Tetrahedron. Vol. 33, pp. 1469 to 1474. Pergamon Press 1977. Printed in Great Britain

ELIMINATION-ADDITION MECHANISM FOR THE BASE CATALYSED CONVERSION OF S-ALKYLISOTHIOUREAS TO UREAS

THOMAS A. BRIODY, ANTHONY F. HEGARTY* and FRANCIS L. SCOTT
Chemistry Department, University College, Cork, Republic of Ireland

(*Received in the UK* 1 October 1976; *Accepted for publication* 21 October 1976)

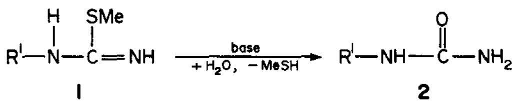
Abstract—The base catalysed hydrolysis of N-aryl and N,N'-diaryl isothioureas (including symmetrically and unsymmetrically disubstituted materials) to ureas has been investigated in water and in methanol-water (9:1). The N-arylisoureas **1** hydrolyse with the intermediacy of N-aryl cyanamides (shown by actual isolation) and give a Hammett ρ value of +0.82 (correlation with σ^-) for substituent variation at constant pH. The corresponding disubstituted materials **5** give smaller substituent constants ($\rho = +0.31$ when $R^1 = R^2$ and $\rho = +0.24$ when $R^1 = Ph$ and R^2 was varied) and the intermediacy of diarylcarbodiimides was demonstrated in this case by trapping with hydrosulphide ion. N,N,N^1-Trisubstituted S-alkylisothioureas which cannot undergo the elimination-addition mechanism and cyclic S-alkylisothioureas (which would form strained carbodiimides) are hydrolysed much more slowly than the disubstituted or acyclic analogues.

Isothioureas have found wide usefulness in organic synthesis as agents for the introduction of the amindino (-N=C-N-) group, and in general the good leaving characteristics of an S-alkyl or S-aryl group is utilized. An example is the conversion of amino groups to substituted guanidines (particularly the guanylation of amino acids[1] and hydrazines[2]) which are then used in further syntheses. The conjugate acids, S-alkylisothiouronium salts, have wide pharmacological properties such as that shown by the anti-radiation drug S-aminoethylisothiouronium hydrobromide;[3,4] anti-tubercular activity[5] and effectiveness against certain tumours[6] have also been reported.

The mechanism of action of S-alkylisothioureas has not received extensive study, although there are isolated reports of the formation of elimination products on pyrolysis and in solution.[7,8] We have examined the reaction of three series of S-alkylisothioureas in aqueous and in mixed aqueous-alcoholic solution with the strong nucleophile hydroxide ion to determine the mechanism of reaction and the structural characteristics which determine reactivity.

RESULTS AND DISCUSSION

The base catalysed conversion of S-alkylisothiouronium salts (**1**.HI) to the corresponding ureas (**2**) takes place smoothly and in high yield when **1**.HI is refluxed in a mixed aqueous solvent with excess base. We have investigated this conversion in aqueous and methanol-water solutions.

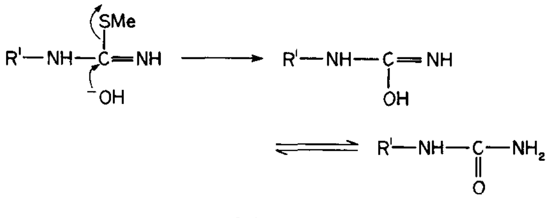


$$R^1\text{—}\overset{H}{N}\text{—}\overset{SMe}{C}\text{=}NH \xrightarrow[+H_2O,\ -MeSH]{base} R^1\text{—}NH\text{—}\overset{O}{\overset{\|}{C}}\text{—}NH_2$$

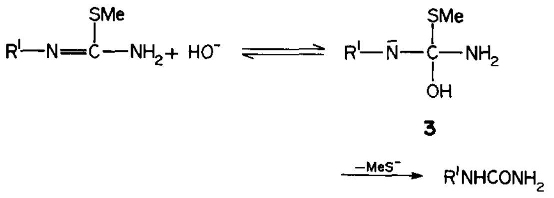
1 **2**

The observed rate constants for the hydrolysis of N-*p*-methoxyphenyl-S-methylisothiourea (**1**, $R = p\text{-}MeOC_6H_4$) as a function of $\{HO^-\}$ are summarised in Table 1. A plot of $\log k_{obs}$ vs $\log\{HO^-\}$ is linear with a slope close to unity, indicating that hydrolysis is first order in $\{HO^-\}$. Under these reaction conditions the isothiourea is present almost entirely as the neutral species (**1**), since the p*Ka* of the conjugate acid (**1**.H$^+$) is *ca.* 7.14 (the value for **1**.H$^+$, R = Ph).[1] Even at the highest hydroxide ion concentrations, the observed rate was still linear in $\{HO^-\}$, showing that under these conditions an appreciable amount of the substrate was not converted to the conjugate anion, i.e. the p*Ka* of **1** ($R^1 = p\text{-}MeOC_6H_4$) is greater than 12.3. This was true of all the isothioureas studied.

Three general mechanisms can be visualised *a priori* for this base catalysed conversion: (a) S_N2 displacement of MeS^- by HO^- (Scheme 1); (b) addition-elimination with the formation of a tetrahedral intermediate (3) where formation or breakdown is rate-determining (Scheme 2); (c) prior elimination to give a cyanamide intermediate (4) which is hydrated to the urea in a subsequent step (Scheme 3). All three mechanisms are consistent with the observed kinetic behaviour of (1). They can be distinguished, however, by varying the structure of the substrate (1) and the trapping of intermediates.

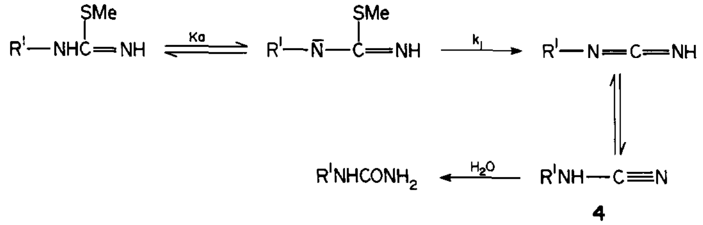


Scheme 1.



Scheme 2.

The rates of hydrolysis of a series of N-aryl-S-methylisothioureas (measured in 9:1 methanol-water containing 10^{-2} M $\{HO^-\}$) are summarised in Table 2. It will be seen that electron-withdrawal in R^1 increases the



Scheme 3.

Table 1. Observed rate constants (s^{-1}) for the hydrolysis of N-(p-methoxyphenyl)-S-methylisothiourea (1, $R^1 = p\text{-MeOC}_6H_4$) at 20° in water ($\mu = 1.0$, KCl)

Substituent X	p-MeO	p-Me	H	p-Cl	p-Br	p-NO_2
$10^4 k_{obs}(s^{-1})$	1.91	2.69	3.52	5.43	5.48	37.0

Table 2. Observed rate constants for the hydrolysis of the isothioureas 1 ($R^1 = XC_6H_4$) in 9:1 methanol-water containing 10^{-2} M NaOH at 25°

$10^2 [HO^-]$, M	20	10	5	2.5
$10^4 k^A_{obs}$	60.1	35.5	15.3	9.05

overall rate of hydrolysis—a plot of log k vs ordinary Hammett σ values gave $\rho = +1.19$ with a relatively poor correlation (r = 0.984). Use of the exhalted σ^- value (1.27) for the p-NO_2 substituted compound gave (r = 0.999) with $\rho = +0.82$. Omitting the data for the p-NO_2 substituent and replotting log k_{obs} vs ordinary σ for the remaining substituents gives $\rho = 0.87$ (r = 0.994). It will thus be seen that the use of the σ^- value for the p-NO_2 substituent gives the best fit to the data.

It would therefore appear that there is a build-up of negative charge on the nitrogen adjacent to the aromatic ring (R^1 in 1) such that a p-NO_2 group is capable of appreciable stabilisation by resonance. In all three mechanisms this is possible, except that less charge build-up would be expected in the case of direct displacement (Scheme 1).

One of the isothioureas (1, $R^1 = p\text{-NO}_2C_6H_4$) was investigated further to discover whether or not the hydrolysis was catalysed by bases other than OH ion, using three amine bases, pyrrolidine, piperidine and morpholine. For the first two, the rate of reaction did in fact increase with amine concentration at constant pH (Table 3). No catalysis was observed with morpholine, a weaker base. The specific rate constants for the other two bases in water at 25° are (pyrrolidine) 1.30 l mol^{-1} s^{-1} and (piperidine) 8.60×10^{-1} l mol^{-1} s^{-1}. From these data, an approximate Bronsted β-value of 0.53 was obtained. The observation of general base catalysis with considerable proton transfer to the base is the transition state could possibly be accommodated by modification of Schemes 1' and 2 by inclusion of amine-catalysed water attack on the isothiourea. Alternatively, the amine could act as a nucleophile (in which case the product would be a guanidine derivative). In the elimination mechanism (Scheme 3) the amine could aid removal of the NH proton, with simultaneous loss of the MeS^- group.

Table 3. Observed rate constants for the reaction of N-(p-nitrophenyl)-S-methylisothiourea (1, $R^1 = p\text{-NO}_2C_6H_4$) at 25° in water with the pyrollidine and piperidine

$10^3 [R_2NH]^A$, M	4.76	9.09	13.94	16.67	20.0
$10^2 k_{obs}(s^{-1})^B$	1.21	2.05	2.67	3.07	3.25
$10^2 k_{obs}(s^{-1})^C$	1.21	1.37	1.55	1.89	2.15

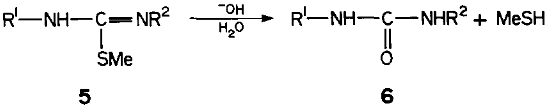
[A] Free amine concentration.
[B] Pyrrolidine at pH 11.70.
[C] Piperidine at pH 11.40.

This ambiguity inherent in the kinetic data can be removed by consideration of the intermediate products of hydrolysis. In this respect, the mechanism of Scheme 3 is unique, since it involves the cyanamide (4). The presence of such an intermediate was therefore probed. Reaction of N - phenyl - S - methylisothiouronium iodide (1.HI, $R^1 = Ph$) with two equivalents of OH ion at room temperature until completion of reaction (measured spectrophotometrically or by evolution of methyl mercaptan) gave, on neutralization of base and removal of solvents, an oil. This material showed a strong absorption at 2212 cm^{-1} characteristic of the nitrile or carbodiimide group. CO absorptions characteristic of the urea (2, $R^1 = Ph$) were absent. The other N - aryl - S - methylisothiouronium iodides were therefore treated on a larger scale under conditions similar to those used to study the kinetics (10^{-2} M NaOH, 90% methanol); the solution was neutralized on completion of reaction and ether extracted. In two cases ($R^1 = p\text{-ClC}_6H_4$ and $R^1 = p\text{-BrC}_6H_4$) solid N-arylcyanamides 4 were obtained. In all of the other cases studied, the products formed did not solidify. However, their IR spectra again showed the presence of cyanamide and the absence of urea absorptions. The UV spectra of N - (p - chloro- or p-bromophenyl) cyanamide in 90% methanol containing 0.01 M NaOH were identical in all respects with those of the products on hydrolysis of the appropriate S - methyl - isothiouronium iodides in the same solvent and at the same concentration of base at 25°. This indicates that under the kinetic conditions, the isothioureas (1) went entirely to the cyanamides (4). After several days (at room temp.) or minutes (at reflux) the ureas 2 were formed in good yield from the cyanamides 4.

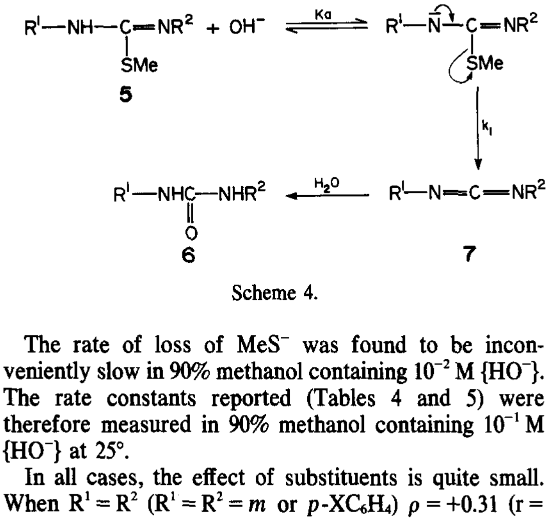
As noted above, under the conditions under which the elimination was studied, none of the S-methyl isothioureas 1 is fully converted to the anion. Therefore the observed first-order rate constants quoted in Table 2 are composite values with $k_{obs} = k_1 Ka$ (Scheme 3). An increase in the electron-withdrawing ability of the R^1 group of 1 would be expected to increase Ka since a more stable anion would be formed. Conversely, k_1 would be expected to decrease under the influence of such a substituent change. The overall effect on k_{obs} would then reflect a balance between these two factors. In the event, Ka appears to be more sensitive to substituent change, since the composite ρ is positive (+0.82). This is not unexpected, since Ka measures an equilibrium between neutral and negatively charged species, while in the transition state for loss of MeS^- from the anion (as measured by k_1) only part of the negative charge has been lost. The fact that a σ^- value is required to correlate the data for the p-nitrophenyl substituted compound (**1**, $R^1 = p\text{-}NO_2C_6H_4$) is probably due to an effect on the dominant *Ka* term; the p-NO_2 group is placed to stabilise the isothiourea anion by resonance.

The N-arylcyanamides **4**, which are formed on tautomerisation of the monosubstituted carbodiimides, are surprisingly unreactive towards hydration under the conditions used to study the kinetics. This is probably due to the fact that they are weak acids (p*Ka* *ca.* 9) and so would exist largely as the conjugate anion in basic solution.

The mechanism of hydrolysis of the N,N′ - diaryl - S - methyl - isothioureas **5** to the corresponding ureas **6** was also investigated, including isoureas where $R^1 = R^2$ and $R^1 \neq R^2$.



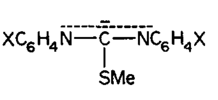
If the elimination mechanism obtained in this case also, the intermediate would be carbodiimide **7** as in Scheme 4.



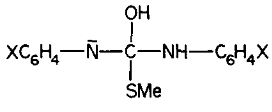
Scheme 4.

The rate of loss of MeS^- was found to be inconveniently slow in 90% methanol containing 10^{-2} M {HO^-}. The rate constants reported (Tables 4 and 5) were therefore measured in 90% methanol containing 10^{-1} M {HO^-} at 25°.

In all cases, the effect of substituents is quite small. When $R^1 = R^2$ ($R^1 = R^2 = m$ or p-XC_6H_4) $\rho = +0.31$ (r = 0.999). The positive ρ value again indicates the presence of negative charge in the transition state.



8



9

Considering the two mechanisms of elimination-addition and addition-elimination the intermediate anions would be **8** and **9** respectively. In **8**, the negative charge is delocalised extensively over both rings and ρ should be approximately half that for the monoaryl-S-Me compounds **1**, which it is. However, in calculating ρ, additive sigma effects were assumed. If the intermediate anions were instead **9**, then one ring is directly linked to the negatively charged nitrogen (and should display a certain ρ), the noninvolved ring may easily display a different ρ value. Thus the evidence (from the magnitude of the ρ value) as to the nature of the negatively charged species is ambiguous.

Table 5. Observed rate constants for the hydrolysis of unsymmetrical N - phenyl - N′ - aryl - S - methylisothioureas (**5**, $R^1 = Ph$, $R^2 = XC_6H_4$) in 9:1 methanol-water containing 10^{-1} M NaOH at 25°

Substituent X	p-MeO	p-Me	H	p-Br	p-Cl	p-NO_2
$10^4\,k_{obs}(s^{-1})$	5.20	5.80	5.85	6.95	7.07	9.19

To study further the effect of charge distribution on the transition state, another series of N,N′ - diaryl - S - methyl isothiouronium salts (**5**.HI, $R^1 = p\text{-}XC_6H_4$; $R^2 = Ph$) with only one ring substituted, was prepared. In this case, it was possible to include the p-NO_2 substituent (**5**.HI; $R^1 = p\text{-}NO_2C_6H_4$; $R^2 = Ph$) and test for exaltation effects. The kinetic measurements were carried out under the same conditions as for the other diaryl series.

Again, the substituent effect was quite small. Using ordinary σ values for the six substitutents (Table 5) $\rho = +0.23$ (r = 0.995). Using a σ^- value of 1.27 for the p-NO_2 substituent and replotting $\rho = +0.15$ (r = 0.970). Omitting the data for the p-NO_2 substitute p-NO_2 substituted compounds and replotting for the five remaining substituents $\rho = +0.24$ (r = 0.986). Thus the best fit to the kinetic data is obtained using ordinary σ values for the six substituents. This means that, in contrast to the monoaryl case, no exaltation effect here operates for the p-NO_2 substituent.

The ρ value thus obtained (+0.23) is similar to that (+0.31) for the disubstituted N,N-diaryl series, as expected. The lack of an exaltation effect for the p-NO_2 substituent, which would be expected for both the addition-elimination and elimination-addition mechanisms is more difficult to account for. Perhaps the much greater degree of delocalisation of negative charge possible in the anion **8**, where both rings can take up the negative charge is responsible. If this is the case then **8** rather than the tetrahedral intermediate **9** is the more likely intermediate, since in **9** delocalisation is possible over only one ring. However, the evidence is somewhat ambiguous. In the case of the elimination-addition mechanism (Scheme 4) there is a carbodiimide intermediate **7** which could conceivably be isolated or trapped with a suitable reagent.

It was first decided to try to isolate a possible carbodiimide intermediate by the same means as were employed in the monaryl case. Three members of the di-substituted diaryl series of S-methylisothiouronium iodides (**5**.HI; $R^1 = R^2 = p\text{-}CH_3C_6H_4$; Ph; $p\text{-}ClC_6H_4$) were treated under the kinetic conditions, namely by reacting them to completion with two equivalents of OH ion in 9:1 aqueous methanol at room temperature. Reaction was

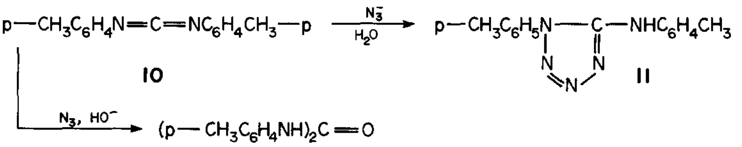
Table 4. Observed rate constants for the hydrolysis of symmetrical diaryl - S - methylisothioureas (**5**, $R^1 = R^2 = XC_6H_4$) in 9:1 methanol-water containing 10^{-1} M NaOH at 25°

Substituent X	p-MeO	p-EtO	p-Me	m-Me	H	p-F	p-Cl	M-Cl	p-Br
$10^4\,k_{obs}(s^{-1})$	4.12	4.28	4.65	5.55	5.85	6.47	8.06	7.35	8.70

judged complete when evolution of methyl mercaptan ceased. On neutralisation with acetic acid and removal of solvent under reduced pressure, the corresponding ureas were obtained quantitatively.

Having failed to isolate the carbodiimide intermediates, it was decided to try to trap them using suitable reagents which would complete with OH ion. The first reagent tried was azide ion which has a rather similar n-value (n = 4.00) to OH ion (n = 4.20).

Four series of experiments were performed along these lines. Firstly di - *p* - tolylcarbodiimide was allowed to react with a slight excess of sodium azide in 50% aqueous ethanol for 24 hr a quantitative yield of 1 - *p* - tolyl - 5 - *p* - tolylaminotetrazol **11** was obtained. When this reaction was repeated with an equimolar amount of sodium hydroxide present, the corresponding urea (**6**, $R^1 = R^2 = p\text{-}CH_3C_6H_4$) was obtained in quantitative yield.



Scheme 5.

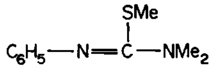
In a second set of experiments, three of the S-methylated compounds (**5**.HI; $R^1 = R^2 = p\text{-}CH_3C_6H_4$; Ph; $p\text{-}ClC_6H_4$) were reacted in 50% aqueous ethanol at *ca.* 0.2 M concentrations with sodium azide (0.5 M) and sodium hydroxide (0.1 M) for 48 hr at room temperature. The products in each case were the corresponding N,N-diarylureas **6** in quantitative yields.

The inability of the azide ion to compete with OH ion was surprising in view of their rather similar nucleophilicities (n = 4.00 for N_3^-; n = 4.20 for HO^-) towards saturated carbon. Accordingly, experiments were run with a much more powerful nucleophile, namely hydrosulphide ion (HS^-, n = 5.1). Thus the same three N,N′-diaryl isothiouronium salts (**5**.HI, $R^1 = R^2 = p\text{-}CH_3C_6H_4$; Ph; $p\text{-}ClC_6H_4$) were reacted with a 5-fold excess of sodium sulphide (which generates both HS^- and OH^- in equivalent amounts in solution), the solvent being 50% aqueous ethanol. After the reaction has been allowed to proceed for 48 hr at room temperature the work-up gave quantitative yields of the corresponding N,N′-diarylthioureas $\{(ArNH)_2C{=}S\}$. Thus hydrosulphide ion competes successfully with hydroxide ion for the intermediate carbodiimide **10**.

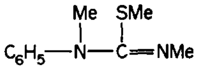
Finally, this competition was examined kinetically using the di - *p* - bromo - S - methyl isothiouronium compound (**5**.HI; $R^1 = R^2 = p\text{-}BrC_6H_4$) as substrate. In one run this compound was treated with 3 M sodium sulphide in pure water at 25° (pH of the solution = 13.60; $\mu = 2.0$ M) and reacted with a rate constant $k = 3.42 \times 10^{-3}\,l\,mol^{-1}\,s^{-1}$. The experiment was repeated (pH = 13.60; $\mu = 2.0$ M) using sodium hydroxide alone as base and this time the rate of reaction was $2.37 \times 10^{-3}\,l\,mol^{-1}\,s^{-1}$. If both HS and OH were functioning as nucleophiles in the reaction, then one would expect k_{HS^-} to be much greater than k_{HO^-}. This is consistent with the elimination-addition (Scheme 4) process. Again, if the rate data represented competitive nucleophilic attack, one would expect the product distribution to be *pro rata*, i.e there should be approximately one-third substituted thiourea present and approximately two-thirds substituted urea. This again did not happen, the product being exclusively the substituted thiourea.

These data are consistent with, and diagnostic of, the presence of a carbodiimide intermediate in the hydrolysis of the symmetrically substituted N,N′ - diaryl - S - methylisothioureas, the carboniimide formed reacting much more selectively in product formation with HS ion rather than OH ion.

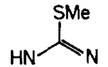
The failure to isolate the carbodiimide intermediates when OH ion was used as the base is consistent with the data of Hunig *et al.*[10] who report that the hydration of carbodiimides is strongly catalysed by bases. These workers studied, for example, the rate of reaction of diphenylcarbodiimide in 75% tetrahydrofuran–water containing 0.02 N NaOH and found that it had a half-life of 18 min. Clearly in the present work, hydration of the carbodiimide intermediates to the corresponding ureas was faster than the initial elimination to form the carbodiimide.


$C_6H_5-N=C(SMe)-NMe_2$

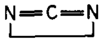
13


$C_6H_5-N(Me)-C(SMe)=NMe$

14



15



16

The following data for structural variation in the isothiourea also supports the elimination mechanism of Schemes 3 and 4. N′,N′S-trimethyl-N-phenylisothiourea (**13**) reacts very slowly ($k_{obs} < 10^{-6}\,l\,mol^{-1}\,s^{-1}$) in 90% methanol containing 10^{-1} M sodium hydroxide at 25°. N,N′,S-trimethyl N-phenylisothiourea (**14**) is also relatively unreactive under these conditions ($k_{obs} = 1.2 \times 10^{-4}\,l\,mol^{-1}\,s^{-1}$). This is slower than the slowest of the symmetrical diaryl isothioureas (**5**; $R^1 = R^2 = p\text{-}MeOC_6H_4$) under the same conditions. Neither of these materials could undergo elimination-addition (without de-N-methylation); it is apparent that nucleophilic attack by the hydroxide ion pathways (Schemes 1 and 2) occurs at a slower rate. 2 - Methylmercapto - 2 - imidazoline (**15**) has an available NH group and can thus form an anion; elimination of MeS^- from this anion would, however, give a strained cyclic carbodiimide **16**. The stability of **15** reflects this, since it is unreactive under conditions where the acyclic analogues (**1** and **5**) would rapidly eliminate to give cyanamides or carbodiimides.

EXPERIMENTAL

Substrates. The N-arylthioureas **1**, $R^1 = XC_6H_4$, with the exception of the unsubstituted and the $p\text{-}NO_2$ compound were prepared by the reaction of equimolar quantities of the appropriate anilines (as hydrochloride salts) and ammonium isothiocyanate in water and subsequently recrystallised to constant m.p. from EtOH. N-Phenylthiourea was obtained commercially. N-*p*-Nitrophenylthiourea was obtained by the reaction of equimolar quantities of *p*-nitrophenyl isothiocyanate and ammonia in aqueous EtOH. Both of these latter thioureas were recrystallised from EtOH. These thioureas had the following m.ps: X = H m.p. 154° (lit.,[11] 154°); *p*-Me, 188–189 (lit.,[12] 190°); *p*-MeO, 210–212° (lit.,[13] 210–212°); *p*-Br, 182–183° (lit.,[11] 183°); *p*-Cl, 177–178° (lit.,[12] 180–181°); *p*-NO_2, 223–225° (Found: C, 56.8; H, 4.4, N, 15.4. $C_{13}H_{11}N_3O_2S$ requires: C, 57.1, H, 4.0, N, 15.4%). These thioureas we converted to the corresponding S-methyl isothiouronium iodides by reflexing in abs EtOH with a 10% excess of MeI. The hydriodides (**1**.HI, $R^1 = p\text{-}XC_6H_4$) were recrystallised to constant m.p. from a 1:1 mixture of chloroform and diethyl ether: X = H, m.p. 144–145° (lit.,[15] 145°); *p*-Me, 128–130° (lit.,[16] 130°); *p*-MeO, 161–162° (lit.,[15] 162°); *p*-Cl, 163–165° (Found: C, 29.4, H, 3.15; N, 8.3. $C_8H_{10}ClIN_2S$ requires: C, 29.2, H, 3.0, N, 8.5%), *p*-Br, 189–191° (Found: C, 26.0; H, 2.9, N, 7.6. $C_8H_{10}BrN_2S$ requires: C, 25.7; H, 2.7; N, 7.5%), *p*-NO_2, 188–190° (Found: C, 28.5; H, 3.1; N, 12.6. $C_8H_{10}IN_3O_2S$ requires: C, 28.3; H, 2.95; N, 12.4%). The arylureas ($p\text{-}XC_6H_4NHCONH_2$) were prepared by refluxing the S-methylisothiouronium iodides in 3:1 water-MeOH containing 0.75 N NaOH until evolution of mercaptan ceased. Those with X = H and X = NO_2 were recrystallised from water, otherwise from abs EtOH. They had the following m.ps X = H, 146–147° (lit.,[17] 147°); *p*-Me, 181–182° (lit.,[18] 181–182°); *p*-MeO, 168° (Found: C, 60.5; H, 5.7; N, 16.4. $C_8H_{10}N_2O_2$ requires: C, 60.7, H, 5.6; N, 16.3%); *p*-Cl, 199–201 (lit.,[19] 206°); *p*-Br 300–315 (d) (Found: C, 37.4; H, 3.4; N, 12.95. $C_7H_7BrN_2O$ requires: C, 37.2; H, 3.3; N, 13.0%); *p*-NO_2, >300° (d) (Found: C, 46.8; H, 3.6; N, 23.0. $C_7H_7N_2O$ requires: C, 46.4; H, 3.9; N, 23.2%). The N,N′-diarylthioureas ($XC_6H_4NHCSNHC_6H_4X$) were prepared by two general routes: (a) refluxing two equivalents of the appropriate aniline (X = H, *p*-Me, *m*-Me, *p*-MeO, *p*-EtO, *p*-Cl and *p*-Br) with CS_2 in EtOH; (b) reaction of equimolar quantities of the appropriate phenylisothiocyanate (X = *p*-F, *m*-Cl and *p*-NO_2) with the corresponding aniline. On recrystallisation from abs EtOH, the N,N′-diarylthioureas had m.ps: X = H, 154–155° (lit.,[20] 154°); *p*-Me, 180–182° (lit.,[13] 176°); *m*-Me, 125–127° (lit.,[13] 111–112°), *p*-MeO, 196–198° (lit., [13] 190–190.5°); *p*-EtO, 175–176° (lit.,[13] 171°); *p*-F, 204–205° (lit.,[21] 208°); *p*-Cl, 179–181° (lit.,[13] 176°); *m*-Cl, 125–127° (lit.,[13] 131.5°); *p*-Br, 195–196° (lit.,[13] 188°); *p*-NO_2, 210–212° (Found: C, 48.9; H, 3.45; N, 17.7. $C_{13}H_{10}N_4O_4S$ requires: C, 49.1; H, 3.15, N, 17.6%). The S-methylisothiouronium iodides were prepared from these thioureas (as above) and recrystallised from 1:1 chloroform-diethyl ether. They had the following m.ps X = H, 160–162° (Found: C, 45.35; H, 4.1, N, 7.6. $C_{13}H_{15}IN_2S$ requires: C, 45.4; H, 4.05, N, 7.4%); *p*-Me, 175–177° (Found: C, 48.1, H, 4.8; N, 7.0. $C_{15}H_{19}IN_2S$ requires: C, 48.2; H, 4.8; N, 7.0%); *m*-Me, 131–133° (Found: C, 48.3; H, 4.95; N, 7.1. $C_{15}H_{19}IN_2S$ requires: C, 48.2; H, 4.8; N, 7.0%); *p*-MeO, 173–175° (Found: C, 44.8; H, 4.6; N, 6.4. $C_{16}H_{19}IN_2O_2S$ requires: C, 44.4; H, 4.4; N, 6.5%); *p*-EtO, 167–169° (Found: C, 47.35; H, 5.2; N, 6.3. $C_{18}H_{23}IN_2O_2S$ requires: C, 47.2; H, 4.8; N, 6.1%); *p*-F, 195–197° (Found: C, 41.3; H, 3.15; N, 6.7. $C_{16}H_{19}F_2IN_2S$ requires: C, 41.4; H, 3.2; N, 6.9%); *p*-Cl, 159–161°. (Found: C, 38.3; H, 3.0; N, 6.5. $C_{14}H_{13}Cl_2IN_2S$ requires: C, 38.3; H, 3.0; N, 6.4%); *m*-Cl, 139–141° (Found: C, 38.3; H, 3.1; N, 6.55. $C_{14}H_{13}Cl_2IN_2S$ requires: C, 38.3; H, 3.0, N, 6.4%); *p*-Br, 175–176° (Found: C, 31.9; H, 2.5; N, 5.55. $C_{14}H_{13}Br_2IN_2S$ requires: C, 31.8; H, 2.5; N, 5.3%).

The N-aryl-N′-phenylthioureas were prepared by the reaction of arylisothiocyanates with aniline or alternatively phenyl isocyanate with substituted anilines in ethanol: X = *p*-Me, m.p. 140–142° (Found C, 69.8; H, 5.95; N, 11.7. $C_{14}H_{14}N_2S$ requires: C, 69.4; H, 5.8; N, 11.6%); *p*-MeO, 151–153° (lit.,[13] 153–156°); *p*-Cl, 154–155° (lit.,[14] 152°); *p*-Br, 168–170° (lit.,[15] 158°); *p*-NO_2 150–152° (Found: C, 56.8; H, 4.4; N, 15.4. $C_{13}H_{11}N_3O_2S$ requires: C, 57.1; H, 4.0; N, 15.4%). The S-methylhydroiodides (**5** . HI, R^2 = Ph) had the following m.ps: X = *p*-Me, 150–152° (Found: C, 47.1; H, 4.6; N, 7.2. $C_{15}H_{17}IN_2S$ requires: C, 46.9; H, 4.4; N, 7.3%); *p*-MeO, 83–85° (Found: C, 44.95; H, 4.6; N, 6.6. $C_{15}H_{17}IN_2OS$ requires: C, 45.0; H, 4.25; N, 7.0%); *p*-Cl, 157–158° (Found: C, 41.5; H, 3.6; N, 6.9. $C_{14}H_{14}ClIN_2S$ requires: C, 41.5; H, 3.6; N, 6.9%), *p*-Br, m.p. 165–167° (Found: C, 37.0; H, 3.3; N, 6.1 $C_{14}H_{14}BrIN_2S$ requires: C, 37.4; H, 3.1; N, 6.2%); *p*-NO_2, 99–101° (Found: C, 40.4; H, 3.7; N, 10.0; $C_{14}H_{14}IN_3O_2S$ requires: C, 40.5; H, 3.4; N, 10.1%). The corresponding N-aryl-N′-phenylureas were prepared as before by the base-catalysed hydrolysis of the S-methylisothioureas. They were recrystallised from abs EtOH and had the following m.ps. X = *p*-Me, 222–223° (Found: C, 74.4; H, 6.4; N, 12.3. $C_{14}H_{14}N_2O$ requires: C, 74.3; H, 6.2; N, 12.4%); *p*-MeO, 177–179° (lit.,[31] 186–190°); *p*-Cl, 246–248° (lit.,[32] 239–240°); *p*-Br, 285–289° (sublimes) (Found: C, 53.8; H, 4.0; N, 9.9. $C_{13}H_{11}BrN_2O$ requires: C, 53.6; H, 3.8; N, 9.6%); *p*-NO_2, >360° (Found: C, 60.7; H, 4.5; N, 16.1. $C_{13}H_{11}N_3O_3$ requires: C, 60.7; H, 4.3; N, 16.3%). N-Phenyl-N,N′-dimethylthiourea ($PhNH{-}CSNMe_2$) was prepared by reacting equimolar quantities of phenylisothiocyanate and dimethylamine in 95% EtOH. It was recrystallised from abs EtOH, m.p. 135–137° (lit.,[33] 134–135°). This compound was converted to the corresponding **13**.HI by the usual method. The product was an oil which was only solidified with difficulty. It was recrystallised from 1:1 dichloromethane diethyl ether and had m.p. 129–130 (lit.,[34] 132–135°). This was converted to the corresponding urea ($PhNHCONMe_2$) by base-catalysed hydrolysis, but, it was so unreactive that it had to be refluxed in 1 N NaOH for over 6 hr before the reaction was complete. The unrecrystallised from abs EtOH, m.p. 102–104° (lit.,[35] 134°). N-Phenyl-N,N′-dimethylthiourea (PhN(Me)CSNHMe) was prepared by the reaction of equimolar quantities of N-methylaniline and methyl isothiocyanate in abs EtOH. Recrystallised from abs EtOH it had m.p. 103–105° (Found: C, 59.95; H, 7.0; N, 15.9. $C_9H_{12}N_2S$ requires: C, 60.0; H, 7.0; N, 15.6%). This was converted as usual into the corresponding **14**.HI. It was recrystallised from 1:1 dichloromethane-diethylether and had m.p. 115–117° (Found: C, 37.3; H, 4.9; N, 8.9. $C_{10}H_{15}IN_2S$ requires: C, 37.3; H, 4.7; N, 8.7%). This compound was converted as usual to the corresponding urea (PhN(Me)CONHMe). This was again recrystallised from abs EtOH and had m.p. 79–81° (Found: C, 65.75; H, 7.2; N, 17.0. $C_9H_{12}N_2O$ requires: C, 65.85; H, 7.3; N, 17.1%). 2-Thioimidazalone was obtained commercially and reacted with MeI to give **15**.HI. Recrystallised from 1:1 dichloromethane-diethylether it had m.p. 141–143° (Found: C, 20.1; H, 3.8; N, 11.8. $C_4H_9IN_2S$ requires: C, 19.7; H, 3.7; N, 11.5%). The di-*p*-tolyl-carbodiimide used in the trapping experiments was obtained commercially. On reaction with azide ion alone it gave **11** which, on being recrystallised from abs EtOH gave m.p. 205–207° (lit.,[36] 207°).

Arylcyanamides

(a) N-Phenyl-S-methylisothiouronium iodide was allowed to stand at room temp. in 9:1 MeOH–water containing 2 mol equivts of NaOH until the evolution of methyl mercaptan ceased. The solvent was evaporated *in vacuo* at room temp. and the residual water was removed by azeotroping with benzene. The gummy material obtained failed to crystallize but showed strong absorptions at 2212 cm^{-1} (–C≡N stretching) and at *ca.* 3200 cm^{-1} (NH stretching). There was no evidence for C=O group absorptions, indicating the absence of urea under these conditions.

(b) The N-aryl-S-methylisothiouronium iodides were dissolved in 1:10 MeOH–water containing 0.1 M NaOH and maintained at room temp. until evolution of methyl mercaptan ceased. The soln was then neutralised (with AcOH) to pH 7 and extracted immediately with diethyl ether. The dried (Na_2SO_4) ether extracts gave on evaporation either gummy materials or solids. In the cases where solids were obtained (the *p*-bromo and *p*-chloro substituted materials), these were recrystallised from 1:1 chloroform-petroleum ether (40–60°) to give *p*-chlorophenylcyanamide m.p. 106–108° (lit.,[37] 108–109°) and *p*-bromophenylcyanamide m.p. 114–116° (Found: C, 42.8; H, 2.65; N, 14.6. $C_7H_5BrN_2$ requires: C, 42.6; H, 2.5; N, 14.2%). These and the other materials which failed to crystallise had IR spectra which clearly showed the presence of –C≡N and NH groups and the absence of C=O.

Competition between HO^- *and* HS^-. Each of the three N,N′-diarylisothiouronium iodides (**5**.HI; $R^1 = R^2 = p\text{-}CH_3C_6H_4$; Ph; $p\text{-}ClC_6H_4$) (5.0 g) was dissolved in 50% EtOH containing 5 mole equivs of $Na_2S.9H_2O$ (laboratory reagent grade) and the solns allowed to stand at room temp. until all evolution of methyl mercaptan ceased. Bulky white solids separated out which proved to be the corresponding thioureas in over 99% yield. They had the same IR spectra, m.ps and m.m.ps as unambiguously prepared samples, and the IR spectra further showed the absence of any urea type C=O absorptions, indicating that HS ion competed completely with OH ion for the substrate.

Kinetic method

The 9:1 MeOH–water used as solvent was prepared by mixing 9 volumes of MeOH (Analar grade) with 1 volume of water (which was deionised and then twice distilled) at 25°. Typically the S-methylisothiouronium iodides were dissolved (2×10^{-4} M) in 9:1 MeOH–water and reaction was initiated by the addition of an equal volume of 9:1 MeOH–water containing 2×10^{-2} M NaOH (in the case of the monoaryl series) or 2×10^{-1} M NaOH (in the case of the two diaryl series). The solns used to study the kinetics were therefore 1×10^{-2} M in $\{HO^-\}$ and 1×10^{-4} M in substrate for the monoaryl series, (giving a base-substrate ratio of 100:1) or 1×10^{-1} M in $\{HO^-\}$ and 1×10^{-4} M in substrate for the diaryls, giving a base-substrate ratio of 1,000:1. These corresponded to pseudo-first-order conditions. The course of the reactions was followed spectrophotometrically at suitable wavelengths using a Unicam model SP 800 UV-visible spectrometer. In all cases repetitive scans showed that the reactions did not involve the build-up of intermediates and tight isobestic points were held. In the case of the monoaryl substrates, the spectra of the products were different from those of the corresponding ureas and were shown to the same as those of the two cyanamides (*p*-bromo- and *p*-chlorophenylcyanamide) isolated from N - (*p* - bromo and *p* - chlorophenyl) - S - methylisothiouronium iodides. The 2×10^{-2} M NaOH was made up as follows: a 1 N NaOH was made up in pure water at 25° from a Volucon capsule. 20 ml of this soln was then added to 900 ml of AnalaR MeOH in a volumetric flask and 80 ml of pure water then added. On cooling to 25° the soln was made up to the mark with 9:1 MeOH. The 2×10^{-1} M NaOH in 9:1 MeOH–water was similarly prepared except that 200 ml of 1 N NaOH was added to the MeOH.

For the pH rate profile four solns of NaOH, made up from a Volucon capsule were prepared: 2×10^{-2} M, 1×10^{-2} M, 5×10^{-3} M, 2.5×10^{-3} M. In each case the ionic strength (μ) was maintained at 2×10^{-2} M using AnalaR NaCl. The rates were measured at 25° under pseudo-first-order conditions.

In the case of the kinetic competition experiments between HS^- and HO^- a 2.0 M soln of laboratory reagent grade $Na_2S\cdot9H_2O$ was prepared. It had pH 13.60. A 1 N NaOH was prepared from a Volucon capsule and 1 N AnalaR NaCl was added to maintain the ionic strength at 2.0 M. The pH was lowered to 13.60 by the addition of a few drops of HCl.

In the case of pyrrolidine and piperidine 2×10^{-1} M solns of these bases were made up in pure water at 25°. These were then half-neutralised with 0.1 N HCl (made up from a Volucon capsule) giving a buffer soln containing 0.1 M base and hydrochloride. Because of its lower p*Ka* value, a soln containing 0.9 M morpholine and 0.1 M morpholine hydrochloride was prepared as previously and used for the buffer dilutions.

The pseudo-first-order rate constants in all cases were calculated using a least-squares programme written for the Olivetti programma 101 dest-top computer. The Hammett ρ values were likewise calculated. Unless otherwise mentioned, r was in all cases >0.99.

REFERENCES

[1] R. Pant, *Z. Physiol. Chem.* **335**, 272 (1964).

[2] E. Lieber and G. B. L. Smith, *Chem. Revs.* **25**, 213 (1939).

[3] D. J. Doherty and W. J. Bennett, *Proc. Soc. Exptl. Biol. Med.* **89**, 312 (1955).

[4] B. G. Croutch and R. R. Overman, *Science* **125**, 1092 (1957).

[5] E. L. Oginsky, M. Solotorousky and H. D. Brown, *Am. Rev. Tuberc.* **74**, 78 (1956).

[6] F. E. Reinhart, J. H. Gray and W. G. Batt, *J. Franklin Inst.* **261**, 669 (1956).

[7] R. F. Pratt and T. C. Bruice, *J. Am. Chem. Soc.* **94**, 2823 (1972).

[8] J. P. Horowitz and C. C. Rila, *Ibid.* **80**, 431 (1958).

[9] J. F. J. Dippy, S. R. C. Hughes and A. Rozanski, *J. Chem. Soc.* 2492 (1959).

[10] S. Hunig, H. Lehmann and G. Grimmer, *Ann.* **579**, 87 (1953).

[11] M. Shimotani, *J. Pharm. Soc. Japan* **72**, 328 (1952).

[12] A. J. Ramchaert, G. J. Benoy and J. F. van Besouw, *Brit. Pat.* 1, 099, 767 (28 Dec 1966).

[13] G. M. Dyson and H. J. George, *J. Chem. Soc.* 1704 (1924).

[14] F. H. Jackson and A. J. Peters, *Ibid* (*B*) 271 (1969).

[15] W. Finnegan, R. Henry and E. Lieber, *J. Org. Chem.* **18**, 779 (1953).

[16] T. B. Johnson and H. S. Bristol, *Am. Chem. J.* **30**, 173 (1903).

[17] E. Cattulain and P. Charbier, *Bull. Soc. Chim. Fr.* 1101 (1947).

[18] J. L. Boivin and P. A. Boivin, *Can. J. Chem.* **29**, 478 (1951).

[19] B. Singh, H. Krall and S. Suhassabudhey, *J. Ind. Chem. Soc.* **23**, 373 (1946).

[20] H. S. Fry, *J. Am. Chem. Soc.* **35**, 1541 (1913).

[21] N. P. B. Hoi, N. D. Xuong and N. H. Ham, *J. Chem. Soc.* 1973 (1955).

[22] J. E. Dixon, *Ibid.* **63**, 318 (1893).

[23] M. R. Patel and B. N. Mankad, *Indian J. Chem.* **5**(3), 107–108 (1967).

[24] G. V. Jadhav, *J. Indian Chem. Soc.* **8**, 683 (1931).

[25] D. Migliacii and R. Gargiulo, *Gazz. Chem. Ital.* **58**, 110–121 (1928).

[26] F. Kurzer, *J. Chem. Soc.* 2292 (1949).

[27] Kyosuke Tsada and Shuraku Sakamoto, *J. Pharm. Soc. Japan* **64**, 221 (1944).

[28] P. A. Smith, *J. Am. Chem. Soc.* **76**, 431 (1954).

[29] J. Otterbacker and F. C. Whitmore, *Ibid.* **51**, 1909 (1929).

[30] L. Dashen and R. W. Breuster, *Trans. Kansas Acad. Sci.* **40**, 103 (1937).

[31] C. Naegeli, A. Tyabji and L. Conrad, *Helv. Chim. Acta* **21**, 1127 (1938).

[32] R. P. Lastowski, *Th. Obs. Khim.* **18**, 912 (1948).

[33] Heilbron's *Dictionary of Organic Compounds* Vol. 4, p. 2730 Eyre and Spottiswoode, London (1965).

[34] *Ibid.* Ref. 7.

[35] *Ibid.* p. 1340.

[36] M. Busch and P. Bauer, *Ber. Dtsch. Chem. Ges.* **33**, 1073 (1900).

[37] F. Kurzer, *J. Chem. Soc.* 3269 (1950).