The Rearrangement of 2-Amino-1,3,4-thiadiazines to 3-Amino-2-thiazolimines. Part 1. The Rates of Rearrangement of a Series of 5-Alkyl- and 5-Aryl-2-amino-1,3,4-thiadiazines at 30 and 50 °C

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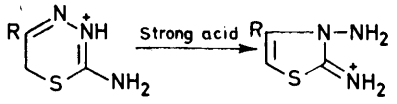
The rates of rearrangement of the series 5-methyl-, 5-ethyl-, 5-isopropyl-, and 5-t-butyl-2-amino-1,3,4-thiadiazines in strong acid have been followed by observing the u.v. absorptions of the protonated thiadiazine substrates or the product thiazolimines. The rates of rearrangement were found to be first order with respect to the thiadiazine concentration and the rates decreased along the series in a manner characteristic of an S_N2 reaction. The rates of rearrangement of 2-amino-1,3,4-thiadiazines with phenyl, *p*-nitrophenyl, and *p*-hydroxyphenyl groups in the 5 position were all extremely slow whereas 2-amino-5-benzyl-1,3,4-thiadiazine rearranged much faster than these arylthiadiazines but more slowly than the 5-methyl and 5-ethyl compounds. The rearrangement rates of 2-amino-5-methyl-1,3,4-thiadiazine were followed at various acid strengths within the range 4.47—8.12M-HCl. The reaction ultimately reached equilibrium, and the measured constant, k_1, was equal to the sum of the velocity constants ($k_r + k_{-r}$) of the forward and backward reactions. Both k_r and k_{-r} were found to be similarly dependent on acidity and water activity. Using H_0 values derived by Long and Paul with substituted anilines, a plot of $\log_{10} k_1$ against $-H_0$ was found to be linear and of slope equal to 0.92. A slope of −5.4 (w^*) was obtained from the Bunnett plot of $\log_{10} k_1/C_{H^+}$ against $\log_{10} a_w$. A Yagil plot of $\log_{10} k_1/C_{H^+}$ against $\log_{10} C_w$ was linear and of slope equal to −2.95 at acidities less than 6.9M-HCl. Replacement of H by D at position 6 in all the thiadiazines was observed in D_2O only in strong acid and D was incorporated both into the unchanged thiadiazine and the product thiazolimine (at position 5). A mechanism is suggested for the rearrangement which involves transannular nucleophilic atack by N(3) at an sp^3 carbon atom in the 5 position of the thiadiazines.

THE rearrangement of 2-amino-1,3,4-thiadiazines (1) and 2-hydrazino-1,3,4-thiadiazines in concentrated hydrochloric acid solution to give corresponding 3-amino-2-thiazole imines (thiazolimines) (2) and the hydrazones of 3-amino-2-oxothiazoles respectively have been reported by Beyer *et al.*[1,2] A similar rearrangement of 2-mercapto-1,3,4-thiadiazines in strong acid was observed by Sandström.[3] Beyer *et al.*[4,5] also showed that 1,3,4-thiadiazines with a 5-phenyl group do not rearrange in concentrated hydrochloric acid but that the reverse reaction, as for instance the rearrangement of 3-amino-4-phenyl-2-thiazolimine to 2-amino-5-phenyl-1,3,4-thiadiazine, does occur in hot concentrated hydrochloric acid. Beyer [4,5] has suggested that the 5-alkyl-1,3,4-thiadiazines behave as cyclic thiosemicarbazones, undergoing hydrolytic ring opening in the presence of strong hydrochloric acid followed by ring closure to the 3-amino-2-thiazolimine. The present paper reports an examination of the rates of the rearrangement in acid solution undergone by 2-amino-1,3,4-thiadiazines (1)



(1) (2)

R = Me, Et, Pr^i, Bu^t, $PhCH_2$, Ph, *p*-$O_2NC_6H_4$, *p*-$HO\text{-}C_6H_4$

with alkyl and aryl groups in the 5 position, and a study of the variation in rearrangement rate of 2-amino-5-methyl-1,3,4-thiadiazine (1) with changing hydrochloric acid concentration. Together with deuterium exchange experiments, which were also carried out, the work was directed towards the determination of the rearrangement mechanism.

EXPERIMENTAL AND RESULTS

Preparation of 5-Substituted 2-Amino-1,3,4-thiadiazine Hydrohalides (1).—These compounds were prepared by the reaction of α-halogeno-ketones with thiosemicarbazide, three different methods being employed. When the α-halogeno-ketone was not commercially available, α-chloro-ketones were prepared from the acid chloride *via* the diazo-ketone: [6]

$$R{\cdot}COCl + CH_2N_2 \longrightarrow R{\cdot}COCHN_2 \xrightarrow{HCl\ gas} RCOCH_2Cl + N_2$$

Physical and analytical data of the hydrochlorides of the products are given in Table 1. The methods of preparation are described below.

Method A.[1] Thiosemicarbazide (0.1 mol) was dissolved in warm 2M-HCl (50 cm^3). The filtered solution was cooled in ice and the α-halogeno-ketone (0.1 mol) was added dropwise with stirring. The resultant precipitate of the thiosemicarbazone was filtered off, washed with ice-cold water, and dried *in vacuo* at 40 °C. The thiosemicarbazone was dissolved in the minimum quantity of boiling absolute ethanol to give an orange-coloured solution. On cooling this solution in ice, pale yellow crystals of the 2-amino-1,3,4-thiadiazine hydrohalide (1) were obtained. The products were recrystallised by dissolution in the minimum quantity of warm water and addition of an excess of acetone; crystallisation occurred rapidly and the products obtained in this way were usually pure white and showed no trace of impurity when examined by t.l.c. About 90% recovery was achieved.

Method B.[7] The thiosemicarbazide (0.1 mol) was refluxed in absolute ethanol (50 cm^3) and to it a solution of the halogeno-ketone (0.1 mol) in absolute ethanol (75 cm^3) was added with stirring. The resultant orange-coloured solution was cooled in ice when yellow crystals of the 2-amino-1,3,4-thiadiazine hydrohalide (1) were obtained. Products were crystallised from water–acetone as described in method A.

Method C. Thiosemicarbazide hydrochloride (0.01 mol) was dissolved in dimethylformamide (15 cm^3) and the halogeno-ketone (0.01 mol) added. The mixture was shaken for a few minutes with gentle warming and then an excess (*ca.* 25 cm^3) of acetone was added. Crystallisation of the 2-amino-1,3,4-thiadiazine hydrochloride (1) usually occurred rapidly. The products obtained by this method were found to be quite pure by t.l.c. and further crystallisation was unnecessary.

Method C was generally found to be most suitable for reactions employing aliphatic α-halogeno-ketones. For preparations using acetophenone derivatives, Method B was usually found to be more successful.

TABLE 1

Preparation, physical and analytical data of 2-amino-1,3,4-thiadiazine hydrochlorides

Substituent in 5-position	α-Halogeno-ketone	Method	Yield (%)	M.p. (*t*/°C)	N.m.r.[a] (δ values, *J* in Hz) Ring CH_2	N.m.r.[a] (δ values, *J* in Hz) Substituent	Analyses (%) Found C	H	N	S	Cl	Required C	H	N	S	Cl	M^+[b] (free base) *m/e*
Me	Chloroacetone	A	34	172	3.75	2.15 (Me)	28.85	4.75	25.8	19.25	21.35	29.0	4.83	25.37	19.33	21.45	129
Me	Chloroacetone	B	68														
Me	Chloroacetone	C	54														
Et	1-Chloro-butanone	C	56	185	3.80	1.10 (t, *J* 7.5, Me), 2.55 (q, *J* 7.5, CH_2)	33.2	5.65	23.1	17.5	19.6	33.42	5.57	23.40	17.83	19.78	143
Pr^i	1-Chloro-3-methyl-butanone	C	21	135	3.80	1.15 (d, *J* 6.5, Me_2), 3.00 (m, CH)	36.35	6.15	20.85	16.05	18.6	37.21	6.20	21.70	16.53	18.35	157
Bu^t	1-Chloro-3,3-dimethyl-butanone	C	72	220	3.80	1.15 (Me_3)	40.25	6.75	20.35	15.6	16.95	40.48	6.75	20.24	15.42	17.11	171
$PhCH_2$	1-Chloro-3-phenyl-acetone	C	58	188	3.70	3.85 (CH_2), 7.30 (Ph)	49.55	5.15	17.3	13.5	14.8	46.69	4.97	17.39	13.25	14.70	205
Ph	α-Chloro-acetophenone	B	51	207	4.32	7.6 and 7.9 (m, Ph)	47.45	4.3	18.5	14.2	15.4	47.47	4.39	18.46	14.06	15.60	191
p-$O_2NC_6H_4$[c]	4-Nitro-α-bromo-aceto-phenone	C	30	236	4.45	8.15 and 8.40 (d, *J* 9.0, Ph)	39.2	3.55	20.4	11.75	12.75	39.63	3.30	20.55	11.74	13.03	236[d]
p-HOC_6H_4	4-Hydroxy-α-chloro-acetophenone	B	27	220	4.25	6.90 and 7.75 (d, *J* 8.5, Ph)	41.75	4.55	16.05	12.1	13.25	41.30	4.59	16.06	12.24	13.58	207

[a] All signals observed in $(CD_3)_2SO$ using a Varian T60 n.m.r. spectrometer. All peaks are singlets unless otherwise indicated. In all cases the 2-amino-group appeared as a broad peak at δ 10—11. [b] M^+ obtained with hydrochlorides using a Hitachi-Perkin-Elmer RMS-4 mass spectrometer. M^+ corresponds to the molecular weight of the free base. [c] The product was recrystallised from HCl to give the pure hydrochloride. [d] M^+ obtained using the free base.

The following thiazolimines were obtained from the corresponding thiadiazines on treatment with concentrated HCl. 3-Amino-4-methyl-2-thiazolimine hydrochloride (2), m.p. 232 °C (Found: C, 29.0; H, 4.73; Cl, 21.2; N, 26.0; S, 19.1%; $C_4H_8ClN_3S$ requires C, 29.0; H, 4.83; Cl, 21.5; N, 25.4; S, 19.3%); n.m.r. [δ, $(CD_3)_2SO$], 2.30 (s, Me), 6.25 (s, N–NH_2), 6.60 (s, =CH), and 9.55 (s, $=N^+H_2$); M^+ at *m/e* 129; free base, m.p. 100 °C (Found: C, 37.2; H, 4.84; N, 32.5; S, 25.2%; $C_4H_7N_3S$ requires C, 37.2; H, 5.43; N, 32.6; S, 24.8%); n.m.r. (δ, $CDCl_3$), 2.1 (slight splitting, Me), 4.2 (s, NH_2), 5.3 (slight splitting, =CH), and 5.9 (s, =NH). 3-Amino-4-ethyl-2-thiazolimine hydrochloride (2), m.p. 190 °C (Found: C, 33.5; H, 5.62; Cl, 19.8; N, 23.3; S, 18.0%; $C_5H_{10}ClN_3S$ requires C, 33.4; H, 5.57; Cl, 19.8; N, 23.4; S, 17.8%); n.m.r. [δ, $(CD_3)_2SO$], 1.15 (t, Me), 2.65 (q, *J* 7.0 Hz, CH_2), 6.25 (s, $-NH_2$), 6.55 (s, =CH), and 9.65 (s, $=N^+H_2$), peaks at δ 6.25 and 9.65 disappear in presence of D_2O. 3-Amino-4-benzylthiazolimine hydrochloride (2), m.p. 220 °C (Found: C, 49.6; H, 5.03; Cl, 14.9; N, 17.4; S, 13.0%; $C_{10}H_{12}ClN_3S$ requires C, 49.7; H, 4.97; Cl, 14.7; N, 17.4; S, 13.3%); n.m.r. [δ, $(CD_3)_2SO$], 4.10 (s, CH_2), 6.15 (s, =CH), 7.35 (s, Ph), 9.80 (s, $=N^+H_2$), and 6.30 (s, NH_2); the peaks at δ 9.80 and 6.30 disappear in presence of D_2O.

Kinetics.—The Beer–Lambert Law was verified for 2-amino-5-methyl-1,3,4-thiadiazine and 3-amino-4-methyl-2-thiazolimine in both acidic and basic solution. In acid solution the biggest difference in absorbance between the thiadiazine and 2-thiazolimine occurs at 210 nm and the former has the greater absorbance at this wavelength. However, measurements at such a low wavelength suffer from greater background 'noise' compared to measurements at longer wavelengths Furthermore, the absorption at 210 nm corresponds to neither a maximum nor a minimum and measurement of absorbance is less accurate when $d\varepsilon/d\lambda$ is not equal to zero In alkaline solution, the absorbance at 260 nm corresponds to an absorption maxi-

mum for the 2-thiazolimine and $d\varepsilon/d\lambda$ for the thiadiazine is fairly small at this wavelength (the absorption minimum of the thiadiazines is at 253 nm). Use of this wavelength requires that portions of the acidic reaction solution be removed and made alkaline before the absorbance is measured. Between pH 4 and 8 the spectra of substrate and product change quite markedly due to the changing concentration of unprotonated and protonated species. However, below pH 4 and above pH 8 constant spectra were obtained. Consequently, absorbances were measured either below pH 4 (by the direct Method 1, see below) or above pH 8 (by the indirect basification Method 2, see below).

Method 1. The thiadiazine hydrochloride solutions (4 mg in 50 cm^3) were made up accurately at the required temperature. The absorbance at 210 nm was recorded by a Unicam SP800 or SP8000 spectrophotometer at 30 or 50 °C using a thermostatically controlled cell carrier.

At the end of each run selected readings were taken from the recorder chart and used in the rate constant determination.

Method 2. At 100—1 000 s intervals, 2 cm^3 portions of an accurately prepared solution (40 mg in 50 cm^3) of the thiadiazine hydrochloride kept at 30 or 50 °C were pipetted into *ca.* 40 cm^3 of aqueous ammonia. The absorbance was measured at 260 nm.

In both methods, an infinity reading was taken after 24 h. The acid concentration was greatly in excess of the thiadiazine concentration (10 000 : 1 in Method 1 and 1 000 : 1 in Method 2). Both methods of measurement were used when 2-amino-5-methyl-1,3,4-thiadiazine was the substrate at 30 and 50 °C, and the values of k_1 obtained by use of the two methods agree to within 25% at 30 °C and 15% at 50 °C.

Plots of ln [thiadiazine] against t in each case show a good linear relationship for the greater part of the reaction but towards the end of the reaction a ' tailing off ' occurs. This suggests the reaction might be reversible. The reversibility was confirmed by t.l.c. experiments which showed that even after 24 h a spot due to the thiadiazine could still be observed in some cases. This was particularly noticeable when 2-amino-5-isopropyl-1,3,4-thiadiazine was the substrate since this compound was still present even after prolonged boiling with concentrated hydrochloric acid.

For a reversible first-order reaction it can be shown that

$$\ln \frac{(E_\infty - E_0)}{(E_\infty - E_t)} = k_1 t$$

where E_0, E_t, and E_∞ are the absorbances at zero time, time t, and infinite time respectively, and k_1 is equal to the sum of the velocity constants ($k_r + k_{-r}$) of the forward (k_r) and backward (k_{-r}) reactions. Since the measurement of values of E_0 and E_∞ is subject to experimental error a computer program using an interative Newton–Raphson procedure programmed for the I.C.C. 1900 computer, developed by Dr. D. N. Waters and previously described,[5] was used to obtain best-fit values (in the least squares sense) of E_0, E_∞, and k_1.

Values of k_1 for the rearrangement of 5-methyl, 5-isopropyl, 5-t-butyl, 5-benzyl, 5-phenyl, 5-(*p*-hydroxyphenyl), and 5-(*p*-nitrophenyl)-2-amino-1,3,4-thiadiazines in hydrochloric acid at 30 and 50° are given in Table 2. The effect of addition of electrolytic (NaCl) on the rearrangement rate of 2-amino-5-methyl-1,3,4-thiadiazine is illustrated in Table 3. The variations in k_1 and of the forward (k_r) velocity constant for the rearrangement of 2-amino-5-methyl-1,3,4-thiadiazine with changing acid concentration are given in Table 4.

TABLE 2 [a]

Rate constants [b] for the rearrangement of 2-amino-1,3,4-thiadiazines in sulphuric acid at 30 °C and in hydrochloric acid at 30 and 50 °C

	Rate constants $k_1 \times 10^4$ (s^{-1})			
Substituent in 5-position	H_2SO_4 (5.0 mol dm^{-3}) 30 °C	H_2SO_4 (6.0 mol dm^{-3}) 30 °C	HCl (5.0 mol dm^{-3}) 30 °C	HCl (5.0 mol dm^{-3}) 50 °C
Me	5.25	8.78	2.73 (2.12)	23.5 (20.3)
Et	4.55	8.23	2.53	20.2
Pr^i	1.64	4.13	0.505	2.44
Bu^t	Very small	Very small	Very small	Very small
$PhCH_2$				1.93

[a] All results quoted were obtained by the indirect method of absorption measurement except for values quoted in parentheses which were obtained by the direct method. [b] The thiadiazines with the 5-aryl substituents phenyl *p*-nitrophenyl and *p*-hydroxyphenyl which are not included in the Table, behaved similar to 2-amino-5-t-butyl-1,3,4-thiadiazine, *i.e.* rearrangement was hardly perceivable in these cases.

TABLE 3

Rate constants for the rearrangement of 2-amino-5-methyl-1,3,4-thiadiazine in 1M-HCl solutions containing varying amounts of NaCl at 50 °C [a]

NaCl concentration (mol l^{-1})	k_1 ($s^{-1} \times 10^4$)
0	0.58
2.0	1.71
4.0	5.06

[a] Absorbances were measured by the direct Method 1.

TABLE 4

Rate constants for the rearrangement of 2-amino-5-methyl-1,3,4-thiadiazine in hydrochloric acid at 30 °C [a]

Acid concentration (mol l^{-1} HCl)	Rate constant k_1 [b] ($s^{-1} \times 10^4$)	Forward velocity constant, k_r ($s^{-1} \times 10^4$)	Unbound water concentration, c_w (l^{-1})
4.47	1.0	1.11	0.588
4.98	2.12	1.46	0.541
5.47	3.11	2.04	0.494
5.67	3.99	2.52	0.472
5.97	4.93	3.45	0.448
6.20	6.62	4.38	0.426
6.46	7.88	5.14	0.402
6.74	10.0	6.24	0.376
6.96	12.1	7.61	0.355
7.25	13.4		0.326
7.55	17.9		0.300
8.2	23.5		0.246

[a] Absorbances were measured by the direct Method 1. [b] $k_1 = k_r + k_{-r}$.

Deuterium exchange experiments. Solutions of the thiadiazines in D_2O of strength 0.5M in each case were made up containing the hydrochlorides of 5-methyl, 5-ethyl, 5-benzyl, 5-t-butyl, and 5-phenyl substituted 2-amino-1,3,4-thiadiazines respectively. After one week, the n.m.r. spectrum of each solution was obtained. A comparison of the signals due to the ring CH_2 group and the 5-substituent group indicated no incorporation of deuterium at the 6-position.

Solutions of 2-amino-5-methyl-1,3,4-thiadiazine hydrochloride (0.5M) were made up in 5.6M-H_2SO_4. After 24 h

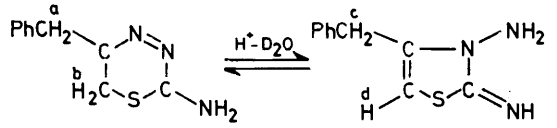
the rearrangement was almost complete and had slowed to an apparent stop. A comparison of the heteroaromatic protons' n.m.r. signal (δ 7.1) and the methyl signal (δ 2.6) indicated 30% inclusion of deuterium into the 5-position of the thiazolimine.

2-Amino-5-phenyl-1,3,4-thiadiazine hydrochloride (0.205 g) and 2-amino-5-t-butyl-1,3,4-thiadiazine (0.200 g) were each dissolved in a mixture of D_2O (1 cm³) and concentrated HCl (1 cm³). Both solutions were heated on a boiling water-bath for 5 min and then cooled in ice to give crystalline products. In each case the n.m.r. spectrum of the crystals, dissolved in $(CD_3)_2SO$, indicated that the thiadiazine hydrochlorides had undergone no rearrangement. The integrals of the ring CH_2 group signal and the 5-substituent were measured and compared. For the 5-phenyl compound, the ratio of the phenyl signal peaks (δ 7.4—8.1) and the ring CH_2 signal peaks (δ 4.35) was 5 : 1.27 which represents *ca.* 37% inclusion of deuterium at the 6-position. For the t-butyl compound the ratio of the signal peaks of t-butyl group (δ 1.15) to the ring CH_2 group (δ 3.8) was 9 : 1.13 which represents *ca.* 44% inclusion of deuterium.

2-Amino-5-benzyl-1,3,4-thiadiazine hydrochloride (0.123 g) was dissolved in a mixture of D_2O (1 cm³) and concentrated H_2SO_4 (0.4 cm³) and the mixture allowed to stand at room temperature. The n.m.r. spectrum of the mixture was taken almost immediately and then after *ca.* 2, 3½, 5½, and 22 h. The values of the n.m.r. signal integrals for the benzyl CH_2 and ring CH_2 groups in the thiadiazine and the thiazolimine are given in Table 5.

TABLE 5

The values of n.m.r. peak integrals for the benzyl and ring methylene groups in 2-amino-5-benzyl-1,3,4-thiadiazine and 3-amino-4-benzyl-2-thiazolimine in sulphuric acid–deuterium oxide solution



Time (h)	N.m.r. peak integrals: *a* (δ 3.75)	*b* (δ 3.35)	*c* (δ 3.85)	*d* (δ 5.80)	*a* + *c*	100 (*a* − *b*)/*a*
0	40	35	0		40	12.5
2	18	11.5	24		42	36
3.5	13	6	28		41	54
5.5	7	2.5	34		41	64
22.5	0	0	42	13	42	

Since the total integral *a* + *c* (Table 5) of the benzylic protons signal remained more or less unchanged, it was assumed that no deuterium was incorporated in the benzyl CH_2 group. The fact that *b* becomes progressively smaller than *a* suggests that deuterium is incorporated at the 6-position of the thiadiazine ring and 100 (*a* − *b*)/*a* gives the approximate percentage deuteriation. After 22½ h, rearrangement was virtually complete. The ratio of *c* to *d* suggests 38% inclusion of deuterium at the 5-position of the thiazolimine.

DISCUSSION

The effect on the value of k_1 of varying the substituent in the 5-position of 2-amino-1,3,4-thiadiazines is shown in Table 2. The reaction is reversible and appears to approach equilibrium after several hours. The observed first-order velocity constant, k_1, is equal to the sum of the forward and backward velocity constants ($k_r + k_{-r}$). It was found that the equilibrium concentration of the reactant increases along the series 5-methyl, 5-ethyl, 5-isopropyl, 5-t-butyl. Thus, the values of the forward velocity constant decrease along the series more rapidly than k_1. Hence it is apparent that as the hydrogen atoms of the 5-methyl group are successively substituted by methyl groups the rate of rearrangement is increasingly slowed down. The greatest change occurs when the α-H atom of the 5-isopropyl compound is replaced by a methyl group. Thus, 2-amino-5-t-butyl-1,3,4-thiadiazine hardly rearranges at all. This behaviour is similar to that observed in the nucleophilic substitution by an S_N2 mechanism of the alkyl bromide series:[9] $MeCH_2Br > MeCH_2CH_2Br \gg Me_2CH{\cdot}CH_2Br \gg\gg Me_3C{\cdot}CH_2Br$. This suggests that the rearrangement involves a rate-determining step characteristic of an S_N2 reaction and that the centre of attack is the carbon atom at position 5. This carbon atom may, therefore, become saturated before the rate-determining stage is reached. Since the 5-phenyl, 5-(*p*-nitrophenyl), and 5-(*p*-hydroxyphenyl) substituted thiadiazines do not react appreciably, the possibility that the carbon atom at position 5 is sp^2 hybridised (as for instance might arise if the charge of a carbonium ion were centred at the 5-position) at the rate-determining stage is unlikely. Furthermore, as there was nothing to choose between the effects of the phenyl, *p*-nitrophenyl, and *p*-hydroxyphenyl groups on the rate of rearrangement, and their effect was powerfully retarding, the most likely explanation is that a large aryl group hinders attack at position 5.

The addition of increasing amounts of sodium chloride to the reaction mixture increases the rate of the rearrangement of 2-amino-5-methyl-1,3,4-thiadiazine (Table 3). This is to be expected if a diprotonated species is involved. However, this finding cannot be conclusive evidence for the involvement of a diprotonated species since an increase in rate could, for instance, arise due to an effective change in the value of the acidity function.

The variation of the observed first-order velocity constant k_1, with changing hydrochloric acid concentration over the range 4.47—8.12M was investigated (Table 4). The Hammett acidity function H_0 could not be determined for thiadiazine bases. It is quite probable that the reaction involves diprotonation since the relatively strongly basic thiadiazines are substantially protonated at acidities lower than pH 4 and reaction rates are hardly apparent until the increasing acid strength approaches 4M-HCl. At this strength of acid, rearrangement rates increase rapidly. Thus, it is possible that the appropriate acidity function in this case is H_+ rather than H_0. A number of workers [10-14] have shown that H_+ acidity functions closely follow the corresponding H_0 scale although this is not always the case. There are examples quoted [15-19] where $\log_{10} k_1$ has been correlated with H_0 (in the absence of appropriate H_+ functions), for reactions which were known to involve

diprotonated species. In these cases a good linear relationship between $\log_{10} k_1$ and H_0 has been quoted [20] as further evidence that H_0 and H_+ are parallel functions. Assuming the H_0 values determined by Paul and Long [21] based on substituted anilines are applicable, a plot of $\log_{10} k_1$ against these $-H_0$ values (Figure 1) in the present case is linear and of slope equal to 0.92, *i.e.* almost unity. The values of H_0 were determined by Paul and Long [21] at 25 °C whereas the present work was carried out at 30 °C. However, Gel'bshtein *et al.*[22,23] have shown that although H_0 functions do vary with temperature over a range of concentration the acidity functions between 20 and 80 °C vary in a parallel manner with respect to each other. However, since k_1 is equal to $(k_r + k_{-r})$ any plots involving k_1, acidity functions, and water activities would only be meaningful if both k_r and k_{-r} were similarly dependent on acidity and water activities. Estimates of k_r and k_{-r} were made using the following relations:

$$x_e = \frac{E_\infty - E_0}{(\varepsilon_A - \varepsilon_B)1} \quad \text{and} \quad K_r = \frac{k_r}{k_{-r}} = \frac{x_e}{(a - x_e)}$$

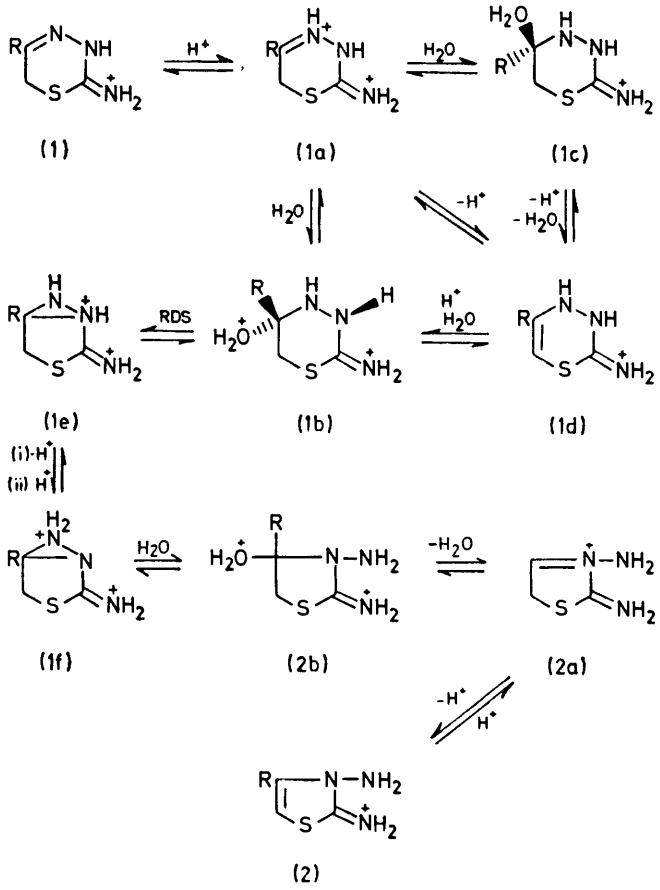
In fact, both k_r and k_{-r} showed the same dependency on H_0 as k_1. Thus K_r (= 1.94 for the 2-amino-5-methyl-1,3,5-thiadiazine ⇌ 3-amino-4-methyl-2-thiazolimine rearrangement at 30 °C) is independent of acidity over the range 4.47—8.12M-HCl. Also, plots of either $\log_{10}$ $(k_r + H_0)$ or $\log_{10}$ $(k_{-r} + H_0)$ against $\log_{10}$ a_w gave similar slopes. Hereafter, therefore, the discussion will refer to the dependency of k_1 rather than either k_r or k_{-r} on acidity. The linearity and unit slope of the $\log_{10}$ $k_1/-H_0$ plot might suggest that either the rate-determining step follows a fast protonating pre-equilibrium (the Zucker–Hammett criterion [24,25] for an *A*-1 type mechanism) to give a diprotonated species or that protonation of some reactive species (in this instance a species probably already carrying a proton) occurs during the rate-determining step.[25,26] A plot of $\log_{10}$ k_1 against $\log_{10}$ c_{H^+} is not linear and the value of the best-line slope is far from unity. A plot of $(\log_{10} k_1 + H_0)$ against $\log_{10} a_w$ is rather scattered about a best-line slope of value 0.47. When $(\log_{10} k_1 + H_0)$ is plotted against $(H_0 + \log_{10} c_{H^+})$ to test the linear free-energy relationship suggested by Bunnett and Olson [27] a curve results.

Another approach to the role of water in reactions carried out in strong acid is provided by the method of Yagil.[28,29] This method uses the model of Bascombe and Bell [30,31] derived from the conclusion of Eigen *et al.*[32,33] that the most probable number of water molecules with which a proton is strongly associated is four. Since the observed velocity constant k_1 is given by $k_1 = k\, c_{H^+}\, c_W^n$ where c_W is the concentration in mol dm^{-3} of unbound water normalised by dividing by $(1000d_0)/18$ (where d is the density of the solvent) and n the order of the reaction with respect to the unbound water concentration, then $\log_{10} k_1/c_{H^+} = n \log_{10} c_W +$ constant. In the presen tcase a plot of $\log_{10} k_1/c_{H^+}$ against $\log_{10} c_W$ (Figure 2 and Table 4) gave a value for n of −2.95 which, according to Yagil's approach could mean that a proton is taken up during the formation of the transition state of the rate-determining step. In such a case four water molecules would be given up by the proton to the solvent thereby increasing c_W, but an n value of −2.95 would require that a water molecule is involved in the transition state of the rate-determining step. Effectively, an almost similar plot to this had already been suggested by Bunnett [34] as a test for the *A*-2 type mechanism, *i.e.* if a plot of $\log_{10} k_1/c_{H^+}$ against $\log_{10} a_w$ is of slope (w^*) less than −2 then water is involved as a nucleophile. In fact this plot in the present case has a slope of −5.4 which is clearly indicative of involvement of water as a nucleophile. Bunnett's treatment is more diagnostic of the role played by water than that of Zucker and Hammett. Also, the former approach differs from that of Yagil in that the latter assumes, not without justification, that the association of four water molecules with each proton is an over-riding factor. There is little that can be said about the plot of $\log_{10} k_1/-H_0$ except that when the value of the slope is less than 1 the corresponding value of w is positive. The present case would appear to be no exception since the plot gives a slope of 0.92 and w is 0.47.

The hydrogen atoms attached to the 6 position in all the thiadiazines investigated are replaceable by deuterium in deuterium oxide solution. But this occurs only in strong acid and not at all in dilute acid. This replacement occurs even when the rearrangement is proceeding apace in strong acid. Thus, during rearrangement deuterium is incorporated into the 6 position of 2-amino-5-benzyl-1,3,4-thiadiazine and also into position 5 of the product thiazolimine. A suggested mechanism involving structures (1) and (1a—d) which could account for the incorporation of deuterium at position 6 of the thiadiazine is given in Scheme 1. The fact that incorporation of deuterium at position 6 of the thiadiazine occurs only when solutions are acidic enough for the rearrangement to take place suggests that there may be a connection between these two processes. It is possible, therefore, that one or a number of the structures represented by (1a—d) that are included in Scheme 1, may also be involved in the rearrangement. The 5-t-butyl- and 5-aryl-thiadiazines, which do not undergo the rearrangement, also incorporate deuterium in the 6 position. Thus, if (1a) and/or (1b) and/or (1c) and/or (1d) lie along the rearrangement route, whichever of them is involved must be formed before the rate-determining step.

Before much can be said about the rearrangement the problem as to whether or not the thiadiazine ring is opened at some stage must be answered. Opening of the ring would allow formation of some hydrazinothiazole as well as thiazolimine. In fact no product other than the thiazolimine was obtained even when the thiadiazines were converted rapidly into thiazolimines in boiling hydrochloric acid. Only with the 5-phenyl-thiadiazine—which hardly rearranges at all—after prolonged boiling with concentrated hydrochloric acid was there any trace of hydrazinothiazole (along with a very small amount of thiazolimine). When attempts were made to carry out rate measurements on 2-amino-5-methyl-1,3,4-thiadiazine at much lower acid concen-

trations (0.1M), higher temperatures were necessary, and under these conditions there was an indication by t.l.c. of a little hydrazinothiazole formation. The C=N thiosemicarbazone linkage would be the most vulnerable part of the thiadiazine ring to succumb to breakage under hydrolytic conditions. However, thiosemicarbazones such as acetone thiosemicarbazone are recovered quantitatively unchanged from hydrochloric acid solutions of strengths able to catalyse the thiadiazine–thiazolimine rearrangement. For instance, acetone thiosemicarbazone is recovered quantitatively unchanged from 7M-HCl at 30 °C after 2 h, whereas the rearrangement of 2-amino-5-methyl-1,3,4-thiadiazine is almost



SCHEME 1 Suggested mechanism {(1) ⇌ (1a) ⇌ (1b) [or (1d)] ⇌ (1c)} for proton (and deuteron) exchange at position 6 in the 2-amino-1,3,4-thiadiazine ring. The Scheme also includes a suggested mechanism for the rearrangement of 5-substituted 2-amino-1,3,4-thiadiazines in strong acid solution

over after an hour under the same conditions. In addition it is difficult to understand how—if the ring were to open—it should close again *via* an S_N2-type mechanism. It is also difficult to understand why the nitrogen atom, which would originally have occupied position 3 in the 1,3,4-thiadiazine ring, could behave as a nucleophile in an opened structure in the strongly acid solutions that are necessary to bring about rearrangement. It will be shown later that the nucleophilicity of this nitrogen atom can feasibly be understood to arise

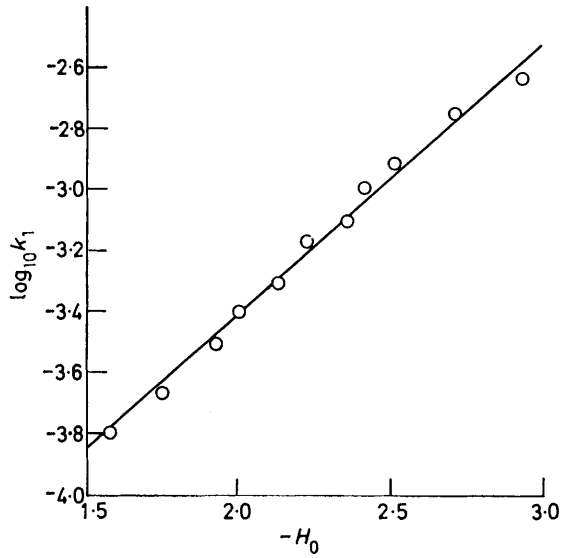


FIGURE 1 Plot of $\log_{10} k_1$ against $-H_0$ for the rearrangement of 2-amino-5-methyl-1,3,4-thiadiazine in various strengths of hydrochloric acid solution at 30 °C. The H_0 values are those of Paul and Long.[21]

from an appreciation of the conformations taken up by a diprotonated thiadiazine species. Contrary to Beyer's suggestion [4,5] it is doubtful, therefore, if the thiadiazine ring is opened at any time during the rearrangement in strong acid in the temperature range 30—50 °C.

Apart from water the most likely nucleophile is the N-3 nitrogen atom in the 1,3,4-thiadiazine ring. The problem arises as to how this nitrogen atom can become

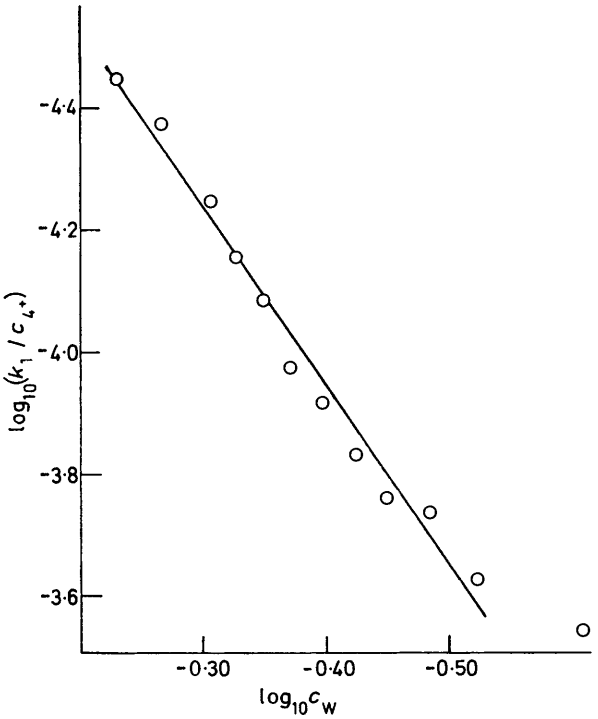
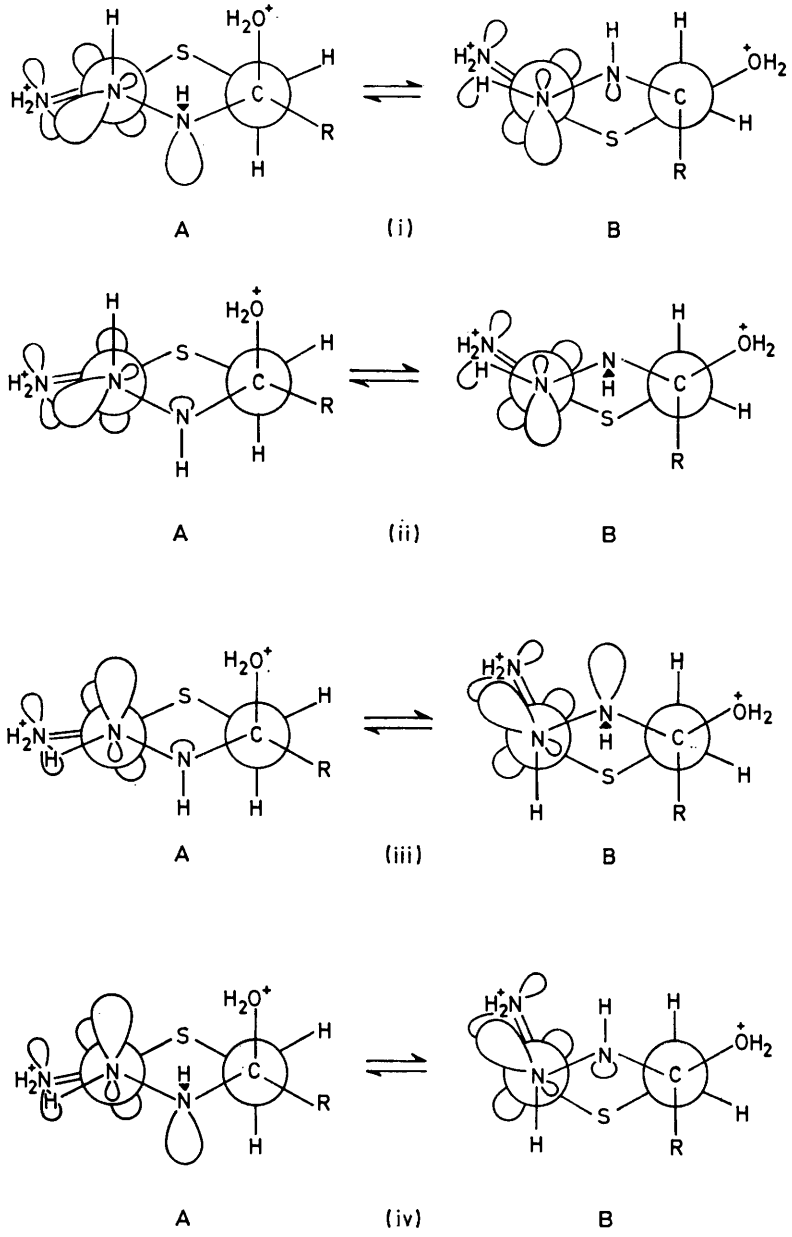


FIGURE 2 Plot of $\log_{10} k_1/c_{H^+}$ against $\log_{10} c_w$ for the rearrangement of 2-amino-5-methyl-1,3,4-thiadiazine in various strengths of hydrochloric acid solution at 30 °C

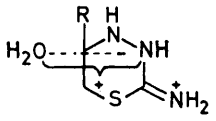
sufficiently nucleophilic in strong acidic media. Provided that the N-3 atom does not participate along with the amino-nitrogen atom in the delocalisation of the positive charge, it is possible that the N-3 atom would be nucleophilic enough to attack the C-5 atom. However, some additional constraint might be necessary since tercovalent nitrogen atoms are not very strong nucleophiles. The C-5 atom would be rendered more susceptible to attack by a nucleophile if it became attached to water. This is quite possible since the protonated thiadiazine (1a) would be susceptible to relatively rapid attack at C-5 by water (1b). A further constraint might arise from the formation of a stable thiazole derivative which would unbalance all previous equilibria towards the forward direction. The saturated carbon atom, C-5, could then undergo S_N2 attack by the N-3 atom provided the latter were to become sufficiently nucleophilic. Thus a structure such as that depicted (1a) in Scheme 1 would be susceptible to attack by water at the C-5 atom. Since water could attack from above or below the ring of the diprotonated structure (1a), eight stereoisomeric forms of (1b) could result. The eight stereoisomers comprise four geometric isomers, (i), (ii), (iii), and (iv) (Scheme 2) each of which can exist as a pair of enantiomorphs. Each stereoisomer can exist in two extreme conformations, A and B (Scheme 2). The equatorially disposed atoms or groups in one of these conformations are axially arranged in the other conformation. Two of the isomers, (iii) and



SCHEME 2 Possible conformations for the hydrated diprotonated 2-amino-1,3,4-thiadiazine intermediate (1b)

(iv), include a conformation B which would closely approximate to the steric requirement for S_N2-type transannular attack by the N-3 atom at C-5. These two conformations, (iii) B and (iv) B, happen to include a nitrogen atom, N-3, which is incapable of delocalising the positive charge on the immonium nitrogen atom. This is because the axis of the lone-pair *p*-type orbital of N-3 is more or less transversely orientated with respect to the *p* orbitals of the immonium nitrogen atom and C-2. Thus, N-3 atom would have the nucleophilic capability of attacking C-5 atom—such as that represented in the structure (1b) (Scheme 1)—which has acquired a vulnerability to nucleophilic attack. If such a reaction took place, half the possible geometric isomers of (1b), (iii) and (iv), could be intermediates which lie along the route to the formation of the thiazolimine (2). A suggested mechanism which includes this possibility is outlined in Scheme 1. The rate-determining stage, (1b) (iii) and (iv) ⟶ (1e), would lead to an intermediate which includes a diaziridine ring (1e). The migration of a proton to that nitrogen atom which had originally occupied position 4 in the thiadiazine ring, would yield the diaziridine (1f). The formation of the monoprotonated thiazolimine (2) could then be envisaged as a rapid S_N2 attack by water to give the imine (2b) followed by loss of water (2a) and completed by loss of a proton from (2a).

The most stable conformations of (1b) might be expected to include the bulky alkyl or aryl group (R, Scheme 2) in the equatorial orientation. However, in the A conformations of the geometric isomers (iii) and (iv), and similarly in the B conformations of (i) and (ii), the axis of the N-3 *p*-type orbital—which includes the lone pair of electrons—is arranged in a skew manner with respect to the *p* orbitals of the C-5 atom and the immonium nitrogen atom. Some degree of overlap would be expected from these orbitals which would stabilise the structure. In the A conformations of (i) and (ii), and similarly in the B conformations of (iii) and (iv), the axis of the N-3 *p*-type orbital carrying the lone pair of electrons is more or less transversely orientated with respect to the *p* orbitals of the C-5 and immonium nitrogen atoms. Thus, the A conformations of (iii) and (iv) should be more stable than (*a*) the corresponding B conformations of each of these isomers and (*b*) either the A or B conformations of the isomers (i) and (ii). Consequently, in a system of equilibria such as that illustrated in Scheme 1, there should be more of the (1b) isomers (iii) and (iv) than the (1c) isomers, (i) and (ii). It is the B conformations in each case of the isomers (iii) and (iv) which represent a steric condition somewhere along the way towards the S_N2 type transition state (1b′) that would be formed in the suggested rate-determining stage (1b) ⟶ (1e). Furthermore, these (1b) B conformations, (iii) and (iv), both include the R group in the axial position. It is unlikely that such bulky groups as t-butyl and aryl could occur in axial positions. This may account for the sudden drop in rate when R is either t-butyl or aryl.



(1b′)

The rearrangement route outlined in Scheme 1 included two successive pre-equilibria. Writing the first of these equilibria after the manner of Bascombe and Bell: [30]

$$(1) + H^+hH_2O \underset{k_{-a}}{\overset{k_a}{\rightleftharpoons}} (1a) + hH_2O \text{ (fast equilibrium)} \quad (i)$$

This is followed by a second equilibrium, and then by the rate-determining stage and the remaining reaction stages:

$$(1a) + H_2O \underset{k_{-b}}{\overset{k_b}{\rightleftharpoons}} (1b) \text{ (fast equilibrium)} \quad (ii)$$

$$(1b) \underset{k_{-e}}{\overset{k_e}{\rightleftharpoons}} (1e) + H_2O \text{ (slow, forward)} \quad (iii)$$

$$(1e) \underset{k_{-f}}{\overset{k_f}{\rightleftharpoons}} (1f) \quad (iv)$$

$$(1f) + H_2O \underset{k_{-2b}}{\overset{k_{2b}}{\rightleftharpoons}} (2b) \quad (v)$$

$$(2b) \underset{k_{-2a}}{\overset{k_{2a}}{\rightleftharpoons}} (2a) + H_2O \quad (vi)$$

$$(2a) + hH_2O \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} (2) + H^+hH_2O \quad (vii)$$

Provided $c_{1a} \ll c_1$ and $c_{1b} \ll c_1$ it can be shown that the first-order velocity constant (k_r) of the forward reaction is given by the following relation:

$$k_r = K_aK_bk_eh_+a_w\frac{\gamma_{1a}}{\gamma_r^{\ddagger}}$$

where $h_+ = \dfrac{a_{H_+}\gamma_1}{a_w^h\gamma_{1a}}$

Further, since $h_0 = \dfrac{a_{H_+}\gamma_{ArNH_2}}{a_w^h\gamma_{ArNH_3^+}}$

$$k_r = K_aK_bk_eh_oa_w\frac{\gamma_1\gamma_{ArNH_3^+}}{\gamma_r^{\ddagger}\gamma_{ArNH_2}}$$

Thus, $\log_{10} k_r = \log_{10} K_aK_bk_e - H_0 + \log_{10} a_w +$

$$\log_{10}\frac{\gamma_1\gamma_{ArNH_3^+}}{\gamma_r^{\ddagger}\gamma_{ArNH_2}}$$

A similar treatment of the alternative rearrangement routes which precede the rate-determining stage, *i.e.* (1) ⟶ (1a) ⟶ (1c) ⟶ (1d) ⟶ (1b) or (1) ⟶ (1a) ⟶ (1d) ⟶ (1b) would lead to a similar expression.

For a given acid strength and when the acid is in large excess compared to c_1, k_r will depend on $K_aK_bk_e$. If the four variations of (1) represented by the series in which R is Me, Et, Pr^i, and Bu^t give rise to different K_a values, such differences should be reflected in changes in the forward velocity constant, k_r. Since k_r is equal to $(k_1 - k_{-r})$ and k_{-r} increases along the series, k_r decreases

more rapidly than k_1. The question arises: is the factor k_e more responsible than the two factors K_AK_B for the variation in rearrangement rate (k_r) when R is changed? The equilibrium constant K_a is a measure of the basicity of the monoprotonated thiadiazine (1). The basicities of the monoprotonated 5-alkylthiadiazines would, at first sight, be expected to vary due to the variation in hyperconjugative stabilisation of the diprotonated species (1a) by the α hydrogen atoms of the side-chain. Thus, in their monoprotonated forms the 5-methylthiadiazine should be more basic than the 5-ethylthiadiazine, the latter should be more basic than the 5-isopropylthiadiazine and the 5-t-butylthiadiazine should be least basic of all. This effect, however, is not expected to be large and does not explain the very big drop in rate (NB, $k_r = k_1 - k_{-r}$ and k_{-r} increases along the series) when the rearrangement rates of the 5-isopropyl- and 5-t-butyl-thiadiazines are compared. In any case the hyperconjugative effect would be offset to some extent by an increasing $+I$ inductive effect acting in the opposite sense as the alkyl series is traversed. The 5-arylthiadiazines would be expected to take up a second proton more easily than any of the 5-alkylthiadiazines and therefore K_a should be greater. But 5-arylthiadiazines hardly rearrange at all. Thus, variation in the basicity of (1) is unlikely to be an important factor in determining the variation of rearrangement. As far as the second equilibrium is concerned, the value of K_b might be reduced to some extent by the presence of an increasingly larger alkyl group. Such a steric effect is not expected to be large since the forward reaction involves attack at an sp^2 rather than a more crowded sp^3 carbon atom. On the other hand, as the hydrogen atoms of the 5-methyl group are successively replaced by methyl groups, the ring double bond in (1) and (1a) would be decreasingly stabilised by hyperconjugation—an effect which would increase K_b along the series. Furthermore, the formation of (1b) [and (1c)] might afford some relief when the size of the 5-substituent is increased. Such differential effects, when balanced, are expected to be relatively small especially when one considers that the over-riding effect that is likely to arise when all substrates are attacked at C-5 by water is the stabilisation of a diprotonated species due to (i) the separation of two like charges to a greater distance and (ii) the saturation of the ring double-bond. The very large decrease in rearrangement rate apparent when the rates of the 5-isopropyl- and 5-t-butyl-thiadiazines are compared cannot be explained by such small differential effects either when applied to the K_b equilibrium or when combined (K_AK_B) with the effect of basicity previously mentioned. Thus, the overall effect would be unlikely to lead to almost complete inhibition of rearrangement. When the substituent at position 5 in the thiadiazine ring is aryl, compared to 5-alkylthiadiazines the value of K_B should be reduced due to steric inhibition to water attack by the bulky aryl group and stabilisation of the ring double bond in (1a) by conjugation with the aryl group. But, this decrease in K_B would be offset by the previously mentioned increase in K_A. Again, the overall effect (K_aK_b) could not account for an almost complete inhibition of the rearrangement. Thus, of the three factors $K_aK_bk_e$, k_e, the velocity constant of the forward rate-determining stage, is most likely to account for large differences in k_r (or k_1) when the 5-alkyl- and 5-aryl-thiadiazines are substrates.

Of the reaction steps outlined in Scheme 1, the change from (2b) to (1f) is most likely to be the rate-determining stage for the backward reaction. In addition to the dependence of k_{-r} on acidity there is other evidence to support this. Beyer [4,5] observed that 3-amino-4-phenylthiazol-2-alkylimines undergo the reverse rearrangement on treatment with concentrated hydrochloric acid. Thus, protonation of (2) would yield a species, (2a), which would be vulnerable to nucleophilic attack at position 4. As with the (1a) ⟶ (1b) change, rapid attack by water at position 4 would be expected to follow the formation of (2a) to give the more stable species (2b). Thence, much slower attack by the nitrogen atom at position 3 would represent the rate-determining stage of the backward reaction. When an aryl group is present in the 4-position of the thiazolimine, the question might be asked: why is (2b) able to undergo nucleophilic attack by a nitrogen atom whereas such attack hardly occurs in (1b) when an aryl group is present in the 5-position of the thiadiazine? The following explanation is offered. The nitrogen atom of the amino-group at position 3 in the thiazolimine is neither protonated nor involved in mesomeric delocalisation of a positive charge. It is therefore able to behave as a nucleophile regardless of the conformation of (2b). Such is not the case in the species (1b). The ring nitrogen at position 3 in (1b) can only assume a nucleophilic role if the aryl group is able to take up an axial position in the saturated ring structure. But, such conformations would be very rare if not impossible of existence. Thus, (1b) could be formed but not in a conformation which allows the nitrogen atom at position 3 in the saturated thiadiazine to behave as a nucleophile.

Since velocity constants have been determined at two temperatures (30 and 50 °C), tentative values of the activation energy, and the enthalpy and entropy of activation can be determined. Thus, the activation energy for the rearrangement of 2-amino-5-methyl-1,3,4-thiadiazine is *ca.* 21 kcal mol^{-1} (88 kJ mol^{-1}) and the corresponding enthalpy and entropy of activation are approximately 20 kcal mol^{-1} (84 kJ mol^{-1}) and −8 cal mol^{-1} K^{-1} (−34 J mol^{-1} K^{-1}) respectively.

CONCLUSIONS

The outstanding features of the rearrangement of 5-substituted 2-amino-1,3,4-thiadiazines to give the corresponding 4-substituted 3-amino-2-thiazolimines are given below.

(i) Rearrangement of the strongly basic 2-amino-1,3,4-thiadiazines hardly occurs, even with the most favourable case, in hydrochloric acid of strength less than 1M at 30 °C. The rate of rearrangement rises rapidly as the acidity is increased beyond 3.5M-HCl.

(ii) Rearrangement rates are increased when sodium chloride is added to the reaction solution.

(iii) Rearrangement rates of the series of 5-alkyl-2-amino-1,3,4-thiadiazines, methyl, ethyl, isopropyl, and t-butyl, decrease in a manner similar to that shown by hydrolysis of the corresponding alkyl bromide series: ethyl, propyl, isobutyl, and neopentyl. This suggests that the rate-determining stage proceeds *via* an S_N2-type mechanism.

(iv) Rearrangement rates of the 5-aryl-2-amino-1,3,4-thiadiazines in which the aryl groups are phenyl, *p*-nitrophenyl, and *p*-hydroxyphenyl, are in each case hardly apparent. Such results support the S_N2 character of the rearrangement mechanism.

(v) During the rearrangement in D_2O the hydrogen atoms at position 6 in the 2-amino-1,3,4-thiadiazine ring and position 5 of the thiazolimine ring are both replaced by deuterium. Furthermore, the hydrogen atoms at position 6 of the 2-amino-1,3,4-thiadiazine ring are replaceable by deuterium in deuterium oxide solution only in acid solutions strong enough to bring about rearrangement.

(vi) Since the 2-amino-1,3,4-thiadiazines are cyclic thiosemicarbazones the possibility of hydrolytic fission at the semicarbazone linkage might have been suspected. But, thiosemicarbazones such as acetone thiosemicarbazone are stable under the acidic conditions necessary to bring about the rearrangement. Ring opening is, therefore, not likely to occur during the rearrangement. Furthermore, the rearrangement leads only to the formation of 2-thiazolimines. Hydrazinothiazoles might have been expected to accompany the 2-thiazolimines if the thiadiazine ring had been opened.

(vii) A plot of $\log_{10} k_1$ against H_0 (values of Paul and Long [21]) is linear and of slope equal to 0.92. A plot of $\log_{10} k_1/c_{H^+}$ against $\log_{10} a_W$ is linear and of slope equal to -5.4 (w^*). According to Bunnett's criteria this suggests the involvement of (*a*) a protonation pre-equilibrium and (*b*) water as a nucleophile. The Yagil approach interprets the slope value of -2.95 obtained by plotting $\log_{10} k_1/c_{H^+}$ against $\log_{10} c_w$ more specifically as being due to the presence of one water molecule in the transition state of the rate-determining stage. This latter interpretation corresponds to the mechanism which was suggested by the other findings given above.

A mechanism is suggested (Scheme 1) in which the C-5 atom becomes saturated, (1b), due to relatively rapid attack by water on the diprotonated thiadiazine (1a). Rate-determining transannular attack by N-3 at C-5 is suggested as leading to the formation of a bridge between these two atoms and ultimately to the final product, 2-thiazolimine (2).

Such an attack by N-3 is possible in a diprotonated species since there is effectively no overlap of the *p*-type orbitals of the N-3 and immonium nitrogen atoms in the conformation (1b), (iii) B, and (iv) B which would be required by the S_N2-type transannular attack.

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