Deuteriodeprotonation of Some Heteroaromatic Bicyclic Compounds

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Rate constants for deuteriodeprotonation in D_2SO_4 at the 2- and 3-positions of the four isomeric thieno[2,3-*b*]-, thieno[2,3-*c*]-, thieno[3,2-*b*]-, and thieno[3,2-*c*]-pyridines and of furo[3,2-*b*]- and seleno[3,2-*b*]-pyridine have been determined. The slopes of the rate profiles give evidence that all the substrates undergo exchange as protonated species. The relative reactivities are given as standard rates and discussed in terms of electronic effects in heteroaromatic systems.

IN connection with previous studies on electrophilic substitution of bicyclic heteroaromatic compounds,[1-4] we report in this paper the reactivities, in the deuteriodeprotonation reaction, of some substrates formally derived by the fusion of a pyridine ring with the five-membered rings of thiophen, furan, and selenophen. Thus, we have determined the reaction rates for exchange in D_2SO_4 of the four isomeric thienopyridines fused in the [2,3-*b*] (I), [2,3-*c*] (II), [3,2-*c*] (III), and [3,2-*b*] (IV) manner, as well as of furo[3,2-*b*]- (VI) and seleno[3,2-*b*]-pyridine (VII).

Kinetic data on the electrophilic substitution of these substrates have previously been unavailable except for one previous study, in which the deuteriation and nitration of thieno[2,3-*b*]pyridine (IV) were reported.[3] Only a few qualitative results are known for the other bicyclic systems: halogenation, nitration, and deuteriation of the isomeric thienopyridines give mainly or exclusively the 3-substituted products.[5-7] It has been claimed that nitration and bromination of seleno[3,2-*b*]-pyridine (VII) predominantly gives the 3-substituted derivatives.[8] No report seems to have appeared on the oxygenated homologue, whereas the kinetics of deuteriation of the correponding pyrrolopyridine (V) have been thoroughly investigated.[2]

The effect of benzo fusion on thiophen (X) and furan (IX) was studied for some halogenation and acylation reactions.[1] The annelated systems exhibited an overall reactivity much lower than the corresponding monocyclic parent compounds. Moreover, the relative reac-

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

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

[3] S. Alunni, S. Clementi, and L. H. Klemm, *J.C.S. Perkin II*, 1976, 1135.

[4] (*a*) S. Gronowitz, C. Roos, E. Sandberg, and S. Clementi, *J. Heterocyclic Chem.*, 1977, **14**, 893; (*b*) A. R. Katritzky, S. Clementi, G. Milletti, and G. V. Sebastiani, *J.C.S. Perkin II*, in the press.

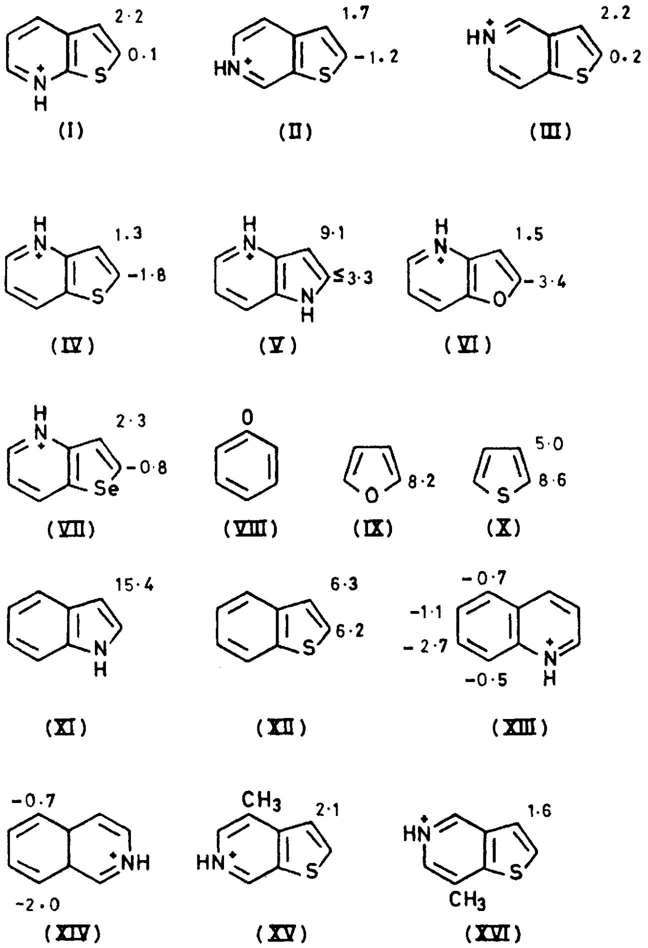
[5] S. Gronowitz and E. Sandberg, *Arkiv Kemi*, 1970, **32**, 249.

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

[7] (*a*) L. H. Klemm, R. Zell, I. T. Barnish, R. A. Klemm, C. E. Klopftenstein, and D. R. McCoy, *J. Heterocyclic Chem.*, 1970, **7**, 373; (*b*) L. K. Klemm, R. E. Merril, and F. H. W. Lee, *ibid.*, 1974, **11**, 535.

[8] F. Outurquin, G. Ah-Kow, and C. Paulmier, *Bull. Soc. chim. France*, 1976, 883.

tivities of the 2- and 3-positions in benzo[*b*]-furan and -thiophen (XII) were shown to be much closer to each other, than in furan (IX) and thiophen (X). Analogously, bromination and acetylation of benzo[*b*]-selenophen give a mixture of the 2- and 3-substituted products.[9,10] A detailed analysis of the partial rate factors permitted the conclusion that benzo fusion leads to a reactivity decrease at the 2-position and an increase at the 3-position for these bicyclic systems, with respect to the monocyclic heteroaromatic compounds.[1]



SCHEME

RESULTS AND DISCUSSION

The kinetics of deuteriation of the six substrates (I)—(IV), (VI), and (VII) were followed by n.m.r. spectroscopy at various concentrations of D_2SO_4 in order to obtain the pseudo-first-order rate constant for each acidity. The experimental results are collected in Table 1. The availability of such data permits the construction of rate profiles (not shown) for each set of measurements, by plotting the log *k*(obs) values against acidity, expressed in terms of the D_0 acidity function.[11] From

TABLE 1

Pseudo-first-order rate constants for hydrogen exchange of some thieno-, furo-, and seleno-pyridine fused systems

	D_2SO_4 (%)	$-D_0(T)$	$10^5k/s^{-1}$	$-\log k$
(i) Thieno[2,3-*b*]pyridine (I) at C-3 (150 °C)	61.4	3.68	10.5	3.98
	60.4	3.62	8.45	4.07
	59.1	3.55	8.47	4.07
	58.3	3.46	6.38	4.19
	58.1	3.43	6.23	4.21
	57.1	3.37	6.23	4.21
	52.1	3.00	2.52	4.60
	51.2	2.94	2.62	4.58
	46.7	2.62	1.27	4.90
	44.5	2.46	0.953	5.02
	43.0	2.37	0.816	5.09
(ii) Thieno[2,3-*c*]pyridine (II) at C-3 (100 °C)	85.0	6.78	144	2.84
	79.3	6.13	35.4	3.45
	76.6	5.80	16.5	3.78
	73.4	5.42	7.45	4.13
	70.8	5.10	3.05	4.52
	67.1	4.67	1.56	4.81
(iii) Thieno[2,3-*c*]pyridine (II) at C-2 (100 °C)	90.7	7.41	2.38	4.62
	86.9	7.00	1.21	4.92
	85.0	6.78	0.455	5.34
	79.3	6.13	0.126	5.90
(iv) Thieno[3,2-*c*]pyridine (III) at C-3 (100 °C)	86.9	7.01	70.7	3.15
	83.6	6.65	25.1	3.60
	78.4	6.04	9.75	4.01
	75.1	5.65	4.92	4.31
	71.7	5.24	2.45	4.61
	68.3	4.81	1.05	4.98
(v) Thieno[3,2-*c*]pyridine (III) at C-3 (150 °C)	54.3	3.15	4.88	4.31
	48.1	2.71	2.45	4.61
	43.7	2.41	1.35	4.87
(vi) Thieno[3,2-*c*]pyridine (III) at C-2 (100 °C)	96.0	8.11	13.0	3.89
	89.6	7.37	3.51	4.45
	86.9	7.01	1.51	4.82
	83.6	6.65	0.825	5.08
	78.4	6.04	0.223	5.65
(vii) Thieno[3,2-*b*]pyridine (IV) at C-3 (100 °C)	86.4	6.94	44.7	3.35
	83.1	6.58	24.3	3.61
	81.5	6.42	16.7	3.78
	80.1	6.23	10.7	3.97
	77.7	5.95	7.40	4.13
	75.9	5.70	4.03	4.39
	70.6	5.08	0.799	5.10
(viii) Thieno[3,2-*b*]pyridine (IV) at C-2 (100 °C)	84.5	6.75	0.0560	6.25
	81.5	6.42	0.0240	6.62
	77.7	5.95	0.0092	7.03
(ix) Seleno[3,2-*b*]pyridine (VII) at C-3 (100 °C)	81.5	6.42	57.8	3.23
	80.3	6.27	27.7	3.56
	79.2	6.14	33.2	3.48
	77.6	5.93	16.5	3.78
	76.0	5.75	12.3	3.91
	75.5	5.69	10.1	4.00
	73.2	5.43	4.85	4.31
	70.7	5.12	1.77	4.58
	69.7	5.00	3.31	4.48
	66.9	4.67	2.28	4.64
(x) Seleno[3,2-*b*]pyridine (VII) at C-2 (100 °C)	84.5	6.75	0.285	5.54
	81.5	6.42	0.152	5.82
	78.8	6.09	0.0706	6.15
(xi) Furo[3,2-*b*]pyridine (VI) at C-3 (150 °C)	70.7	4.71	13.8	3.86
	67.7	4.39	8.18	4.09
	65.6	4.17	5.40	4.27
	63.5	3.96	3.68	4.43
	58.6	3.58	1.83	4.74
	54.6	3.24	1.12	4.95
	50.3	2.96	0.675	5.17
(xii) Furo[3,2-*b*]pyridine (VI) at C-2 (150 °C)	96.2	7.33	2.18	4.66
	90.7	6.85	0.524	5.28
	86.7	6.44	0.251	5.60
(xiii) Furo[3,2-*b*]pyridine (VI) at C-2 (100 °C)	84.6	6.77	0.0110	6.96
	81.5	6.42	0.0046	7.34

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[9] N. N. Magdesieva and V. A. Vdovin, *Khim. Geterotsikl Soedinennii*, 1972, 15.

[10] T. Quang Minh, F. Mantovani, P. Faller, L. Christiaens, and M. Renson, *Bull. Soc. chim. France*, 1972, 3955.

[11] J. Sieva, M. Ojeda, and P. A. H. Wyatt, *J. Chem. Soc.* (*B*), 1970, 1570.

the slopes of the rate profiles the species undergoing reaction can be determined, and from the intercepts the standard rates at D_0 0 are obtained.[12] The statistical analysis of the rate profiles is shown in Table 2.

The extrapolated values at D_0 0 and T 100° have been suggested as standard rates since they represent comparable rate constants, obtainable from any set of measurements reported for each substrate in various acidity ranges. The standardisation procedure is described in ref. 12. The use of standard rates permits a meaningful comparison of substrate reactivity independent of the acidity range covered in the kinetic study.*

The slopes of the rate profiles given in Table 2, which are all close to unity, clearly indicate that all the substrates undergo exchange as protonated species, in both positions susceptible to attack. The linearity of the profiles is always very good (as shown by the correlation coefficients) and therefore the extrapolated values for the standard rates (log k_0) are highly reliable from a statistical point of view. The difference between the extrapolated figure for the set of measurements given in Table 1 for thieno[2,3-*b*]pyridine (log k_0 −9.18) and that previously reported (log k_0 −8.45) [3] gives the magnitude of the error involved in the standardisation procedure as ±0.35, in agreement with the previous statement.[13]

TABLE 2

Statistical analysis of the rate profiles for hydrogen exchange of some thieno-, furo-, and seleno-pyridine fused systems

Substrate	Position	T/°C	Acidity range	No. of points	Slope	Intercept	Corr. coeff.	$-\log k_0$	Average
(I)	3	150	46—61	11	0.85	−7.10	0.998	9.18	8.8
(I) [a]	3	100	61—86	8	0.67	−8.45	0.993	8.45	
(I) [a]	2	100	84—96	4	0.83	−10.93	0.977	10.93	10.9
(II)	3	100	67—85	6	0.95	−9.32	0.998	9.32	9.3
(II)	2	100	79—91	4	1.03	−12.21	0.989	12.21	12.2
(III)	3	100	68—87	6	0.80	−8.81	0.997	8.81	8.8
(III)	3	150	44—54	3	0.75	−6.67	0.998	8.75	
(III)	2	100	74—96	5	0.85	−10.77	0.999	10.77	10.8
(IV)	3	100	71—86	7	0.93	−9.74	0.995	9.74	9.7
(IV)	2	100	78—85	3	0.97	−12.80	0.997	12.80	12.8
(VII)	3	100	67—82	10	0.83	−8.67	0.977	8.67	8.7
(VII)	2	100	79—85	3	0.92	−11.77	0.998	11.77	11.8
(VI)	3	150	50—71	7	0.75	−7.40	0.999	9.48	9.5
(VI)	2	150	87—96	3	1.06	−12.48	0.991	14.56	14.4
(VI)	2	100	82—85	2	1.09	−14.31		14.31	

[a] From ref. 3.

The deuteriodeprotonation of thieno[2,3-*b*]- and thieno[3,2-*c*]-pyridine (I) and (III) is a clean and quantitative reaction. In all the other cases, a side reaction occurs at the same time, leading to unidentified aromatic by-products, most probably sulphonic acids. In these cases the kinetic study was carried out only in the early stages of the reaction (up to 50%), where the extent of by-product formation was negligible.

The relative reactivities are reported in the Scheme, in terms of logarithms of partial rate factors, *i.e.* referred to one position of benzene, the standard rate of which is known as log k_0 −11.[14] In the Scheme some more substrates of related structure previously studied [2-4] or recalculated from data collected in other laboratories [12,14] are included for comparison (see refs. 3 and 14 for details). The relevant results can be summarised as follows.

Isomeric Thienopyridines.—All four isomeric thienopyridines (I)—(IV) react predominantly in the 3-position, which is in agreement with the calculated indices of reactivity (frontier electron density, FED) for these systems.[15] The overall reactivity, which accordingly is mainly the result of attack at the 3-position, is substantially the same in all four systems. In this context it should be noted that no conjugative interactions are possible between the 3-carbon of the thiophen ring and any of the atoms of the pyridine ring. For the 2-position, however, such interactions, with some of the positions in the six-membered ring, are feasible, and as expected the 2-positions of the [2,3-*b*]- and [3,2-*c*]-isomers (I) and (III) were found to be more reactive than the 2-positions of the [2,3-*c*]- and [3,2-*b*]-isomers (II) and (IV), as in the latter cases one of the resonance structures of the Wheland intermediate bears a positive charge on the pyridine nitrogen. This leads to a higher C-3 : C-2 reactivity ratio in the [2,3-*c*]- and [3,2-*b*]-fused isomers (II) and (IV) (*ca.* 1 000) than in the [2,3-*b*] and [3,2-*c*]-fused isomers (I) and (III) (*ca.* 100).

It is evident from the Scheme that the fusion of a protonated pyridine ring onto a thiophen ring leads to a deactivation of the thiophen 3-position with 2.8—3.7 log units [no conjugative interactions,† (I)—(IV)], and of the 2-position with *ca.* 8.5 [no conjugative interactions,† (I) and (III)] and 9.8—10.4 [conjugative interactions,† (II) and (IV)] log units. Hence, while benzo fusion causes a decrease of the reactivity of the 2-position (2.4 log units) and an increase of the reactivity of the 3-position (1.3 log units), the fusion of a positively charged

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* The applicability of partial rate factors obtained from standard rates at D_0 0 is discussed in detail in ref. 4*b*: these appear to be generally applicable, independently of the acidity extrapolation involved, for substrates of closely related structure.

† This refers to interactions in the Wheland intermediate with the positively charged nitrogen atom.

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

[13] S. Clementi, A. El-Anani, A. R. Katritzky, and B. R. O'Neill, *Gazzetta*, 1975, **105**, 539.

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

[15] A. Helland and P. N. Skancke, *Acta Chem. Scand.*, 1972, **26**, 2601.

ring leads to a decrease of the reactivity of both positions of the five-membered thiophen ring, for all the positions of the azonium group. The decrease in reactivity obtained by exchanging a $=\overset{+}{N}-$ for a ring $=CH-$ system of benzo[*b*]thiophen is thus 4—5 log units at the 3-position and 6—8 log units at the 2-position.

Another interesting point which arises from the Scheme is that the fusion of a positively charged pyridine ring causes much larger deactivation of the thiophen positions [thiophen (X) *versus* thienopyridines (I)—(IV)] than of the corresponding benzene positions [benzene (VIII) *versus* quinoline (XIII) and isoquinoline (XIV)]. In the latter case the deactivation is only 0.5—1.1 log units for positions with no conjugative interactions † and 0.7—2.7 for positions with conjugative interactions.† This means that in deuteriodeprotonation the fusion of a protonated pyridinium ring to some extent levels out the inherent reactivity differences between the thiophen (X) and benzene (VIII) rings.

Finally, it is interesting to note that certain structural modifications of the six-membered rings, such as the introduction of methyl groups in certain positions, have little, if any, effect on the reactivity of the five-membered ring [(II) and (III) compared with (XV) and (XVI), respectively].[4]

In conclusion, all four isomeric thienopyridines (I)—(IV) are more reactive in deuteriodeprotonation than benzene (VIII), quinoline (XIII), and isoquinoline (XIV), but less so than thiophen (X) and benzo[*b*]thiophen (XII), and they all react predominantly in the 3-position.

Series of [3,2-b]-*fused Pyrrole, Furan, Thiophen, and Selenophen.*—In protiodedeuteriation of furan (IX), thiophen (X), and selenophen the 2-position is the preferred site of attack.[16] In the case of pyrrole, however, the 2- and 3-positions are of roughly equal reactivity.[16,17] It should be noted, however, that these studies were carried out in organic solvents and therefore are not strictly comparable with our work. Indole (XI) reacts predominantly in the 3-position,[2] while the reactivity of the 2- and 3-positions of benzo[*b*]thiophen (XII) are of a similar magnitude.[3] No data seem to be available for the deuteriodeprotonation of benzo[*b*]-furan and -selenophen. However, in other types of electrophilic aromatic substitutions benzo[*b*]furan is known to react preferably in the 2-position.[1] The scant and somewhat divergent data for benzo[*b*]selenophen do not allow any such sweeping generalization.[9,10] As can be seen from the Scheme, fusion of a positively charged pyridinium ring in the [3,2-*b*]-mode leads to a more uniform positional selectivity. Thus, all four systems (IV)—(VII) react predominantly in the 3-position. The lower reactivity of the 2-position in these cases, at least to some extent, could be attributed to conjugative interactions with the positively charged nitrogen atom in the Wheland intermediate (see above), but mainly depends on the reactivity decrease induced by annelation.[1]

For the parent five-membered heterocycles the C-2 : C-3 reactivity ratio in electrophilic aromatic substitution generally increases in the order pyrrole $\ll$ selenophen $\simeq$ thiophen $\ll$ furan.[18] Unfortunately the literature data for protiodedeuteriation [16] does not allow any affirmation of this order, since the values given for the β-position of furan and selenophen are only upper limits. In thieno-(IV) and seleno-[3,2-*b*]pyridine (VII) the C-2 : C-3 reactivity ratio at standard conditions (D_0 0, T 100°) is *ca.* 10^{-3}, in furo[3,2-*b*]pyridine (VI) *ca.* 10^{-5}, and in pyrrolo[3,2-*b*]pyridine [2] (V) $\leqslant 10^{-6}$. Evidently fusion of a positively charged pyridinium ring has not a unique and uniform effect on the reactivity of the different positions of all the five-membered rings. The comparatively low C-2 : C-3 reactivity ratio for furo[3,2-*b*]pyridine (VI) might have some connection with the fact that furan is the most sensitive of the five-membered heterocycles to structural modifications in conventional electrophilic aromatic substitution.[18,19] In contrast the low C-2 : C-3 ratio for pyrrolo[3,2-*b*]pyridine (V) is probably a consequence of the large reactivity difference caused by annelation on a system (pyrrole) exhibiting the lowest C-2 : C-3 ratio, as already observed in substitutions of indole.[20]

It is interesting to note that for acid-catalysed hydrogen exchange, the order of reactivity of compounds (IV)—(VII) at the 3-position is the same as that reported for the parent five-membered heterocycles at the 2-position in ref. 16. Nevertheless this fact, in view of the different conditions used in the latter work (methanol; H_0 2), might be fortuitous, as the reactivities of the oxygenated, sulphurated, and seleniated compounds are very near in both cases. Moreover the comparison of sets of data obtained in different media must be regarded as doubtful.[2] In fact from the Scheme the reactivity of thiophen appears to be greater than that of furan, at variance with available data from other substitutions,[18] but this might simply be due to a slight decomposition of [2-^{2}H]furan in the acidic medium.[21]

Unfortunately, standard rate constants are not available for pyrrole and selenophen in sulphuric acid. Accordingly, it is impossible to make any quantitative statement about how the fusion of a positively charged pyridinium ring affects the reactivity of the different positions in the five-membered rings. However, in the light of the results presented above and the known standard rate constants for the 2-position in furan and thiophen, it seems safe to assume that pyridine fusion decreases the reactivity of all four five-membered heterocyclic systems.

In conclusion, fusion of a positively charged pyridin-

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† See note on p. 863.

[16] K. Schwetlick and K. Unverferth, *J. prakt. Chem.*, 1972, **314**, 603.

[17] (*a*) G. P. Bean, *Chem. Comm.*, 1971, 421; (*b*) D. M. Muir and M. C. Whiting, *J.C.S. Perkin II*, 1975, 1316.

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

[19] (*a*) S. Clementi and G. Marino, *J.C.S. Perkin II*, 1972, 71; (*b*) S. Clementi, F. Fringuelli, P. Linda, G. Marino, G. Savelli, A. Taticchi, and J. L. Piette, *Gazzetta*, 1977, **107**, 339.

[20] A. Cipiciani, S. Clementi, P. Linda, G. Marino, and G. Savelli, *J.C.S. Perkin II*, 1977, 1284.

[21] K. Schwetlick, K. Unverferth, and R. Mayer, *Z. Chem.*, 1967 **7**, 58.

ium ring leads in these cases to a general decrease of reactivity. The 3-position is, in all four systems (IV)—(VII), the preferred site of attack, while the C-2 : C-3 reactivity ratio strongly depends on the heteroatom.

EXPERIMENTAL

Materials.—Thieno[2,3-*b*]pyridine (I), b.p. 61—62° at 0.2 mmHg,[3] thieno[2,3-*c*]pyridine (II), m.p. 55—56°,[22] thieno-[3,2-*b*]pyridine (IV), b.p. 107—108° at 10 mmHg,[23] thieno-[3,2-*c*]pyridine (III), m.p. 42—43°,[22] seleno[3,2-*b*]pyridine (VII), m.p. 35—37°,[23] and furo[3,2-*b*]pyridine (VI), b.p. 79—80° at 12 mmHg,[23] were available from previous related studies. Deuteriosulphuric acid and D_2O were commercial products $\geqslant 99.5\%$ isotopically pure. The n.m.r. spectra of the six substrates in D_2SO_4 solutions are reported in Table 3.

Kinetic Procedure.—Deuteriation was followed by n.m.r. spectrometry on a JEOL JNM-C-60HL instrument according to a well established procedure.[24] A weighed amount of substrate (*ca.* 35 mg) and D_2SO_4 (*ca.* 1 g) of known composition were heated in an n.m.r. tube, and the spectrum was recorded at appropriate intervals. Since deuteriation leads to a decrease of the signal of the exchanging proton, the extent of reaction was evaluated by means of the ratio R_t of integrations of the signal for H-3 or -2 to that of the signal invariant with time *t* and therefore taken as a reference, and reported, for each substrate, in Table 3. The first-order rate constant was then calculated from a plot of ln (R_0/R_t) against *t*.

TABLE 3

^{1}H N.m.r. chemical shifts (δ) for the protons of some thieno-, furo-, and seleno-pyridine fused systems in D_2SO_4 at 60 MHz

Substrate	H-2	H-3	H-4	H-5	H-6	H-7
(I)	8.56	8.28	9.40 *	8.60	9.40 *	
(II)	8.70	7.95	8.50	8.50		8.95*
(III)	8.13	7.86	9.22 *		8.44	8.44
(IV)	8.67	7.90		8.92 *	8.05	9.25*
(VII)	9.40	8.28		9.02 *	8.09	9.40
(VI)	8.34	7.20		8.50 *	7.78	8.60*

* Signals due to protons taken as internal reference for evaluating the reaction extent in the kinetic runs.

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[22] S. Gronowitz and E. Sandberg, *Arkiv Kemi*, 1970, **32**, 217.

[23] S. Gronowitz, C. Westerlund, and A.-B. Hörnfeldt, *Acta Chem. Scand.*, 1975, **29**, 233.

[24] 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.