonated aza-group is more effective in the azaindoles than in thienopyridine.

Nevertheless, it is difficult to interpret the reactivities of bicyclic aromatic systems on a rigorous quantitative basis because of the variability of inter-ring electronic effects.[18] The main result of the fusion of a pyridinium ring is deactivation at both positions of the five-membered ring, as noted for the azaindoles.[4] This same deactivation is found in the thienopyridinium ion where reactivity is lowered (from that of thiophen) by 8.5 log units at C-2, and even by 2.4 log units at C-3. In contrast, the reactivity of position 2 is decreased while that of 3 is increased on fusion of a benzene ring to that of thiophen (see Scheme 1 and ref. 1).

A comparison with benzothiophen shows that the 7-aza-substituent causes a much greater deactivation at the 2-position than at the 3, although it is conjugated with neither; 2-substitution may be relatively disfavoured because of the juxtaposition of two positive charges in the Wheland intermediate.*

No direct evidence can be given on the reactivity of thienopyridine as a free base. Even at the lower acidities used in this study, the slope of the rate profile clearly indicates a majority species reaction. However, the free base should be more reactive (by several log units) than its conjugate acid, as reasoned by analogy with the measured system, *N*-methylpyrazole (Δ log units 6.4),[15] and an estimate for the pyridine system (Δ log units 9).[14] A comparison of the reactivities of thienopyridinium ion (at C-3) with that of isothiazole, reacting as a free base,[14] shows that deactivation by the

---

* A referee is thanked for suggesting this explanation.

[11] J. Banger, C. D. Johnson, A. R. Katritzky, and B. R. O'Neill, *J.C.S. Perkin II*, 1974, 394.

[12] S. Clementi, C. D. Johnson, and A. R. Katritzky, *J.C.S. Perkin II*, 1974, 1294.

[13] S. Clementi and A. R. Katritzky, *J.C.S. Perkin II*, 1973, 1077.

[14] S. Clementi, P. P. Forsythe, C. D. Johnson, A. R. Katritzky, and B. Terem, *J.C.S. Perkin II*, 1974, 399.

[15] S. Clementi, P. P. Forsythe, C. D. Johnson, and A. R. Katritzky, *J.C.S. Perkin II*, 1973, 1675.

[16] R. Baker, C. Eaborn, and R. Taylor, *J.C.S. Perkin II*, 1972, 97.

[17] G. Marino, *Adv. Heterocyclic Chem.*, 1971, **13**, 235.

[18] S. Clementi, P. Linda, and C. D. Johnson, *J.C.S. Perkin II*, 1973, 1250.

protonated aza-group in the fused six-membered ring is almost equally effective with that of a non-protonated aza-group included in the same five-membered ring.

No modification of the signal for 5-H in the n.m.r. spectrum of thieno[2,3-*b*]pyridine was observed. It is estimated that position 5 must be at least 1 000 times (3 log units) less reactive than position 2. This low reactivity of the pyridine ring is expected on the basis of results for 4-methyl-7-azaindole,[4] where position 5 is *ca.* 8 times less reactive than position 2 despite activation by the *o*-methyl group.

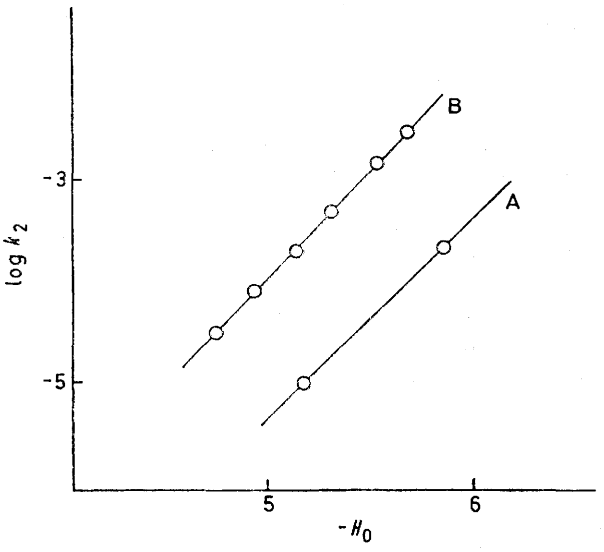


FIGURE 3 Rate profiles for nitration of thieno[2,3-*b*]pyridine at C-3: A, at 40°; B, at 60°

Nitration.—Nitration of thieno[2,3-*b*]pyridine gives only the 3-nitro-derivative. Kinetic data which were obtained from u.v. measurements are recorded in Table 2 and plotted as rate profiles in Figure 3. The rate profile at 60° shows a very good correlation (r 0.999, s_{est} 0.02, confidence level >99.9%) and a slope of 2.1. This slope[9] indicates that thieno[2,3-*b*]pyridine also reacts as the conjugate acid in the nitration reaction. Conversion of the kinetic data to standard conditions (H_0 −6.6, T 25°) was made in two stages: first the linear rate profile at 60° was extrapolated to standard acidity (log k_2 −0.62), and then correction to standard temperature (log k_2^0 −3.31) was made by use of $\Delta\bar{H}^{\ddagger}$ = 35 kcal mol^{-1}. The value of k_2^0 applies only to reactivity at C-3.

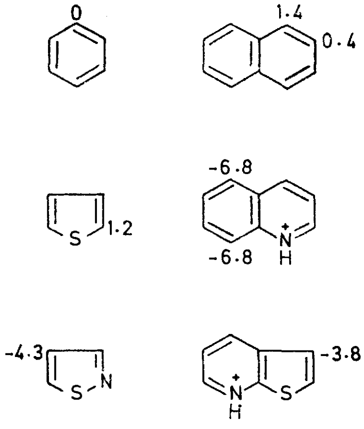
TABLE 2

Observed second-order rate constants for nitration of thieno[2,3-*b*]pyridine in sulphuric acid

H_2SO_4 (%)	$-H_0(T)$	10^4k_2/l mol^{-1} s^{-1}	$-\log k_2$
(i) Reaction at 60°			
66.5	4.77	0.300	4.523
67.8	4.95	0.766	4.115
69.2	5.14	1.95	3.711
70.5	5.32	4.55	3.342
72.1	5.54	14.2	2.848
73.3	5.71	29.5	2.530
(ii) Reaction at 40°			
67.8	5.21	0.101	4.995
72.1	5.88	2.20	3.657

Scheme 2 records the logarithms of the partial rate factors for nitrations of some relevant compounds.[9,19] Unfortunately, benzothiophen is missing since its nitration has not yet been studied kinetically. Again the standard rate constant of benzene (log k_2^0 0.45)[9] is taken as a reference, with log f = 0. The first striking difference observed on comparing Schemes 1 and 2 is that the thienopyridinium ion is some 400 times as reactive as benzene in deuteriation, but some 6 000 times less reactive in nitration. This reversal in order seems to be another example of the recent observation[20] that there is no simple correlation between the standard rates of the two reactions, *i.e.* that there is no unique order of susceptibility of individual ring positions towards electrophilic attack.

Another observation limits the general use of nitration data. This is the proximity of some individual rates to the encounter rate, which corresponds to a reactivity *ca.* 40 times higher than that of benzene.[19] As a consequence all compounds usually known to be more reactive than benzene undergo nitration at a levelled rate (log f *ca.* 2).[19] Thiophen and naphthalene (particularly at C-1) are relevant examples. Hence correlation of reactivities in nitration with structure is justified only for compounds with reactivities far below that of benzene. Thus, it seems pertinent to note that the reactivity of the thienopyridinium ion is comparable to that of isothiazole and *ca.* 1 000 times as large as that of quinolinium ion, in agreement with the hydrogen exchange data.



SCHEME 2

From the reactivity data in Table 2 one can calculate thermodynamic parameters for thienopyridine; either from data at constant H_0 (to give $\Delta\bar{H}^{\ddagger}$ and $\Delta\bar{S}^{\ddagger}$), or from data at constant % H_2SO_4 (to give $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$). Attention was recently focused on the difference between the two types of parameters; and an algebraic relation-

---

[19] A. R. Katritzky, S. Clementi, and H. O. Tarhan, *J.C.S. Perkin II*, 1975, 1624.

[20] S. Clementi, A. R. Katritzky, and H. O. Tarhan, *Tetrahedron Letters*, 1975, 1395.

ship between them was derived[9] [equation (1)] where m is the slope of the rate profile and K measures the

$$\Delta H^{\ddagger} = \Delta H^{\ddagger} + 4.574\ mK \qquad (1)$$

dependence of H_0 on temperature.[21] Moreover, it was suggested that a mean value of $\Delta\bar{H}^{\ddagger}$, 35 kcal mol^{-1}, could be taken for nitration of any compound, since most of the variation in reaction rate is included in the $\Delta\bar{S}^{\ddagger}$ term, while $\Delta\bar{H}^{\ddagger}$ remains nearly constant.[9] Application of the Eyring equation to the thienopyridine data (at 60 and 40°) gives $\Delta H^{\ddagger}$ values of 21.7 and 20.0 kcal mol^{-1} and $\Delta S^{\ddagger}$ values of 10.7 and 11.4 cal mol^{-1} K^{-1} at 67.8 and 72.1% H_2SO_4, respectively. From equation (1), one then finds $\Delta\bar{H}^{\ddagger}$ 35.7 and 36.0 kcal mol^{-1}, in good agreement with the suggested value. Furthermore, direct application of the Eyring equation at constant H_0 of -5.3 using log k_2 values interpolated on the rate profiles gives $\Delta\bar{H}^{\ddagger}$ 35.0 kcal mol^{-1} and $\Delta\bar{S}^{\ddagger}$ 54 cal mol^{-1} K^{-1}. The large positive $\Delta\bar{S}^{\ddagger}$ term is in agreement with previously reported values,[9] perhaps due to a transition-state structure which is less solvated than the ground state.[9]

EXPERIMENTAL

Materials.—Thieno[2,3-*b*]pyridine[5] and 3-nitrothieno-[2,3-*b*]pyridine[6] were prepared according to previously described procedures. Reagents and solvents for kinetic determinations were AnalaR grade or >99.5 wt % isotopically pure.

Hydrogen Exchange Kinetics.—Exchange was followed by n.m.r. spectrometry on a JNM-C-60HL instrument according to a well established procedure.[22,23] A weighed amount of thienopyridine (*ca.* 40 mg) and D_2SO_4 (*ca.* 1 g) of known composition were heated in an n.m.r. tube at 100° and the spectrum was recorded at appropriate intervals. Initially the spectrum showed peaks at δ 9.40 (m, H-4 and -6), 8.60 (dd, H-5), 8.56 (d, H-2), and 8.28 (d, H-3). Modifications of the spectrum are illustrated in Figure 1. Proton signals were integrated at least five times. The extent of reaction was determined by means of the ratio (R_t) of integrations of the signal for H-3 or for H-2 + -5 with that of the standard signal for H-4 + -6 (invariant with time t). The first-order rate constant was then calculated from a plot of $\ln(R_t/R_0)$ against t.

The calculation of D_0 values at the experimental temperature and the complete procedure for obtaining standard rate constants are reported in ref. 8.

Nitration Kinetics.—The change in u.v. absorption of 3-nitrothieno[2,3-*b*]pyridine under conditions where both the parent thienopyridine and the nitro-product exist only in the free base form was followed by means of a Beckman DB-CT spectrophotometer at a wavelength at which the reactant shows no absorption. The absorption maxima of thienopyridine and its nitro-derivative are given in Table 3.

TABLE 3

U.v. absorption of thieno[2,3-*b*]pyridine and 3-nitrothieno-[2,3-*b*]pyridine at pH 7 (aqueous Na_2SO_4) and pH 0 (1M-H_2SO_4)

	λ_{max}/nm (ε)	at pH 7
Substrate	233 (24 200),	287 (3 580)
Product	224 (26 900),	313 (8 970)
	λ_{max}/nm (ε)	at pH 0
Substrate	239 (28 000),	295 (5 700)
Product	226 (27 100),	307 (10 200)

In similar studies reaction mixtures were usually quenched by dilution with water.[24] If this procedure were followed in the present case the pH of the resultant solution would fall close to the pK_a values for thienopyridine (2.75) and its nitro-derivative (estimated as 0.6). In order to avoid measured absorptions due to both the protonated and non-protonated forms, the portions of the reaction mixture were, therefore, quenched with NaOH solutions instead, so that the resulting pH was *ca.* 6—7. A solution of Na_2SO_4 of comparable concentration was used in the reference cell. Absorption measurements were taken at 335 nm, where ε of the nitro-product is 6 230 and no absorption by the parent thienopyridine can be detected.

Reactions were carried out in a volumetric flask, to which were added a weighed quantity (*ca.* 40 mg) of thienopyridine, H_2SO_4 (of known composition) nearly to the mark, and, finally, a measured excess (*ca.* 0.5 g) of 65% HNO_3. The flask was placed in a thermostatted bath. At appropriate intervals, portions (1 ml) were removed and carefully poured into NaOH solutions as described above. The spectrum was recorded for each point and the absorption at 335 nm was measured. The extent of reaction is given by (A_t/A_∞), since $A_0 = 0$. Experimental A_∞ values (<5% lower than expected values) were used in the computations. The pseudo-first-order rate constants were determined from a plot of $\ln[A_\infty/(A_\infty - A_t)]$ against t. The second-order rate constants thereby derived were finally corrected for variations in density of the measured solutions.

Thanks are due to Professor A. R. Katritzky for encouragement and advice, and to CNR (Rome) for financial support.

[5/1844 *Received*, 24*th September*, 1975]

---

[21] C. D. Johnson, A. R. Katritzky, and S. A. Shapiro, *J. Amer. Chem. Soc.*, 1969, **91**, 6654.

[22] G. P. Bean, C. D. Johnson, A. R. Katritzky, B. J. Ridgewell, and A. M. White, *J. Chem. Soc.* (*B*), 1967, 1219, and following papers in the series.

[23] A. El-Anani, P. E. Jones, and A. R. Katritzky, *J. Chem. Soc.* (*B*), 1971, 2363, and previous papers in the series.

[24] C. D. Johnson, A. R. Katritzky, B. J. Ridgewell, and M. Viney, *J. Chem. Soc.* (*B*), 1967, 1204.