The Kinetics and Mechanism of Electrophilic Substitution of Heteroaromatic Compounds. Part XVI.[1] Acid-catalysed Hydrogen Exchange of Some Pyridazine Derivatives

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4-Aminopyridazine exchanges in acid solution as the conjugate acid at the 5-position. In the low acidity region, the conjugate acid exchanges by the ylid mechanism at the 3- and 6-positions. Pyridazin-4-one exchanges by the acid-catalysed mechanism as the neutral species at the 5-position; ylid-mechanism exchange on the conjugate acid occurs at the 3- and 6-positions. Pyridazin-3-one exchanges in acid solution at the 5-position; the mechanism probably involves a hydrated species. Rate constants are measured and discussed.

CONTINUING our mechanistic survey of electrophilic substitutions of heterocycles,[2] we have now studied pyridazine derivatives. Because of the expected large deactivation of the ring by the two nitrogen atoms, compounds with one or two strongly activating substituents were selected. Reactions were followed by changes in n.m.r. spectra in deuteriosulphuric acid–deuterium oxide. Unfortunately, many of the compounds did not show sufficient stability to hot acid, the n.m.r. spectral changes in these cases indicating hydrolytic loss of substituent or ring opening (see Table 1). However, satisfactory results were obtained with 4-aminopyridazine and pyridazin-3- and -4-one.

In deuteriosulphuric acid solution, the n.m.r. spectra of 4-aminopyridazine showed a continuous decrease in the absorption due to all ring protons, with the 5-proton signal decreasing most rapidly, and two new lines appeared near τ 1·0 (Figures 1A, B). The spectral changes are explained by two competitive reactions: exchange of the 5-proton and hydrolysis to pyridazin-4-one. Under the conditions used, pyridazin-4-one itself exchanges very rapidly at the 5-position, and the extra two lines found are due to the 3- and 6-protons in 5-deuteriopyridazin-4-one. This interpretation is supported by the spectrum obtained by heating 4-aminopyridazine in protiosulphuric acid (Figure 1C) where the pyridazin-4-one formed now shows both the 3- and the 6-protons coupled to the 5-proton (which itself is obscured by the sulphuric acid signal). In neutral or alkaline media, by contrast, the 3- and 6-protons of 4-aminopyridazine undergo exchange, at approximately equal rates (Figures 1D, E).

TABLE 1

Qualitative exchange reactions with substituted pyridazines

Substituents			Conditions: Solvent D_2SO_4 (%)	Temp.	Time (hr.)	Observed change: Decomposition	Exchange
3	4	6					
OMe	H	OMe	83	160°	1	Complete	Slight
NH_2	H	OMe	29	148	3	30%	Nil
NH_2	H	Cl	29	148	3	Appreciable	Nil
OH	H	OH	83	148	19	?	50%
			87 *	148	16	22%	
OH	Me	OH	83	169	30	?	50% in CH_3, 25% in ring
			87 *	169	185	50%	
OH	Cl	OH	83	148	40	?	50%
H	OMe	H	10	186	10	Complete	

* H_2SO_4.

In strongly acidic media, pyridazin-4-one undergoes exchange solely at the 5-position (Figure 2A, B). However, in weakly acidic media, the compound undergoes

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[1] Part XV, P. Bellingham, C. D. Johnson, and A. R. Katritzky, preceding paper.

[2] For a review see A. R. Katritzky and C. D. Johnson, *Angew. Chem. Internat. Edn.*, 1967, **6**, 608.

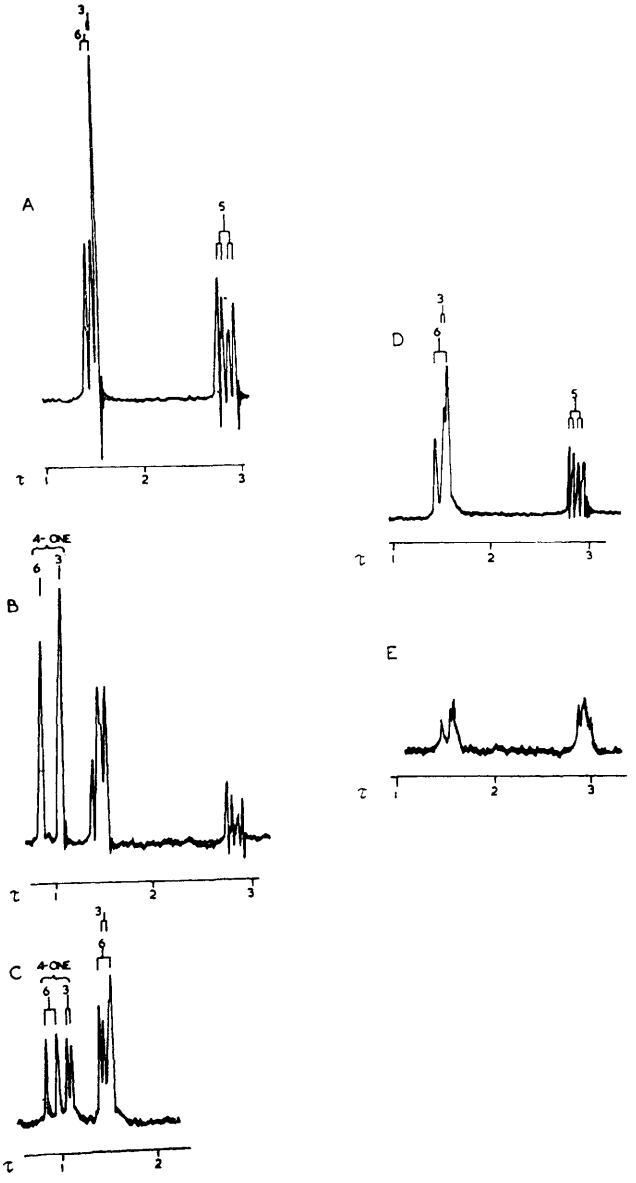


FIGURE 1 N.m.r. spectra at 60 Mc./sec. of 4-aminopyridazine: (i) in D_2SO_4 of $H_0 = -0.84$, A, initially; B, after heating for 21 hr. at 186°. (ii) in H_2SO_4 of $H_0 = -1.20$, C, after heating for 19 hr. at 186°. (iii) in D_2SO_4 of pD = 5·80, D, initially, E, after heating for 186 hr. at 127°

exchange at all the ring positions. At pD 2·1, for example, the 3-proton exchanges most rapidly, and the 6-proton slightly faster than the 5-proton. This is demonstrated by Figure 2D which shows the 3-protons mainly, and the 5- and 6-protons partly, exchanged,

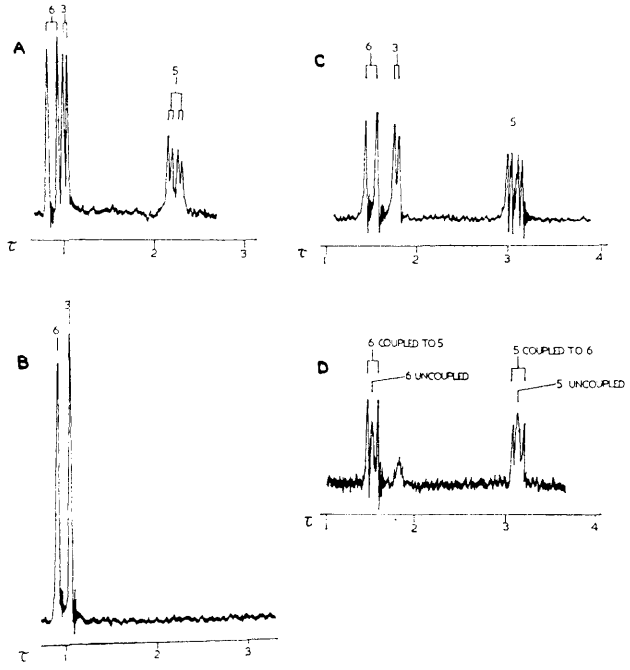


FIGURE 2 N.m.r. spectra at 60 Mc./sec. of pyridazin-4-one in D_2SO_4: (i) of $H_0 = -3.35$, A, initially; B, after heating at 186° for 49 hr. (ii) of pD = 2·10, C, initially; D, after heating at 186° for 15 hr.

with the residual 6-protons in part coupled to the 5-protons and *vice versa*. Pyridazin-3-one undergoes hydrogen exchange at the 5-position, and more slowly at the 4-position (Figures 3A, B, C).

EXPERIMENTAL

Compounds.—4-Chloro-3-hydroxypyridazin-6-one and 3-amino-6-methoxypyridazine were recrystallised commercial specimens. 3-Hydroxypyridazin-6-one, m.p. 300°

TABLE 2

N.m.r. data for pyridazines studied

Substituents			Aromatic proton pattern	Chemical shifts in τ units					Solvent D_2SO_4 (%)	Coupling constants [a] in c./sec. (±0·3)
3	4	6		3-H	4-H	5-H	6-H	Substituent groups		
OMe	H	OMe	A_2		2·10	2·10		OMe 5·78	83·0	
NH_2	H	OMe	A_2		2·55	2·55		OMe 6·07	29·5	
NH_2	H	Cl	AB		2·41	2·17			29·5	J_{45} 9·75
OH	H	OH	A_2		2·24	2·24			45·2	
OH	Me	OH	A			2·44			45·2	
OH	Cl	OH	A			2·00			83·0	
NH_2	H	H	AMX		2·40	2·00	1·45		29·5	J_{45} 9·6; J_{56} 4·2; J_{46} 1·5
OH	H	H	AMX		2·96	2·51	2·04		pD = 1·20	J_{45} 9·3; J_{56} 4·2; J_{46} 1·2
H	NH_2	H	AMX	1·49		2·84	1·45		$H_0 = -1·32$	J_{35} 2·8; J_{56} 7·6
H	OH	H	AMX	1·10		2·34	0·88		$H_0 = -0·23$	J_{35} 3·0; J_{56} 7·0
H	OMe	H	AMX	1·07		2·18	0·72	OMe 5·77	$H_0 = 0·0$	J_{35} 3·0; J_{56} 7·2

[a] First-order treatment.

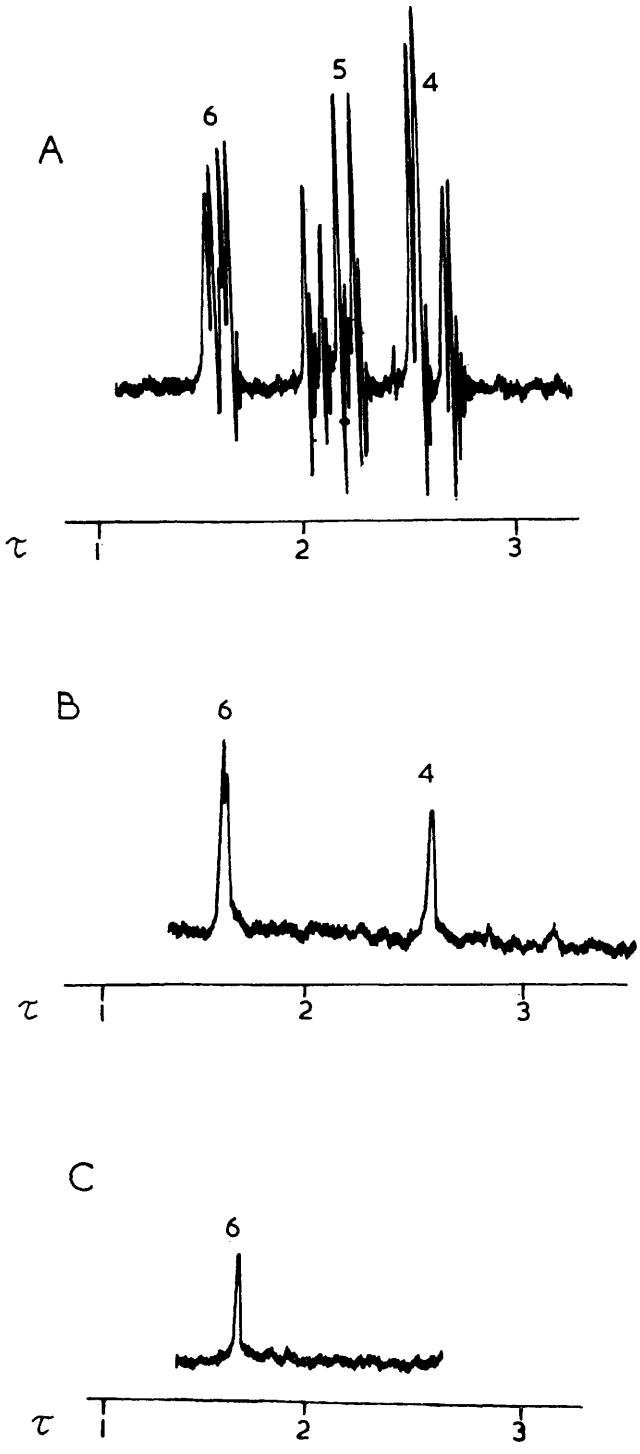


FIGURE 3 N.m.r. spectra at 60 Mc./sec. of pyridazin-3-one in D_2SO_4 of $H_0 = -0{\cdot}87$, A, initially; B, after heating at 186° for 306 hr.; and C, after heating at 186° for 760 hr.

(lit.,[3a] 300°) and its 4-methyl derivative, m.p. 300—302° lit.,[3b] 286·5—287°), were prepared by a literature method.[4]

3-Amino-6-chloro-, m.p. 220—222° (lit.,[5] 210°); 3-amino-, m.p. 167—168° (lit.,[6] 170—171°); 4-amino-, m.p. 126—129° (lit.,[7] 129—131°); and 4-methoxy-pyridazine, m.p. 32—36° (lit.,[8] 43—44°) and pyridazin-3-one, m.p. 96—98° (lit.,[9] 102—103°), were prepared by modifications of the literature methods indicated.

4-Methoxypyridazine (2·8 g.) and 12N-hydrochloric acid (25 ml.) were heated at 155° (sealed tube) for 16 hr. The whole was evaporated to dryness and passed through Amberlite IR120 resin in the H^+ form. Elution with N-ammonia and evaporation to dryness gave pyridazin-4-one which crystallised (1 g.), m.p. 254—255°, from methanol (lit.,[10] 245—246°).

Deuteriosulphuric Acid Solutions.—These were made up as previously described.[11] The H_0 values were calculated

TABLE 3

First-order rate constants for 4-aminopyridazine

Acidity		Temp.	$-\log k$ (sec.$^{-1}$) 3-H + 6-H	$-\log k$ (sec.$^{-1}$) 5-H
pD	8·36	127·0°	4·511	
	7·97	127·0	4·574	
	7·59	127·0	4·725	
	6·80	127·0	4·928	
	6·35	127·0	5·298	
	6·00	127·0	5·569	
	5·75	127·0	5·920	
	0·06	186·0		6·025
H_0	−0·84	186·1		5·580
	−0·84	199·0		5·005
	−0·84	208·3		4·486
	−0·84	215·4		4·340
	−1·32	186·0		5·193
	−2·15	186·0		4·632
	−3·33	186·0		4·032
	−7·20	186·0		Too fast

allowing for protonation and deducting 0·35 H_0 units for the salt effect (for justification see ref. 12).

N.m.r. Spectra.—These were measured on a Perkin-Elmer R10 instrument with spinning, and the spectral parameters are recorded in Table 2.

Kinetic Runs.—These were carried out as previously reported.[11] As some compounds showed competitive hydrolytic decomposition under conditions for exchange, exchange rates were measured from ratios of exchanging protons and non-exchanging protons. Thus, for 4-aminopyridazine, in the H_0 region $A_{5\text{-H}}/(A_{3\text{-H}+6\text{-H}})$ was used, and $(A_{3\text{-H}+6\text{-H}})/A_{5\text{-H}}$ for the pH region. For pyridazin-3-one rates at acidities above H_0 −0·87 were measured as $A_{5\text{-H}}/A_{6\text{-H}}$, and at lower acidities as $A_{5\text{-H}}/A_{4\text{-H}}$. Results for a typical run are shown in Figure 4, and the results are recorded in Tables 3—5.

[3] R. H. Mizzoni and P. E. Spoerri, (*a*) *J. Amer. Chem. Soc.*, 1951, **73**, 1873; (*b*) 1954, **86**, 2201.
[4] H. Feuer, E. H. White, and J. E. Wyman, *J. Amer. Chem. Soc.*, 1958, **80**, 3790.
[5] J. Druey, Kd. Meier, and K. Eichenberger, *Helv. Chim. Acta*, 1954, **37**, 121.
[6] E. A. Steck, P. Brundage, and L. T. Fletcher, *J. Amer. Chem. Soc.*, 1954, **76**, 3225.
[7] T. Kuraishi, *Chem. and Pharm. Bull.* (*Japan*), 1956, **4**, 137.
[8] K. Eichenberger, R. Rometsch, and J. Druey, *Helv. Chim. Acta*, 1956, **39**, 1755.
[9] P. Coad and R. A. Coad, *J. Org. Chem.*, 1963, **28**, 1919.
[10] T. Kuraishi, *Chem. and Pharm. Bull.* (*Japan*), 1957, **5**, 376.
[11] P. Bellingham, C. D. Johnson, and A. R. Katritzky, *J. Chem. Soc.* (*B*), 1967, 1226.
[12] G. P. Bean, C. D. Johnson, A. R. Katritzky, B. J. Ridgewell, and A. M. White, *J. Chem. Soc.* (*B*), 1967, 1219.

TABLE 4

First-order rate constants for pyridazin-4-one at 186·0°

Acidity		$-\log k$ (sec.$^{-1}$) 5-H	3-H	6-H
pD	2·40	5·375	4·385	4·782
	2·10	5·001	4·407	4·883
	1·70	4·506	4·469	4·934
	1·32	4·173	4·593	5·037
	0·70	3·839	5·013	5·495
	0·20	3·836	5·550	5·915
H_0	−0·23	3·838	5·805	6·336
	−3·35	4·131		
	−6·61	4·844		

TABLE 5

First-order rate constants for pyridazin-3-one at 186·0°

Acidity		$-\log k$ (sec.$^{-1}$) 5-H
pD	0·67	6·996
	0·37	6·345
H_0	−0·43	5·831
	−0·87	5·649
	−1·24	5·860
	−2·30	6·304
	−3·65	6·310
	−7·50	6·860

RESULTS AND DISCUSSION

4-Aminopyridazine (Figure 5).—Exchange of the 5-proton at 186·0° increases linearly with acidity with a

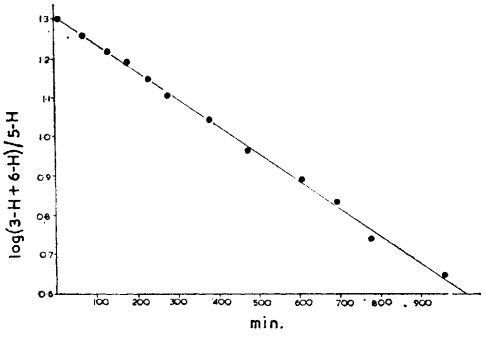


FIGURE 4 Exchange at positions 3 and 6 of 4-aminopyridazine at pD = 7·97 and 127°

slope of −0·60. This is strong evidence for conjugate-acid exchange; the conjugate acid of 4-aminopyridine has a slope of −0·58.[12] Activation parameters were determined at H_0 −0·84 (see Table 3) as $\Delta H^{\ddagger} = 44$ kcal./mole and $\Delta S^{\ddagger} = 13$ e.u. The positive entropy value is unexpected for the conjugate-acid reaction;[2,13] however, previous $\Delta S^{\ddagger}$ values have usually referred to H_0 values < -5 and $\Delta S^{\ddagger}$ values for the 2,4,6-trimethylpyrimidinium ion become more positive as the acidity decreases in the range −8 to −5.[14]

[13] L. L. Schaleger and F. A. Long, *Adv. Phys. Org. Chem.*, 1963, **1**, 1.
[14] A. R. Katritzky and B. J. Ridgewell, *J. Chem. Soc.*, 1963, 3753.
[15] G. P. Bean and A. R. Katritzky, *J. Chem. Soc.* (*B*), 1968, 864.

The relative basicities of 3- and 4-aminopyridine indicate that the predominate conjugate acid of 4-aminopyridazine has the structure (I), and this would also be expected to be the most reactive of the conjugate acids. Previous work on *para*-substituted anilines,[15] and extrapolation of our present data to 107° ($\log k_2 = -9{\cdot}45$; $\rho = -3{\cdot}51$) enables calculation of the total σ^+ value for the group $=NH^+-N=$ as 2·49 with respect to the

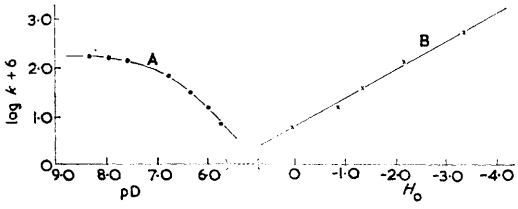
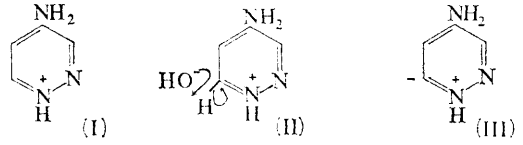


FIGURE 5 Rate profiles for hydrogen exchange in 4-aminopyridazine A, at the 3- and 6-positions at 127°, and B, at the 5-position at 186°

position *meta* to $=NH^+-$ and *para* to $=N-$. The results for 4-aminopyridine give σ_m^+ for the group $=NH^+-$ as 1·82;[15] hence the contribution of σ_p^+ for the unchanged hetero atom $=N-$ is 0·67. This agrees well with the figure of 0·76 given by Blanch[16] for σ_p for $=N-$.



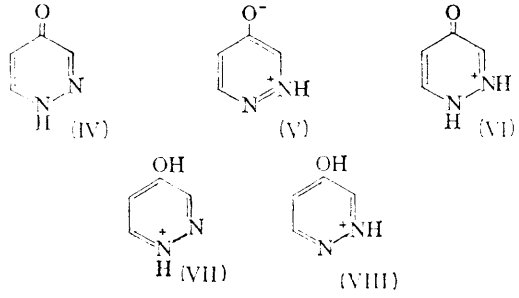
In neutral and alkaline media, exchange occurs at the 3- and 6-positions, which react at practically the same rate as shown by the straight-line plot of log $A_{3\text{-H}} + A_{6\text{-H}}$ against time to over 75% conversion. Below the pK_a value (6·69 in H_2O),[17] the rate profile has a slope of 1·02; above this point the slope is *ca.* zero (Figure 5). This is consistent with exchange *via* the ylid mechanism[18] (II) ⟶ (III), which is strongly supported by the orientation found. The rate for the ylid mechanism $= k[(I)][OH^-] = k'[(I)][H^+]^{-1}$ for the formation of (III) will be rate determining. In solutions more alkaline than the pK_a value of 6·69 for 4-aminopyridazine, $[(I)] \propto [(I)]_{stoich}[H^+]$ add the ylid exchange rate $\propto [(I)]_{stoich}$. At pH values below this pK_a, $[(I)] = [(I)]_{stoich}$ leading to the rate $\propto [(I)_{stoich}][H^+]^{-1}$ as observed. Detailed comparison with the results reported[18] for pyridine at 218° is not possible as the activation parameters are not available, but the rate is clearly much faster in the pyridazine series, as would be expected.

Pyridazin-4-one (Figure 6).—The rate profile for 5-position exchange shows a break at pD 1·0, near the

[16] J. Blanch, *J. Chem. Soc.* (*B*), 1966, 931.
[17] A. Albert, in 'Physical Methods in Heterocyclic Chemistry,' ed. A. R. Katritzky, Academic Press, New York and London, 1963, vol. 1, p. 74.
[18] J. A. Zoltewicz and C. L. Smith, *J. Amer. Chem. Soc.*, 1967, **89**, 3358.

reported [19] pK of 1·07: at stronger acidities the slope is *ca.* zero, while it is −1·12 in more weakly acidic media. This behaviour is typical of acid-catalysed exchange on a free-base species and parallels that of 2- and 4-pyridone.

Direct comparison of the rate found with those measured for 4-pyridone exchange at the 3- and 5-positions [11] indicates that pyridazin-4-one reacts at *ca.* 0·7 times the rate of 4-pyridone. Interpretation of this unexpected result is hindered by lack of knowledge of the tautomerism of pyridazin-4-one. Pyridazin-4-one probably exists predominantly in the 1*H*-form (IV);



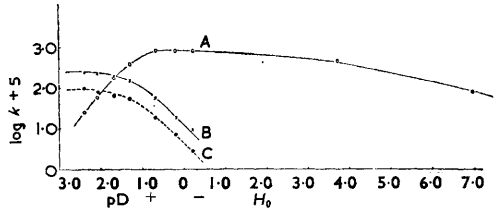


FIGURE 6 Rate profiles for hydrogen exchange at 186° in pyridazin-4-one A, at the 5-position; B, at the 3-position; and C, at the 6-position

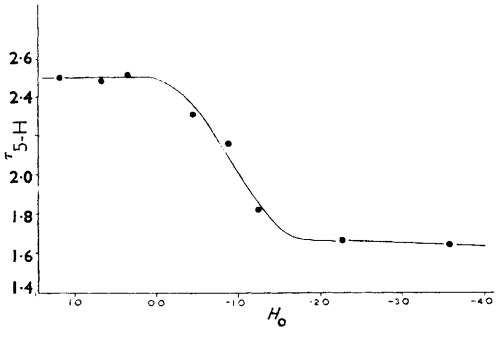


FIGURE 7 Rate of change of τ-values of the 5-hydrogen in pyridazin-3-one with H_0

however, in aqueous solution it could occur mainly in the zwitterionic tautomeric form (V), and without appropriate model compounds this question cannot be settled.

The rate profiles for exchange at the 3- and 6-positions also show breaks near pH 1, but now the slope is *ca.* zero at lower acidities and positive (0·86 for the 3-position, 0·95 for the 6-position) at higher acidities. This

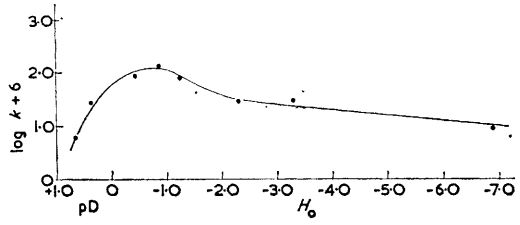
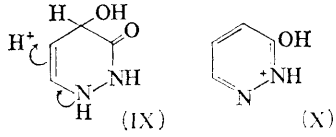


FIGURE 8 Rate profile for hydrogen exchange at 186° in pyridazin-3-one at the 5-position

behaviour accords with a ylid mechanism of type (II), occurring on one of the conjugate acid species of pyridazin-4-one. There are three possible conjugate acids (VI)—(VIII), but the details of their tautomeric equilibria are not known, and detailed interpretation must be deferred.

Pyridazin-3-one.—The percentage of protonation near the pK value (−1·8 [19]) was calculated from the chemical shift, using the graph in Figure 7; because use of the usual method means that the H_0 values near the pK_a are sensitive to the exact correction made to the pK_a value for changing to deuteriated media.



The rate profile for exchange at the 5-position is similar to that found for pyridazin-4-one except for a weak maximum near H_0 −0·8 (Figure 8). However, the orientation of reaction is curious and suggests that a mechanism other than simple acid-catalysed hydrogen exchange is occurring (this would be expected to prefer the 4-position). A possible explanation is that acid-catalysed exchange occurs in a small proportion of covalently hydrated species (IX) or alternatively that the cation (X) is attacked by a water molecule.

Preliminary experiments showed that further exchange could be induced under forcing conditions: the 4-hydrogen reacted at H_0 −0·84 on prolonged heating at 186°, whereas at pD + 1·20 preferential exchange occurred at the 6-position. However, these reactions were inconveniently slow for the detailed investigation.

We thank Dr. M. Kingsland for help in this work.

[19] A. Albert and J. N. Phillips, *J. Chem. Soc.*, 1956, 1294.

[7/1580 *Received, November 30th,* 1967]