Reactions of *S*-Acylisothioureas. II. Effects of Structure and Stereochemistry on the Rates of Hydrolysis, Thiol Elimination, and S to N Acyl Migration in Acylic Systems

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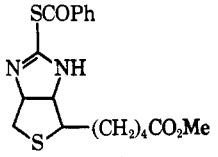
Abstract: The reactions in aqueous solution of the *S*-benzoylisothiouronium salts **3–10** have been studied kinetically and by product analysis. Three types of reactions have been distinguished. (a) Hydrolysis of the thiol ester functional group leads to benzoic acid and the parent thiourea. This is the predominant reaction of **3–10** at low pH and in several cases at high pH; it is the only reaction of **10** observed. (b) The thiol benzoate is displaced from the isothiourea by substitution or elimination. These reactions have been studied in more detail by the use of the *S*-phenylisothioureas **11–13** as models for **3**, **4**, and **6**, respectively. Two modes of reaction have been observed. One is proposed to involve elimination of thiolate anion from an anionic isothiourea species (**17**) (and is thus only available to isothioureas with an N–H group present) and the other elimination from the neutral isothiourea or possibly hydroxide ion attack on the protonated isothiourea (observed with the trisubstituted species **6**, **7**, **8**, and **13**). The former of these, elimination from an anion, is a particularly favorable reaction of the unsubstituted compounds **3** and **11**. (c) At intermediate pH (5–10) the predominant reaction of **3–9** leads to the corresponding *N*-benzoylthioureas as products. This reaction, believed to be an intramolecular 1,3 (S → N) benzoyl migration, is thought to involve nucleophilic attack at the benzoyl carbonyl group by a lone pair of electrons from the isothiourea imino nitrogen atom (**19**). The kinetics of this reaction for **3**, **4**, **5**, and **9** (sigmoid pH–rate profiles) are in accord with this picture. The pH–rate profiles of compounds **6** and **7**, however, are bell shaped rather than sigmoid. The decrease in benzoyl transfer rate at high pH for these compounds seems best interpreted as indicating rate-determining isomerization of the isothiourea at high pH from the sterically favored isomer into the form necessary for the S → N migration, *i.e.*, where the *S*-benzoyl group and the nucleophilic nitrogen lone pair are cis to each other. This isomerization is thought to proceed most readily by rotation about a C–N bond in the protonated isothiourea. Isomerization where necessary in **3**, **4**, and **5** is available *via* a series of rapid acid–base equilibria so that in these cases this step does not become rate determining. The behavior of **8** is significantly different from that of **6** and **7**. Differences include the apparent absence of rate-determining isomerization at high pH and the presence of benzoyl migration to the amino as well as to the imino isothiourea nitrogen atom. Rationalization of these differences has been achieved in terms of the steric effects of the bulky *tert*-butyl group of **8**.

We have investigated the reactions of a series of *S*-benzoylisothioureas in aqueous solution. The reactions (hydrolysis and S → N benzoyl migration) of some cyclic members of this class of compounds, including *S*-benzoylisothiobiotin methyl ester (**1**), have



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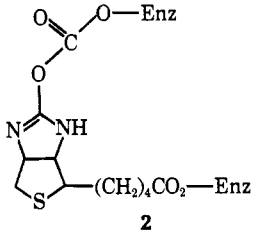
been reported elsewhere.[2] The latter compounds were used as models for *O*-carboxybiotin which has been recently proposed[3] as the active form of carbon dioxide in the enzyme–biotin–CO_2 complexes (**2**) of a variety



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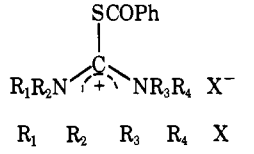
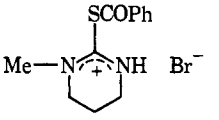
of carboxylating enzymes. In the present paper we present the results of a kinetic study of the reactions of the *S*-benzoylisothioureas **3–10** with particular em-



	R_1	R_2	R_3	R_4	X
3	H	H	H	H	Cl
4	Me	H	Me	H	Cl
5	Me	Me	H	H	Cl
6	Me	Me	Me	H	Br
7	Me	Me	Et	H	Br
8	Me	Me	*t*-Bu	H	Br
10	Me	Me	Me	Me	Br



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phasis on the S → N benzoyl migrations of the acyclic compounds.

Experimental Section

Materials. *S*-Benzoylisothiouronium halides[4,5] were prepared in essentially quantitative yields from the reaction between thioureas and benzoyl halides in acetone at room temperature. 1,1-Dimethyl-3-alkylthioureas were prepared from the reaction of alkyl isothiocyanates with dimethylamine. 1-Methyltrimethylenethiourea (mp

(1) Postdoctoral Fellow, University of California at Santa Barbara.
(2) R. F. Pratt and T. C. Bruice, *Biochemistry*, 10, 3178 (1971).
(3) T. C. Bruice and A. F. Hegarty, *Proc. Nat. Acad. Sci. U. S.*, **65**, 805 (1970).
(4) A. E. Dixon and J. Hawthorne, *J. Chem. Soc.*, 101, 2502 (1912).
(5) A. E. Dixon, *ibid.*, 83, 550 (1903); 89, 892 (1906); A. E. Dixon and J. Taylor, *ibid.*, 91, 912 (1907); 101, 2502 (1912); A. E. Dixon and R. T. J. Kennedy, *ibid.*, 117, 80 (1920); A. E. Dixon and J. Taylor, *ibid.*, 117, 720 (1920).

121.5–122°, from ethanol) was prepared by the method used by McKay and Kreling[6] for the preparation of 1-methylethylenethiourea.

S-**Benzoylisothiouronium chloride** (**3**) showed mp 130–132° (from acetone). Dixon and Hawthorne[4] report mp "about 116°" for a sample prepared in benzene. *Anal.* Calcd for $C_8H_9ClN_2OS$: C, 44.34; H, 4.19; N, 12.93; Cl, 16.36. Found: C, 44.15; H, 4.21; N, 12.77; Cl, 16.59.

S-**Benzoyl-1,3-dimethylisothiouronium Chloride** (**4**). The preparation and characterization are described in the earlier paper.[2]

S-**Benzoyl-1,1-dimethylisothiouronium chloride** (**5**) showed mp 123–125° (from acetone). *Anal.* Calcd for $C_{10}H_{13}ClN_2OS$: C, 49.07; H, 5.35; N, 11.45; Cl, 14.49. Found: C, 49.39; H, 5.45; N, 11.42; Cl, 14.38.

S-**Benzoyl-1,1,3-trimethylisothiouronium bromide** (**6**) showed mp 120–125° (from acetone). *Anal.* Calcd for $C_{11}H_{15}BrN_2OS$: C, 43.57; H, 4.99; N, 9.24; Br, 26.36. Found: C, 43.65; H, 5.04; N, 9.13; Br, 26.39.

S-**Benzoyl-1,1-dimethyl-3-ethylisothiouronium bromide** (**7**) exhibited mp 129–131° (from acetone–ether). *Anal.* Calcd for $C_{12}H_{17}BrN_2OS$: C, 45.43; H, 5.40; N, 8.83; Br, 25.19. Found: C, 45.30; H, 5.52; N, 8.85; Br, 25.42.

S-**Benzoyl-1,1-dimethyl-3-*tert*-butylisothiouronium bromide** (**8**) showed mp 69–71° (from acetone–ether). *Anal.* Calcd for $C_{14}H_{21}BrN_2OS$: C, 48.70; H, 6.13; N, 8.11; Br, 23.14. Found: C, 48.51; H, 6.34; N, 8.11; Br, 23.01.

S-**Benzoyl-1-methyltrimethyleneisothiouronium bromide** (**9**) showed mp 135–138° (from acetone). *Anal.* Calcd for $C_{12}H_{15}BrN_2OS$: C, 45.72; H, 4.80; N, 8.89; Br, 25.35. Found: C, 45.57; H, 4.93; N, 8.84; Br, 25.29.

As discussed in the previous paper[2] the spectral characteristics of these compounds (infrared, ultraviolet, and nuclear magnetic resonance) are fully in accord with the assignment of an *S*-benzoylisothiouronium structure to them. The nuclear magnetic resonance spectra of all these compounds were recorded (DCl, D_2O, DSS). All showed a five-proton multiplet at about τ 2.5 (Ar–H); details of the aliphatic regions of the spectra are given in Table I for compounds **4**–**8** and **10**.

Table I. Proton Magnetic Resonance Spectral Data (DCl, D_2O, DSS) for Compounds **4**–**8** and **10**

Compd	Chemical shift, τ
4	6.83 (s, 6)
5	6.55 (s, 3), 6.58 (s, 3)
6	6.48 (s, 3), 6.54 (s, 3), 6.78 (s, 3)
7	6.30 (q, 2), 6.50 (s, 3), 6.51 (s, 3), 8.72 (t, 3)
8	6.49 (s, 6), 8.43 (s, 9)
10	6.57 (s, 12)

S-**Benzoyl-1,1,3,3-tetramethylisothiouronium Bromide** (**10**). Equimolar quantities of 1,1,3,3-tetramethylthiourea and benzoyl bromide were mixed together and warmed gently till homogeneity was obtained. The clear, sticky, hygroscopic gum obtained on cooling the mixture did not crystallize after several months in a desiccator over P_2O_5. The infrared spectrum showed strong absorptions at 1690 (thiolester, $\nu_{C=O}$) and 1610 cm^{-1} and no strong absorption in the 2500–3500-cm^{-1} range, the ultraviolet spectrum showed $\lambda_{max}^{H_2O}$ 265 nm, and the nuclear magnetic resonance spectrum is reported above. In addition the nmr spectrum showed an additional sharp singlet at τ 6.65 corresponding to tetramethylthiourea (<10%). These spectral data and the results from the hydrolyses (see below) are sufficient to identify **10** as the main component in the reaction mixture.

S-**Phenylisothiourea** (**11**) was prepared by the method of Arndt[7] from the reaction of cyanamide with thiophenol in ether. After recrystallization from chloroform–petroleum ether the melting point (rapid heating) was 96–97° (lit.[7] mp 96–97°).

S-**Phenyl-1,3-dimethylisothiourea** (**12**). 1,3-Dimethylthiourea was converted by the method of Eilingsfeld, *et al.*,[8] into 1,3-dimethylchloroformamidinium chloride. This material was not isolated but allowed to react with thiophenol in the presence of triethylamine as described by Bock[9] for the reaction of alcohols with chloroformamidinium compounds. The product was distilled as a colorless oil, bp 98–100° (1 mm), yield *ca.* 20%. Spectral data supported the identity of this compound as **12** as did the analysis. *Anal.* Calcd for $C_9H_{12}N_2S$: C, 59.96; H, 6.71; N, 15.54; S, 17.79. Found: C, 59.93; H, 6.86; N, 15.71; S, 17.63.

S-**Phenyl-1,1,3-trimethylisothiourea** (**13**) was prepared analogously to **12**. The product, a colorless oil, distilled at 86–87° (0.8 mm), yield *ca.* 20%. *Anal.* Calcd for $C_{10}H_{14}N_2S$: C, 61.81; H, 7.26; N, 14.42; S, 16.50. Found: C, 61.66; H, 7.37; N, 14.70; S, 16.69.

Qualitative Hydrolyses. These were carried out routinely by addition of samples (0.1–0.2 g) of **3**–**10** to 0.2 *M* hydrochloric acid, dilute bicarbonate or phosphate buffer (pH 7 or 9), and 0.2 *M* potassium hydroxide solutions and the products were identified in the manner described previously.[2] Product analyses were also carried out at spectral concentrations (10^{-5}–10^{-4} *M*).

Compound **4** reacts in aqueous solution to give 1,3-dimethylthiourea and benzoic acid at very high and at low pH and the S → N acyl transfer product, 1-benzoyl-1,3-dimethylthiourea, at intermediate pH.[2] Analogous reactions were observed with **5** and **9**. At pH 7–9, **5** yielded 1-benzoyl-3,3-dimethylthiourea, mp 137–138°, from ethanol (lit.[10] mp 117°). Spectral data supported this identification, as did the analysis. *Anal.* Calcd for $C_{10}H_{12}N_2OS$: C, 57.66; H, 5.81; N, 13.45. Found: C, 57.60; H, 5.72; N, 13.38. Under the same conditions **9** yielded 1-benzoyl-3-methyltrimethylenethiourea, mp (from benzene–hexane) 108–109°. *Anal.* Calcd for $C_{12}H_{14}N_2OS$: C, 61.51; H, 6.02; N, 11.96; S, 13.69. Found: C, 61.30; H, 6.24; N, 12.10; S, 13.46.

In acid solution all of the compounds **3**–**9** reacted to form benzoic acid and the parent thiourea.

Compound **3** yielded 1-benzoylthiourea (mp 174–175°, from ethanol, lit.[11] mp 169–170°) at pH 7. At higher pH, however, the reaction mixture yielded, on acidification, a foul-smelling yellow oil which was identified by comparison of infrared and ultraviolet spectra and thin layer chromatographic behavior (silica gel, $CHCl_3$) with an authentic sample of thiolbenzoic acid. The latter compound was also detected as a product of reaction of **5**, **6**, and **7** in 0.2 *M* potassium hydroxide solution.

At pH 7–9 the product of reaction of **6** was 1-benzoyl-1,3,3-trimethylthiourea, mp 104.5–105° from aqueous ethanol (*Anal.* Calcd for $C_{11}H_{14}N_2OS$: C, 59.43; H, 6.35; N, 12.60. Found: C, 59.41; H, 6.44; N, 12.54), and that of **7** was 1-benzoyl-1-ethyl-3,3-dimethylthiourea, colorless oil from molecular distillation (*Anal.* Calcd for $C_{12}H_{16}N_2OS$: C, 60.98; H, 6.82; N, 11.85; S, 13.57. Found: C, 60.95; H, 6.67; N, 11.94; S, 13.35).

In 0.2 *M* potassium hydroxide and at pH 7–9 four products of reaction of **8** were observed. Addition of **8** to these solutions gave a pale yellow oil which was taken up into chloroform. Acidification of the aqueous solution then afforded thiolbenzoic acid. An infrared spectrum of the residual oil obtained after evaporation of the chloroform from the dried chloroform extracts showed strong absorptions at 2100 and 1650 cm^{-1} (broad). The peak at 2100 cm^{-1} strongly suggests the presence of an isothiocyanate. *tert*-Butyl isothiocyanate was identified by comparison of vpc retention times (20% XF 1150 Silicon on Chromosorb W 60–80) at two column temperatures. The other components of the mixture were separated by a rapid fractional distillation in a zonal sublimation apparatus and identified as *N*,*N*-dimethylbenzamide (by comparison of infrared, ultraviolet, and nmr spectra with those of an authentic sample) and 1-benzoyl-1-*tert*-butyl-3,3-dimethylthiourea (colorless oil). *Anal.* Calcd for $C_{14}H_{20}N_2OS$: C, 63.60; H, 7.62; N, 10.60. Found: C, 63.95; H, 7.72; N, 10.83. The latter compound was unstable and decomposed on heating into *N*,*N*-dimethylbenzamide and *tert*-butyl isothiocyanate. This decomposition was also observed to occur at room temperature over a period of weeks. The compound was, however, stable for the time intervals over which the reactions of **8** were studied so that the *N*,*N*-dimethylbenzamide and *tert*-butyl isothiocyanate in the original reaction mixture must come from reaction of **8** rather than decomposition of the *N*-benzoyl compound.

The products of reaction of **10** were benzoic acid and 1,1,3,3-tetramethylthiourea at all pH's. The structures of all *N*-benzoyl compounds were supported by infrared, ultraviolet, and nmr spec-

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(7) F. Arndt, *Justus Liebigs Ann. Chem.*, **384**, 322 (1911); **396**, 1 (1913).
(8) H. Eilingsfeld, G. Neubauer, M. Seefelder, and H. Weidinger, *Chem. Ber.*, 97, 1232 (1964).
(9) G. Bock, *ibid.*, 100, 2870 (1967).
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(11) W. H. Pike, *Ber.*, **6**, 755 (1873).

Table II. Ultraviolet Spectra of Thioureas

Thiourea	$\lambda_{max}^{dioxane}$, nm	ϵ
1,1,3-Trimethyl	292.5 (sh)	100
1,1-Dimethyl-3-ethyl	293 (sh)	113
1,1-Dimethyl-3-isopropyl	295 (sh)	115
1,1-Dimethyl-3-*tert*-butyl	304 (sh)	97
1,1,3,3-Tetramethyl	318	293

Table III

Products from	pH 0	pH 3	pH 10	pH 14
3–7, 9	Benzoic acid and thiourea	*N*-Benzoylthiourea (the N → S transfer product)		Benzoic acid, thiourea, and/or thiolbenzoic acid
8	Benzoic acid and thiourea	*N*-Benzoylthiourea, thiolbenzoic acid, *N,N*-dimethylbenzamide, and *tert*-butyl isothiocyanate		

Table IV. Empirical Rate Constants Used to Define pH–Rate Profiles of Compounds **3–10**

Compd	$k_0 \times 10^4$, sec^{-1}	k_a, sec^{-1}	pK_a	pK_b	k_o, sec^{-1}	k_b, $sec^{-1}\ M^{-1}$	f_0
3	9.25	0.71	8.22			1.26×10^5	0.82
4[a]	2.8	21.0	8.40			293	0.97
5	4.5	17.8	8.95			350	0.92
6	0.80	5.18	8.60	9.32	0.0054	0.715	1.0
7	0.56	3.4	8.60	9.82	0.10	0.50	1.0
8	0.178	29.5	9.57				
9	1.86	316	10.02				1.0
10	0.69					380	

[a] From ref 2.

tra. Ultraviolet spectra indicate that **3–10** yield the same products as described above at low concentrations (10^{-5}–10^{-4} *M*). In the case of **8**, where detection of *N,N*-dimethylbenzamide and *tert*-butyl isothiocyanate was not possible spectrally in the presence of the other products, a preparative reaction with 10^{-4} *M* **8** indicated that these products were still present.

Final spectra showed that one product of alkaline hydrolysis of the *S*-phenylisothioureas **11–13** was the thiophenoxide ion. Cyanamide was detected as a hydrolysis product of **11** and of **3** in the following way. A 5-mg sample of **11** or **3**, dissolved in a few drops of 10^{-3} *M* HCl, was added with stirring to 20 ml of 0.01 *M* potassium hydroxide solution. After approximately 1 min the pH of the solution was reduced to 7 and a thin layer chromatogram (silica gel, 4:1:2 *n*-BuOH–EtOH–H_2O)[12] of the reaction mixture run alongside authentic cyanamide. The chromatogram after drying was sprayed with a solution obtained from mixing equal volumes of 10% solutions of sodium nitroprusside, potassium ferricyanide, and sodium hydroxide.[12] The presence of a spot on the chromatogram of the reaction mixtures of the same color (red-violet) and R_f as that of cyanamide confirms that the latter is a product of reaction of **11** and **3** in alkaline solution. Neither thiophenol, thiobenzoic acid, nor thiourea gave a color reaction at these concentrations.

Ultraviolet Spectra. Details of the ultraviolet spectra of some trisubstituted thioureas are given in Table II with that of 1,1,3,3-tetramethylthiourea for comparison. Wavelengths and extinction coefficients reported for shoulders are those at the midpoint between the two inflection points defining the shoulder.

Kinetic Measurements. All kinetic measurements were made in aqueous solution at 30 ± 0.1° and at ionic strength 1 μ (adjusted with potassium chloride). The hydrolyses of **11**, **12**, and **13** were followed spectrophotometrically at 260 nm and their pK_a's determined by spectrophotometric titration.

Results

Product Analyses. The qualitative approach to these has been described in the previous section, and the results are summarized in Table III.

(12) M. Takimoto and K. Koeda, *Kogyo Kayaku Zasshi*, **63**, 797 (1960); *Chem. Abstr.*, **56**, 6639 (1962).

Kinetics. *S*-Benzoylisothioureas. The observed pseudo-first-order rate constants for the disappearance of *S*-benzoylisothioureas from aqueous solution were independent of substrate concentration over the range of the latter involved (10^{-5}–10^{-4} *M*). Plots of logarithms of these rate constants (log k_{obsd}) *vs.* pH for compounds **3** and **5–10** are shown in Figures 1a and b. The plot for **4**, which is very similar to that of **5**, has been previously reported.[2] The points on these plots are experimental and the lines theoretical, having been derived for compounds **3–5** and **8–10** from the empirical eq 1 and for **6** and **7** from eq 2. The second form of

$$k_{obsd} = k_0 + \frac{k_a K_a}{K_a + a_H} + k_b K_w / a_H \equiv \frac{k_0 a_H + k_a K_a + k_b K_a K_w / a_H}{K_a + a_H} \quad (1)$$

$$k_{obsd} = k_0 + \frac{k_a K_a a_H}{a_H^2 + K_a a_H + K_a K_b} + k_c + k_b K_w / a_H \equiv \frac{k_0 a_H^2 + k_a K_a a_H + k_c K_a K_b + k_b K_a K_b K_w / a_H}{a_H^2 + K_a a_H + K_a K_b} \quad (2)$$

eq 1 is equivalent to the first as far as the experimental results are concerned because the pH dependence of k_0 and $k_b K_w / a_H$ cannot be observed when $a_H \sim K_a$ but only when $a_H \gg K_a$ and $a_H \ll K_a$, respectively. Empirical constants fitting these equations for compounds **3–10** are given in Table IV. Before mechanisms for these reactions can be considered, it is necessary to try to correlate the empirical rate constants with reaction products. The pH *vs.* product scheme above suggests that k_0 is associated with hydrolysis to benzoic acid and the parent thiourea, k_a with the S → N transfer reaction, and k_b and k_c with other hydrolytic processes leading to benzoate and the thiourea and/or to thiolbenzoate. In order to verify these ideas the final spectra after kinetic runs were analyzed quantitatively. From the measured extinc-

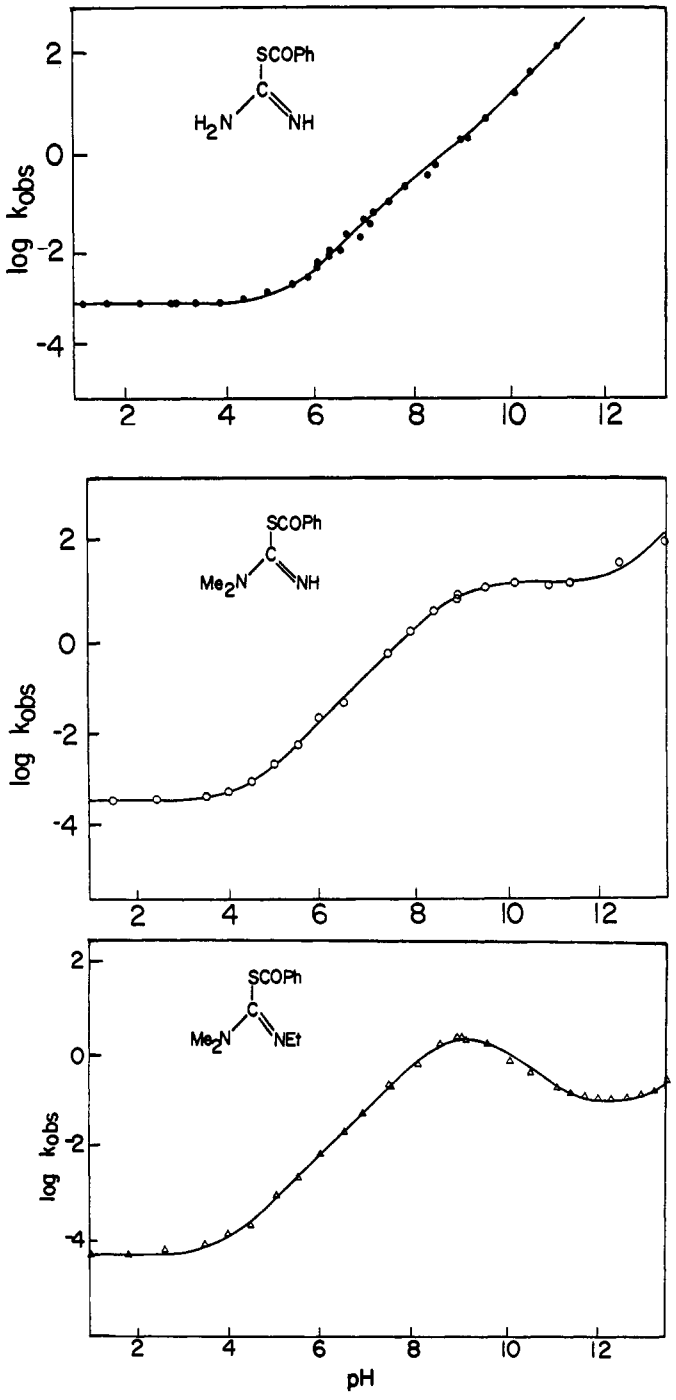


Figure 1a. Plots of log k_{obsd} (k_{obsd} in sec^{-1}) *vs.* pH for the disappearance of *S*-benzoylisothioureas (H_2O solvent, 30°, μ = 1.0): **3** (●), **5** (○), and **7** (△). The points are experimental and the lines theoretical, being derived from eq 1 and 2.

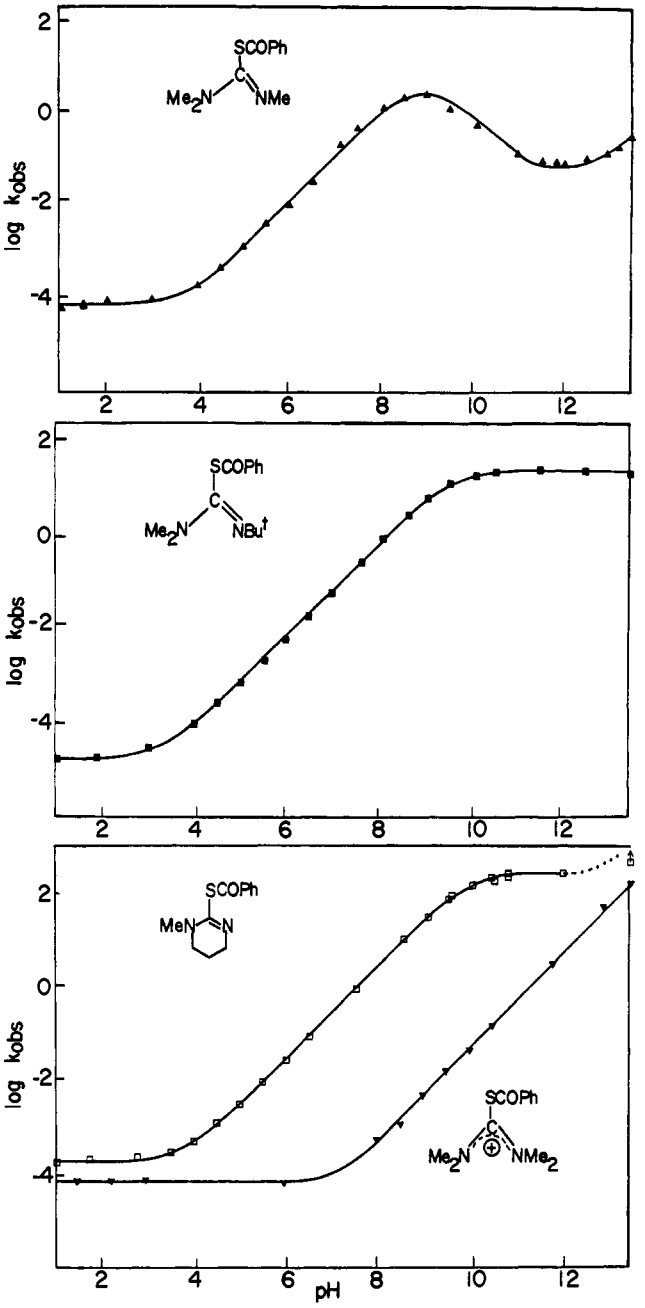


Figure 1b. Plots of log k_{obsd} (k_{obsd} in sec^{-1}) *vs.* pH for the disappearance of *S*-benzoylisothioureas (H_2O solvent, 30°, μ = 1.0): **6** (▲), **8** (■), **9** (□), and **10** (▼). The points are experimental and the lines theoretical, being derived from eq 1 and 2.

tion coefficients of the products at a number of wavelengths, the amount of each product present could be calculated as a function of pH from these spectra.

Consider firstly the lower pH part of the profiles where the observed product changes from benzoic acid and thiourea to *N*-benzoylthiourea as the pH rises. If the plateau in the pH–rate, defined by k_a and K_a, describes the pH dependence of the acyl transfer reaction, then the fraction f_C of *N*-benzoylthiourea produced at any pH is given by eq 3. This applies for

$$f_C = f_0 k_a K_a / (k_0 a_H + k_a K_a) \qquad (3)$$

all compounds **3–9** since at pH's where this change in products occurs $k_0 a_H + k_a K_a \gg k_b K_a K_w / a_H$ (eq 1) and $a_H^2 + K_a a_H \gg K_a K_b$ and $k_0 a_H^2 + k_a K_a a_H \gg k_c K_a K_b + k_b K_a K_b K_w / a_H$ (eq 2). f_0 is the fraction of *N*-benzoylthiourea arising *via* k_a, *i.e.*, $k_a = k_{s_1}$ (leading to *N*-benzoylthiourea) + k_{h_1} (leading to hydrolysis) and $f_0 = k_{s_1}/(k_{s_1} + k_{h_1})$. Plots of f_C *vs.* pH for compounds **3** and **7** are given in Figure 2. The points are experimental, derived from final spectra, and the lines are calculated using eq 3, the kinetic constants from Table IV ,and f_0 as a variable parameter. This type of plot for **4** has been presented elsewhere.[2] In all cases excellent agreement was obtained between the kinetic and product analysis data which confirm that the pH dependence of the acyl transfer reaction is

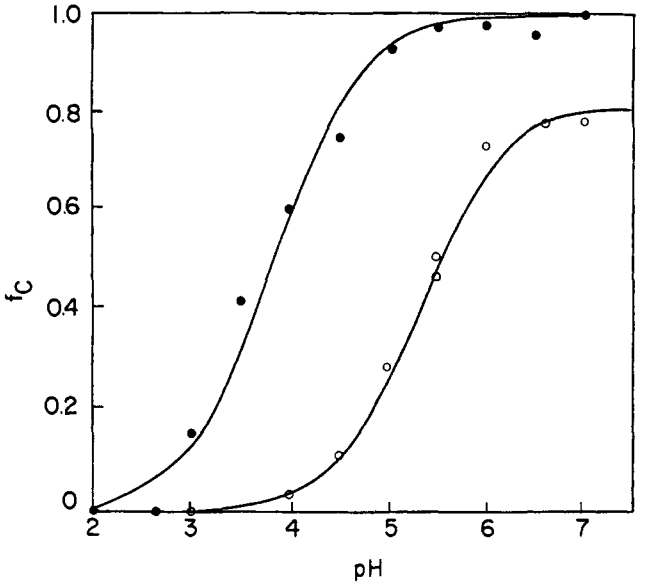


Figure 2. Plots of f_C (raction of *N*-benzoylthiourea product *vs.* pH for compounds **3** (○) and **7** (●). The points are experimental and the lines theoretical (eq 3).

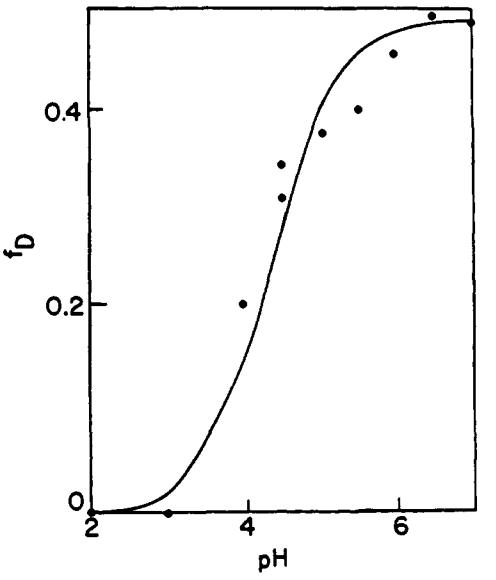


Figure 3. Plot of f_D (fraction of thiolbenzoic acid product) *vs.* pH for compound **8**. The points are experimental and the lines theoretical (eq 4).

sigmoid and defined by f_0k_a and K_a. f_0 values are recorded in Table IV.

The products of reaction of compound **8** change at low pH from benzoic acid and 1,1-dimethyl-3-*tert*-butylthiourea to the mixture described above. Here k_a must include terms leading to 1-benzoyl-1-*tert*-butyl-3,3-dimethylthiourea (k_{s_1}), thiolbenzoate (k_{h_2}), and *N*,*N*-dimethylbenzamide and *tert*-butylisothiocyanate (k_{s_2}), *i.e.*,

$$k_a = k_{s_1} + k_{s_2} + k_{h_2}$$

The fraction, f_D, of thiolbenzoate at any pH is given by eq 4. A plot of f_D *vs.* pH is shown in Figure 3.

$$f_D = k_{h_2}/(k_0a_H + k_aK_a) \quad (4)$$

Here the points are experimental and the line is theoretical, calculated from eq 4, the constants of Table IV, and using $k_{h_2}/k_a = 0.49$. At pH above 6 the final spectrum after reaction did not change with pH and yielded the information that $k_{s_1}:k_{s_2}:k_{h_2}::0.25:0.27:0.48$. These results indicate that the pH dependences of all three reactions of **8** at high pH are sigmoid about K_a.

At high pH the predominant product of reaction of **3** changes from 1-benzoylthiourea to thiolbenzoate. The fraction of thiolbenzoate in the reaction mixture at any pH is given by eq 5. For **3**, however, k_a is not

$$f_D = k_b/(k_b + k_aa_H/K_w) \quad (5)$$

well defined because of the form of the pH–rate profile for this compound (Figures 1a and b) and considerable variation of k_a and K_a (although k_aK_a is well defined) is possible without significantly changing the fit to the experimental points. In this case then the product distribution data was used to define k_a. Experimentally, from the final spectra, the ratio of thiolbenzoate to 1-benzoylthiourea was determined as a function of pH. The fraction, f_D', of thiolbenzoate is then given in eq 6 where k_{s_1}, as above, is that part of

$$f_D' = k_b/(k_b + k_{s_1}a_H/K_w) \quad (6)$$

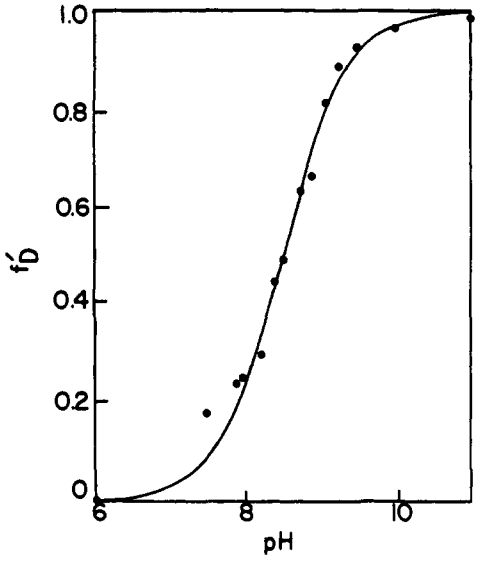


Figure 4. Plot of f_D' *vs.* pH for compound **3**. The points are experimental and the lines theoretical (eq 6).

k_a representing the rate constant for 1-benzoylthiourea formation. A plot of f_D' *vs.* pH is given in Figure 4 and from this, knowing k_b which leads exclusively to thiolbenzoate, k_{s_1} could be determined. From the previously determined f_0 value from the product distribution at lower pH (Figure 2), k_a and hence K_a could be obtained. These values are those reported in Table IV.

The variation with pH of the products obtained from **6** and **7** at high pH is quite complex, as might be expected from the more complex pH–rate profiles. It can, however, be rationalized by assuming that k_a is associated with the S → N transfer product, k_b with benzoate, and k_c with both thiolbenzoate and benzoate. From eq 2 then, at high pH, the variation of fractions of benzoate, f_B, *N*-benzoylthiourea, f_C, and thiolbenzoate, f_D, in the product mixture would be given by

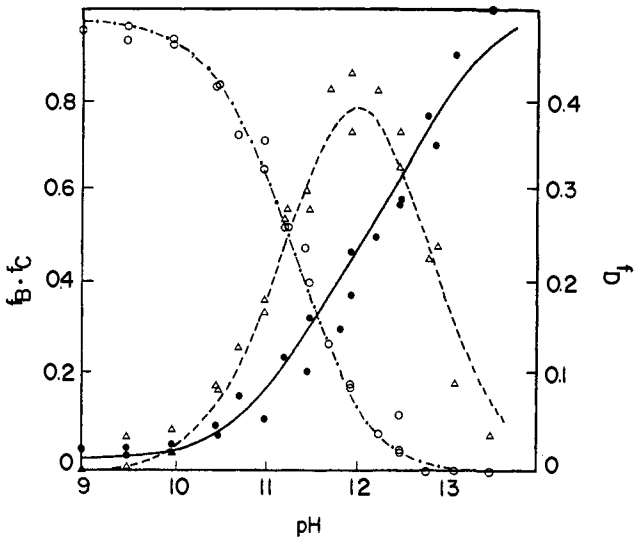


Figure 5. Plots of f_B (fraction of benzoic acid plus thiourea product) (●,——), f_C (○, -·-·-), and f_D (△, ---) *vs.* pH for compound **6**. The points are experimental and the lines theoretical (eq 7, 8, and 9).

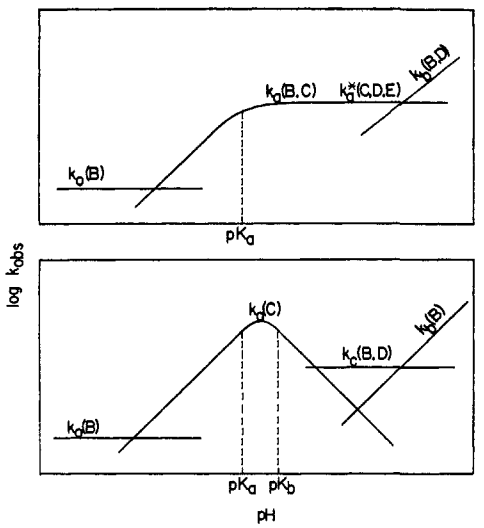


Figure 6. Schematic pH–rate profiles for reactions of *S*-benzoylisothioureas **3**–**10** showing the relationship between empirical rate constants and the reaction products. The upper diagram applies to compounds **3**, **4**, **5**, **8**, **9**, and **10** (k_a* applies to **8**, k_a to the others) and the lower to compounds **6** and **7**. The products are **B** (benzoic acid plus thiourea), C (*N*-benzoylthiourea), D (thiolbenzoic acid), and E (*N*,*N*-dimethylbenzamide plus *tert*-butyl isothiocyanate).

eq 7, 8, and 9, respectively; where $M = k_a a_H^2$

$$f_B = [(1 - x)k_c K_b a_H + k_b K_b K_w]/M \quad (7)$$

$$f_C = k_a a_H^2/M \quad (8)$$

$$f_D = x k_c K_b a_H/M \quad (9)$$

$+ k_c K_b a_H + k_b K_b K_w$ and x is the fraction of k_c associated with thiolbenzoate as product. Plots of f_B, f_C, and f_D for **6** are shown in Figure 5. The points are experimental from final spectra after kinetic runs and the lines are theoretical, being derived from eq 7, 8, and 9, the constants of Table IV, and $x = 0.55$. In practice, of course, the parameters of eq 2 were varied slightly to yield best fit to both the kinetic and product analysis data, and these values are those in Table IV. A similar analysis was applied to compound **7** where a value of x of 0.57 was used.

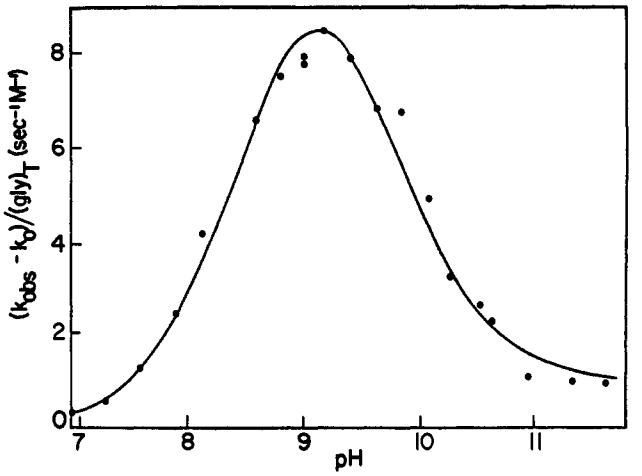


Figure 7. Plot of $(k_{obsd} - k_0)/(Gly)_T$ *vs.* pH for the reaction of compound **6** in aqueous glycine buffers (30°, μ = 1.0). The points are experimental and the lines theoretical (eq 10).

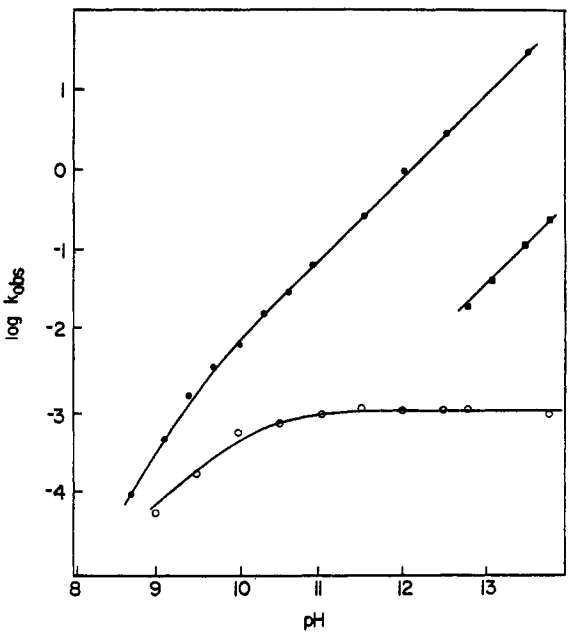


Figure 8. Plots of log k_{obsd} (k_{obsd} in sec^{-1}) *vs.* pH for the reactions in aqueous solution (30°, μ = 1.0) of *S*-phenylisothioureas **11** (●), **12** (■), and **13** (○). The points are experimental and the lines theoretical (eq 11).

The kinetic and product analyses described above allow the rates and pH dependences of the various reactions of **3**–**10** occurring in aqueous solution to be obtained. These are shown schematically in Figure 6.

Glycinolysis of 6. On a preparative scale (addition of 0.1 g of **6** to 10 ml of 1 *M* glycine, pH 9.2, followed by acidification), hippuric acid was detected as a major product of reaction of **6** with glycine. This suggests that the reaction involves nucleophilic attack of glycine on the thiol ester group of **6** as would be expected from the previously studied[2] reactions between *S*-benzoylisothioureas and nucleophiles. At pH 9.63 the observed pseudo-first-order rate constants (k_{obsd}) for disappearance of **6** in glycine buffers varied linearly with total glycine concentration up to 1 *M*. In Figure 7 a plot of

$(k_{obsd} - k_0)/[Gly]_T$ *vs.* pH is presented. Here k_0 is the background rate calculated from eq 2 and the constants of Table IV and $[Gly]_T$ is the total glycine concentration. This curve was fitted with eq 10. Here K_a is the acid dis-

$$\frac{k_{obsd} - k_0}{[Gly]_T} = \frac{K_a}{a_H + K_a} \times \frac{k_x a_H + k_y K_x}{a_H + K_x} \quad (10)$$

sociation constant of glycine, measured as 9.61 under the reaction conditions. The solid curve of Figure 6 requires $pK_x = 8.65$, $k_x = 144$ sec^{-1} M^{-1}, and $k_y = 1$ sec^{-1} M^{-1}.

***S*-Phenylisothioureas.** Plots of logarithms of pseudo-first-order rate constants (log k_{obsd}) *vs.* pH for the hydrolysis of compounds **11–13** in alkaline solution are given in Figure 8. The points on these plots are experimental and the lines theoretical, having been derived from the empirical eq 11. Empirical constants

$$k_{obsd} = \frac{k_d + k_e K_c/a_H}{K_c + a_H} \quad (11)$$

fitting this equation are given in Table V along with

Table V. Empirical Constants Used to Define pH–Rate Profiles of Compounds **11–13**

Compd	k_d, sec^{-1}	k_e, sec^{-1}	pK_c	pK^a
11		8.75×10^{-13}	9.30	9.35
12		3.62×10^{-15}		
13	6.96×10^{-14}		10.20	10.12

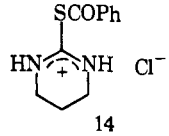
[a] Spectrophotometrically determined dissociation constant of the *S*-phenylisothiourea conjugate acid.

the acid dissociation constants of the protonated isothioureas **11** and **13**. At $[OH^-] = [OD^-] = 0.15$ *M*, a kinetic deuterium solvent isotope effect (k_{H_2O}/k_{D_2O}) of 0.72 ± 0.02 was measured for the hydrolysis of **12**.

Discussion

The reactions of *S*-benzoylisothiouronium salts **3–10** in aqueous solution have been studied kinetically and by product analysis. The pH–rate profiles for the disappearance of these species by reaction in aqueous solution in the absence of added buffer are shown in Figures 1a and b. Empirical eq 1 and 2 have been fitted to these curves, yielding the constants of Table IV. The results of product analysis in conjunction with the kinetics are shown schematically in Figure 6.

In an earlier paper[2] the reactions of compounds **4**, **14**, **15**, and **1** in HBr were examined. Two modes



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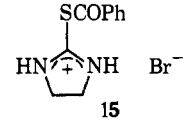

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of reaction were observed here, hydrolysis of the thiol ester group to yield benzoic acid and the parent thiourea and an intramolecular S → N acyl transfer reaction leading to *N*-benzoylthioureas. Scheme I seemed sufficient to explain the kinetic and product analysis data for these compounds. From Scheme I the following kinetic equation can be derived

$$k_{obsd} = \frac{k_1[H_2O]a_H + (k_2K_w + k_5K_1) + k_4K_1K_w/a_H}{K_1 + a_H} \quad (12)$$

Then from the empirical eq 1 which applied to compounds **4**, **14**, **15**, and **1** in HBr we have

$$k_0 = k_1[H_2O] \quad (13)$$

$$k_a = k_2K_w/K_1 + k_5 \quad (14)$$

$$K_a = K_1 \quad (15)$$

$$k_b = k_4 \quad (16)$$

and from the product analysis data at low pH (eq 3)

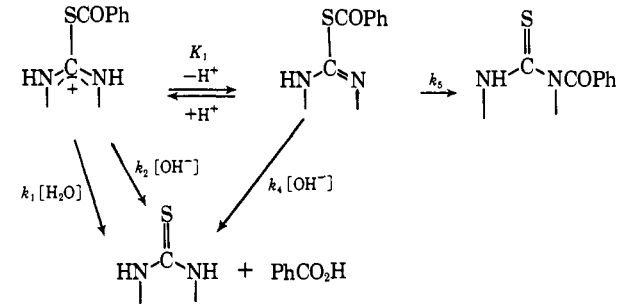
$$f_0 = k_5/k_a \quad (17)$$

or

$$k_{s_1} = k_5 \text{ and } k_{h_1} = k_2K_w/K_1$$

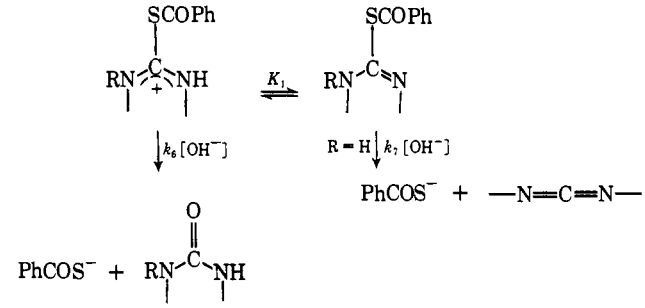
This scheme and eq 5 and 13–17 can also be applied to compounds **3**, **5**, **9**, and **10** of the present series with the addition of further terms to take into account another mode of reaction observed, that leading to thiolbenzoate as product. Two forms of this mode

Scheme I



are apparent: one giving rise to a kinetic term first order in hydroxide ion at high pH (seen in **3** and **5**) and the other to a kinetic term independent of hydroxide ion at high pH (**6**, **7**, and **8**). The terms $k_6[HO^-]$ and $k_7[HO^-]$ have been added to Scheme I and are shown in Scheme II. Equation 12 then becomes (18),

Scheme II



(14) becomes (19), and (16) becomes (20).

$$k_{obsd} = \frac{k_1[H_2O]a_H + (k_2K_w + k_5K_1 + k_6K_w) + (k_4 + k_7)K_1K_w/a_H}{K_1 + a_H} \quad (18)$$

$$k_a = k_2K_w/K_1 + k_5K_1 + k_6K_w/K_1 \quad (19)$$

$$k_b = k_4 + k_7 \quad (20)$$

With these equations and the empirical constants of Table IV, the constants of Schemes I and II can be obtained for compounds **3**, **4**, **5**, **9**, and **10**. These are presented in Table VI.

Table VI. Rate Constants of Schemes I and II for Compounds **3**, **4**, **5**, **9**, and **10**

	$k_1 \times 10^6$, $sec^{-1}\ M^{-1}$	k_2, $sec^{-1}\ M^{-1}$	k_4, $sec^{-1}\ M^{-1}$	k_5, sec^{-1}	k_7, $sec^{-1}\ M^{-1}$	pK_1
3	16.7	5.34×10^4		0.58	1.26×10^5	8.22
4[a]	5.05	1.61×10^5	293	20.4		8.40
5	8.10	1.06×10^5	*b*	16.4	350[b]	8.95
9	3.35			316		10.02
10	1.24	3.80×10^2				

[a] From ref 2. [b] The figure given for k_7 here probably includes some contribution from k_4; detailed product analysis was not carried out here.

Hydrolyses Leading to Benzoic Acid and Thiourea. The hydrolysis reactions leading to benzoic acid and thiourea (k_1, k_2, and k_4) were discussed previously[2] and need not be extensively dealt with here. A decrease in the spontaneous rate k_2 (interpreted[2] as hydroxide ion attack on the protonated *S*-benzoylisothiourea) and k_4 (hydroxide ion attack on the *S*-benzoylisothiourea free base form) with increased methyl substitution is indicated by examination of the data of Table VI and including values for **6** and **7** from Table VIII (see below). The reason for this is not clear. Steric effects, either involving direct hindrance or a change in electronic structure of the isothiourea leaving group, might be considered as an explanation, but it is not obvious why the rate decrease caused by these effects and seen in k_2 and k_4 should be so much smaller in k_1 (water attack on the protonated *S*-benzoylisothiourea).

Table VII. Rate Constants of Scheme II for Compounds **11**, **12**, and **13**

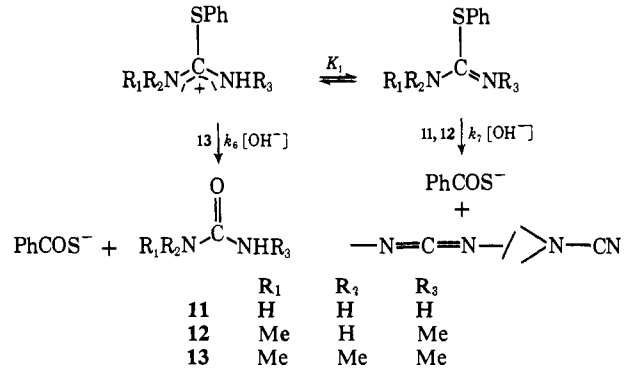
Compd	k_6, $sec^{-1}\ M^{-1}$	k_7, $sec^{-1}\ M^{-1}$	K_1
11		59	9.30
12		0.244	
13	4.7		10.20

The apparent K_a's from the kinetics were also discussed previously,[2] and it was concluded that these were much as would be anticipated for the acid dissociation constants of *S*-acylisothioureas. The identity of these quantities (eq 15) is required by Scheme I.

Hydrolyses Leading to Thiolbenzoate. The reactions leading to thiolbenzoate as product will be considered here in more detail. Of particular interest is the very large rate constant (k_7) associated with the reaction of hydroxide ion with the neutral isothiourea of **3** to yield this product. This reaction was only observed elsewhere in **5** and here to a much smaller extent.

It would be reasonable to suppose that the displacement of -SCOPh from *S*-benzoylisothioureas would be independent of the carbonyl group; *i.e.*, the carbonyl group does not participate directly so that the characteristics of these reactions suggested by Figure 6 and Table VI should be seen whatever the substituent on sulfur. To test this idea the alkaline hydrolyses of the *S*-phenylisothioureas **11**, **12**, and **13** were examined. The pH–rate profiles for hydrolysis of these compounds to thiophenoxide and presumably, for the moment, the corresponding ureas are presented in Figure 8 which can be fitted by the empirical eq 11 and the constants of Table V. These results are best interpreted in terms of Scheme III, from which the following kinetic equation can be derived.

Scheme III



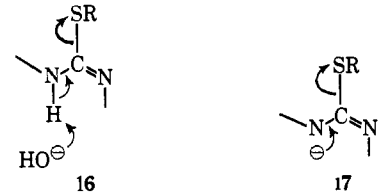
	R_1	R_2	R_3
11	H	H	H
12	Me	H	Me
13	Me	Me	Me

$$k_{obsd} = \frac{k_6K_w + k_7K_1K_w/a_H}{K_1 + a_H} \qquad (21)$$

In terms of this interpretation the empirical constants of Table V lead to the constants reported in Table VII. The assignment of K_a to K_1 required by Scheme II is supported by the good agreement between the K_1 values and the dissociation constants of **11** and **13** obtained spectrophotometrically (see Table V).

A distinct resemblance is noticed between the behavior of **11**–**13** under alkaline conditions and that of the analogous *S*-benzoyl compounds. In particular, the nitrogen unsubstituted compounds (**3** and **11**) show a very favorable hydroxide mediated path to produce the corresponding thiols; with the 1,3-dimethyl compounds (**4** and **12**) this path is much less favorable (not observed for **4** above the acyl shift reaction), and with the 1,1,3-trimethyl compounds (**6** and **13**) it is not observed at all. On the other hand, with the 1,1,3-trialkyl compounds **6**, **7**, **8**, and **13** a reaction producing thiol but pH independent at high pH is observed. The values of k_6 and k_7 are considerably less for the *S*-phenyl than the *S*-benzoyl compounds: $k_6(\mathbf{6})/k_6(\mathbf{13}) = 950$, $k_7(\mathbf{3})/k_7(\mathbf{11}) = 2100$. These ratios are of the same order as the ratio of leaving group K_a's.

The finding that a product of reaction of **3** and of **11** at high pH is cyanamide suggests that the reaction in these cases is an elimination, either **16** or **17**, rather than a substitution. It would certainly not be surprising to find an elimination mechanism here. Elim-



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ination of thiols by the action of heat on *S*-alkylisothioureas is a well-known[13] method of preparation of carbodiimides. This is, of course, the reverse reaction to that used in the preparation of **11**. There is also evidence that certain other substitution reactions of isothioureas, *e.g.*, with amines to form guanidines,[14] proceed by way of intermediate carbodiimides or cyanamides. Bases have also been implicated in such eliminations. For instance, Forman, *et al.*,[15] have shown that *O*-alkyl-1,1- or 1,3-disubstituted isoureas undergo a facile transalkylation reaction with alkoxides but not with alcohols. Under the same conditions no transalkylation occurred with *O*-alkyl-1,1,3-trisubstituted isoureas. Similarly in the present work, no k_7 term was observed with 1,1,3-trialkylisothioureas **6**, **7**, **8**, and **13**. In both cases the reason for this must be the absence of an acidic hydrogen bound to nitrogen which is necessary for an elimination reaction.

A distinction between the kinetically equivalent mechanisms **16** and **17** can be attempted on the basis of a kinetic deuterium solvent isotope effect. The alternative equations are set out below.

$$\text{HA (16)} \xrightarrow{k_2[OH^-]} \text{products}$$

$$k_{obsd} = k_2[OH^-]$$

$$\frac{k_7^H}{k_7^D} = \frac{k^H{}_{obsd}/[OH^-]}{k^D{}_{obsd}/[OD^-]} = \frac{k_2^H}{k_2^D} \qquad (22)$$

$$\text{HA} \underset{+H^+}{\overset{\overset{K_a}{\longrightarrow}}{\overset{-H^+}{\longleftarrow}}} \text{A}^- \text{ (17)} \xrightarrow{k_1} \text{products}$$

$$k_{obsd} = \frac{k_1 K_a}{K_a + a_H}$$

$$= k_1 K_a / a_H \text{ (where } a_H \gg K_a)$$

$$= k_1 K_a [OH^-]/K_w$$

$$\frac{k_7^H}{k_7^D} = \frac{k_1^H K_a^H K_w^D}{k_1^D K_a^D K_w^D} \qquad (23)$$

Addition of these compounds to D_2O can be assumed to lead to rapid exchange of hydrogen for deuterium on nitrogen as occurs for protonated amines. Equation 22 then suggests that for the concerted process (**16**) a considerable isotope effect should be observed (k_7^H/k_7^D considerably greater than one) since it includes direct fission of an N–H *vs.* an N–D bond in the transition state. The deuterium solvent isotope effect on the kinetically equivalent process (**17**) is given by eq 23. Now k_1^H/k_1^D should be close in value to 1.0 (compare, for example, the solvent isotope effect observed on elimination of phenoxide ions from acetoacetate ester carbanions)[16] and $K_w^D/K_w^H = 0.137$.[17] The value of k_7^H/k_7^D will then be greater or less than 1.0 depending on the value of K_a^H/K_a^D. The measured isotope effect for the hydrolysis of **12** (which, like **11**, shows a k_7 term) of 0.72 requires a value of K_a^H/K_a^D (using the values of k_1^H/k_1^D and K_w^D/K_w^H as assumed above) of 5.25. For such a weak acid (pK_a is unknown but must be above 14) this value of K_a^H/K_a^D is certainly small, but not impossibly so in view of the extent of variation observed for such isotope effects (see, for example, the compilation of Laughton and Robertson).[18] The fact that the overall observed isotope effect is below 1.0, however, does seem to rule out **16** (eq 22) and suggests that the correct mechanism is **17** (eq 23), elimination from an anion obtained *via* a fast preequilibrium.

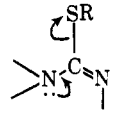
This conclusion needs some qualification, however, since k_H/k_D for **16** could be less than unity if the primary isotope effect were small (*e.g.*, if the transition state was product like) because OD^- is more basic than OH^-. Bender and Homer,[19] however, give more complete evidence for analogous elimination–addition mechanism *via* a rapidly formed anion for the alkaline hydrolysis of *p*-nitrophenyl *N*-methylcarbamate; they obtained $k_{H_2O}/k_{D_2O} = 0.56$ for this compound.

The much smaller k_7 value for **12** compared to that for **11** (and for **4** compared to **3**) could be reflection of the product stability in each case. The product from **12** and from **4** must be 1,3-dimethylcarbodiimide, while that from **11** and **3** can be cyanamide (although as written, **17**, the product will be initially carbodiimide). Cyanamides are known to be more stable than similar carbodiimides. Carbodiimide itself and monoalkyl carbodiimides for instance are known to exist completely as the cyanamide tautomer.[13] The k_7 value for **5**, where the product is also a cyanamide, although considerably smaller than for **3**, must be larger than for **4**.

The rate constant k_6 has been interpreted in Scheme III as associated with a mechanism involving attack of hydroxide ion on the protonated isothiourea. Kinetically equivalent mechanisms a and b could also be considered.

(a) Attack of water on the neutral isothiourea. This seems unlikely since if water could attack the neutral species there seems no reason why hydroxide ion could not; *i.e.*, there should be a k_7 term for **13**.

(b) A spontaneous elimination from the neutral isothiourea, *e.g.*, **18** analogous to that envisaged for



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the anions of the less substituted compounds (**17**). This cannot be ruled out but since substitution reactions, *e.g.*, hydrolysis[20] and aminolysis[21] reactions of 1,1,3,3-tetraalkylisothiouronium salts, are known to occur, nucleophilic displacement at isothiouronium carbon is certainly not impossible. The absence of k_6 term leading to a thiolate product with **9** could be construed as evidence for the elimination mechanism, but an explanation at least as likely is that the reaction producing thiolate is merely swamped out in this case by the very rapid S → N acyl transfer (as it would, in fact, be for

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(20) H. Lecher and C. Hueck, *Justus Liebigs Ann. Chem.*, 438, 169 (1924).
(21) M. Schenck, *Z. Phys. Chem.*, 77, 328 (1912).

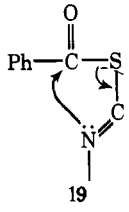
Table VIII. Rate Constants of Schemes I and II (Excluding k_3) for Compounds **6** and **7**

Compd	$k_1 \times 10^6$, sec^{-1} M^{-1}	k_2, sec^{-1} M^{-1}	k_4, sec^{-1} M^{-1}	k_6, sec^{-1} M^{-1}	pK_1
6	1.44	4.10×10^3	0.715	5.05×10^3	8.60
7	1.01	7.30×10^4	0.50	9.68×10^3	8.60

6 and **7** if not for the anomalous decrease in the rate of the latter reaction at high pH).

The *S*-benzoylisothioureas then behave as typical thiol esters, undergoing hydrolysis to benzoic acid and thiourea, and, as typical isothioureas, undergoing elimination or substitution reactions with displacement of thiol. There is no reason to believe that these reactions are anything but completely independent of the S → N benzoyl transfer reaction to be discussed below.

S → N Benzoyl Migration. Compounds **3–9** (and **14, 15,** and **1**) are distinguished by a facile migration of the benzoyl group from S to N. The rates of these reactions are independent of substrate concentration (at low concentrations)[2] and buffer species.[2] The kinetic results with **3, 4, 5, 9, 14, 15, and 1** suggest that the reactive species is the neutral isothiourea (Schemes I and II). The reaction then would appear to be simply an intramolecular rearrangement involving nucleophilic attack of a nitrogen lone pair on the ester carbonyl group (**19**). This mechanism has also been suggested



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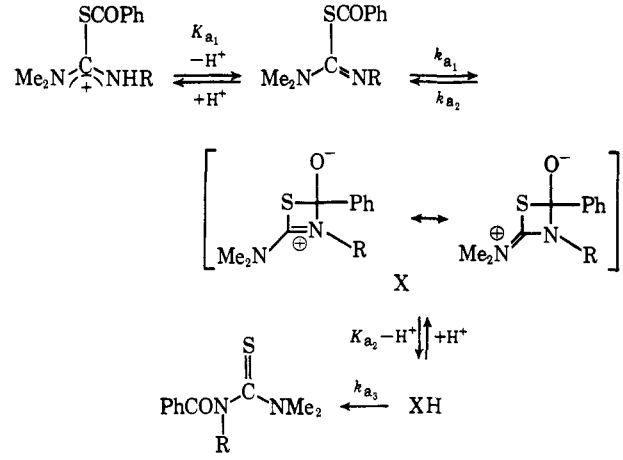
by Curtin and Miller[22] for the analogous rearrangement of isoimides. These workers discussed and rejected an alternative mechanism involving participation of the C–N double bond, *i.e.*, an electrocyclic type process, on two grounds, one theoretical (the difficulty of the required orbital overlap) and the other experimental (analogous rearrangements of enol esters to β-diketones (O → C acyl migration) only occur at high temperatures and even then probably by a free-radical mechanism). In the present case rearrangement is depicted as migration to the doubly bonded nitrogen atom because of the analogy with the isoimides and because the preferred nucleophilic center of amides, thioamides, ureas, thioureas, and amidines is usually the double bonded atom.[23]

The only difficulty with this simple interpretation of acyl transfer reaction (**19** and Schemes I and II) lies in the understanding of the kinetic results for the trisubstituted *S*-benzoylisothioureas **6** and **7**. Here the kinetics (Figures 1a and b, eq 2) and the product analysis (Figure 6) suggest that the pH–rate profile for the acyl transfer reaction is bell shaped; *i.e.*, unlike the other compounds, the rate falls off with increase in pH after a maximum is reached. Interpretation of the remainder of the profile for **6** and **7** *via* Schemes I and II (using eq 13–16 and $k_c = k_2K_w/k_1 + k_6K_w/K_1$ and from the product analyses $k_6/(k_2 + k_6) = 0.55$ for **6** and 0.57 for **7**) leads to the constants of Table VIII. This interpretation is made since it seems, as discussed above, that the reactions leading to benzoic acid and thiolbenzoate are quite independent of the acyl migration reactions. The remainder of this paper will be devoted to interpretation of the bell-shaped pH–rate profile for the acyl transfer reaction for these compounds. This is important since the simplicity of the kinetics and mechanism of S → N acyl transfer for the other compounds could be apparent rather than real.

The following explanations for the anomalous kinetics have been considered.

(1) The first involves a change in rate-determining step in the acyl transfer reaction. This requires the presence of an intermediate on reaction path which could be imagined, by analogy with other substitution reactions at acyl carbon, as a tetrahedral intermediate (Scheme IV). A steady-state treatment with respect

Scheme IV



to the tetrahedral intermediate (X ⇄ XH) leads to eq 24 for the observed pseudo-first-order rate constant

$$k_s = \frac{k_{a_1}K_{a_1}a_H}{a_H^2 + (K_{a_1} + k_{a_2}K_{a_2}/K_{a_3})a_H + k_{a_2}K_{a_1}K_{a_2}/k_{a_3}} \quad (24)$$

(k_s) for the overall acyl transfer.

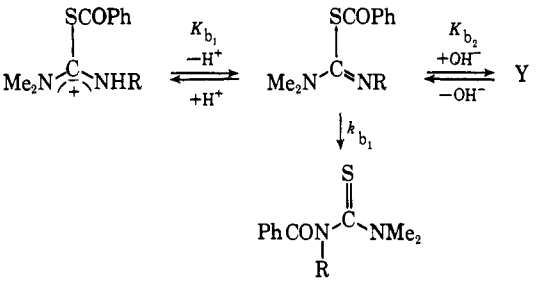
Although mathematically feasible this scheme lacks chemical plausibility. It is too difficult to understand how protonation of X could give an intermediate which could decompose to products whereas X itself could not. It also seems unlikely that the departure of such a good leaving group should require general acid catalysis, and in fact no evidence for this is observed in the intramolecular aminolyses. More tellingly the rearrangements of **6** and **7** in the region of the pH–rate profile of negative slope are not subject to buffer catalysis. Finally, it is also difficult to see why the necessity for protonation should appear with **6** and **7** alone, *i.e.*, why k_{a_3} should become rate limiting in only these cases.

(2) A second explanation requires the formation at high pH of an inert species. This scheme is shown

(22) D. Y. Curtin and L. L. Miller, *Tetrahedron Lett.*, 1869 (1965); *J. Amer. Chem. Soc.*, 89, 637 (1967).

(23) P. A. S. Smith, "The Chemistry of Open-Chain Organic Nitrogen Compounds," Vol. 1, W. A. Benjamin, New York, N. Y., 1965, p 271.

Scheme V

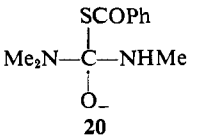


(Scheme V) to involve addition of hydroxide ion to the neutral isothiourea; the alternative, removal of a proton, is not possible. This scheme leads to eq 25 which

$$k_s = \frac{k_{b_1}K_{b_1}}{a_H{}^2 + K_{b_1}a_H + K_{b_1}K_{b_2}K_w} \qquad (25)$$

is again of the required form.

Again, however, it is necessary to link the proposed scheme with chemistry. At pH 12, **6** will be almost entirely in the form of Y. Y then must have a half-life of breakdown to any product (it could, for instance, react to give either benzoic acid or thiolbenzoic acid, the observed products from **6** at this pH) of at least 10 sec. It is difficult to propose a reasonable structure for Y along these lines. The only even remotely acceptable candidate would be the tetrahedral species **20** or one of its conjugate acid or base species. This,



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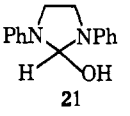
however, is extremely unlikely. The longest lived species of this type known in aqueous solution seems to be **21** obtained by reaction of 1,3-diphenyl-2-imidazo-



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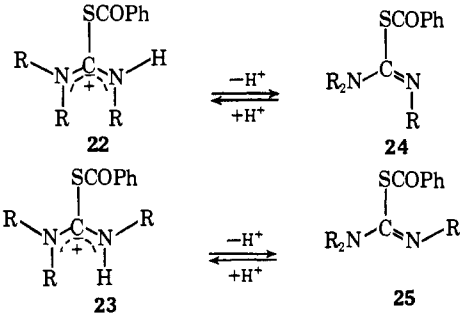
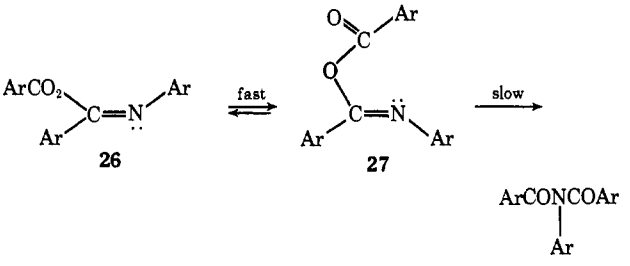
linium chloride with hydroxide ion[24] which has a lifetime of the order of milliseconds. The suggestion that **20**, where a much better leaving group (PhCOS–) is available, might have a much longer half-life seems quite unreasonable. Certainly no spectral evidence suggested the conversion of **6** or **7** into another species at high pH. Spectra of **6** (and of **4**) were close enough to identical at pH's 3 and 12 as far as could be judged from stop-flow measurements. There was no evidence either for addition of hydroxide ion to the *S*-phenylisothiourea **13** (where a poorer leaving group is present) to yield a stable species. Hence the rationale of Scheme V, like that of IV, seems chemically unreasonable in the form proposed.

(3) Any explanation for the anomaly must indicate why it is only seen with **6** and **7**. Approaches such as 1 and 2 above run into difficulties here. It is useful then to consider what structural features of **6** and **7** are exceptional in the series of compounds available. Merely the presence of a trisubstituted nitrogen atom is insufficient to yield the anomalous behavior since **5** does not exhibit it. Compounds **6** and **7** are fully substituted isothioureas, but this too is an insufficient condition because so too is **9** which does not behave abnormally; nor does **8** as far as the pH dependence of the acyl transfer reaction is concerned.

It is necessary at this stage to consider the structure of these compounds more fully and in particular to assess the possibility of the presence of geometrical isomers. A protonated trisubstituted isothiourea such as **6** or **7** can theoretically exist in two isomeric forms **22** and **23**, and these, on loss of a proton, can yield



two distinct neutral isothioureas **24** and **25**, respectively. In only one of these, **24**, can the lone pair of the imino nitrogen react with the acyl group and lead to the *N*-acylthiourea. It is clear that the possibility of unreactive forms of the neutral isothioureas in solution could lead to greater complexity than indicated by Scheme I, particularly if the rates of interconversion of the two forms by rotation about C=N bonds (in the neutral or protonated species) or by inversion at nitrogen (in the neutral form) were slower than or comparable with the rates of acyl transfer. Curtin and Miller[22] suggest that their isoimides exist preferentially in the trans form **26** and that reaction occurs



via the cis form **27** which is formed in a fast preequilibrium.

Clear evidence for hindered rotation about the C–N bonds in the *S*-benzoylisothiouronium cations **5**, **6**, and **7** is available from their proton magnetic resonance spectra (Table I) where nonequivalence of the dimethylamino methyl group is indicated. This suggests that distinct geometrical isomers such as **22** and **23**, which are not rapidly interconvertible *via* rotation, could exist in solutions of **6** and **7**. Hindered rotation has previously been observed in analogous compounds, *e.g.*, amidinium,[25,26] guanidinium,[27,28] and *S*-arylisothiouronium[28] cations and in various other mono- and diprotonated carbonic acid derivatives.[29,30] Given the

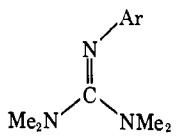
(24) D. R. Robinson, *J. Amer. Chem. Soc.*, 92, 3138 (1970).

(25) G. S. Hammond and R. C. Neuman, *J. Phys. Chem.*, 67, 1655, 1659 (1963).
(26) J. Ranft and S. Dähne, *Helv. Chim. Acta*, 57, 1160 (1964).
(27) H. Kessler and D. Leibfritz, *Tetrahedron*, 25, 5127 (1969).
(28) H. Kessler and D. Leibfritz, *Tetrahedron Lett.*, 427 (1969).
(29) G. A. Olah and A. M. White, *J. Amer. Chem. Soc.*, 90, 6087 (1968).
(30) G. A. Olah, A. M. White, and D. H. O'Brien, *Chem. Rev.*, 70, 561 (1970).

presence of hindered C–N rotation in the *S*-benzoylisothiouronium cations, it is useful to consider more fully the modes of interconversion available between **24** and **25**.

The free base forms **24** and **25** can be compared with imines where syn–anti isomers are well known and their interconversion often slow. This topic has been reviewed recently by Kessler[31] who favors inversion at nitrogen rather than rotation (torsion) about a C=N bond as the mechanism for imine isomerization. Raban and Carlson[32] have also discussed this matter recently. They suggest the existence of a continuum of transition states for imine isomerization between the extremes of pure inversion and pure rotation; the proximity of any given transition state to the extremes would depend on the structure of the imine involved. Attachment of a heteroatom bearing a lone pair of electrons α to the carbon atom of an imine function is known to reduce the barrier to isomerization.[33] This is also seen in (thio) amides where the addition of a heteroatom α to the carbonyl group as in (thio) carbamates or (thio) ureas[31,34] increases the rate of rotation about the C–N bond. Reduction of the C–N bond order by the additional resonance available ($X-C{=}N \leftrightarrow X^{+}{=}C-N^{-}$) is supposedly responsible for this effect. Although it has been argued[35] that this heteroatom effect is still consistent with an inversion mechanism, support for a rotation mechanism is strong for these cases.[33,36] Raban[37] has made semiempirical CNDO/2 calculations with simple imine systems which suggest that an α heteroatom does markedly reduce the barrier to rotation and, if anything, increase slightly the barrier to inversion. Isomerization of the free base *S*-acylisothioureas could apparently then proceed either by an inversion or rotation path or by one intermediate between them.

Kessler and Leibfritz[27] have examined a series of *N*-arylguanidines (**28**) and the corresponding *N*-aryl-



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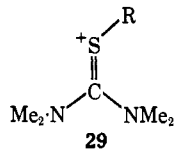
guanidinium salts. The rate of isomerization (strictly topomerization[31] since the isomers are degenerate) about the C=N bond in the conjugate acid of the *N*-phenyl compound, which must proceed by rotation, was only slightly smaller than the rate of isomerization (by inversion, these workers suggest) of the free base (although this difference increased markedly with orthoalkyl substitution on the phenyl ring). On the other hand Bauer, *et al.*,[38] have concluded from their studies of *N*-methoxyguanidines that isomerization is faster in the cationic species.

The point of this discussion has been to lead to the suggestion that, *a priori*, it is not possible to predict the relative rates of the various modes of isomerization available to the *S*-benzoylisothiourea species **22**–**25**.

Kessler and Leibfritz[28] have also studied the isomerization of isothiouronium salts of the type **29**. They



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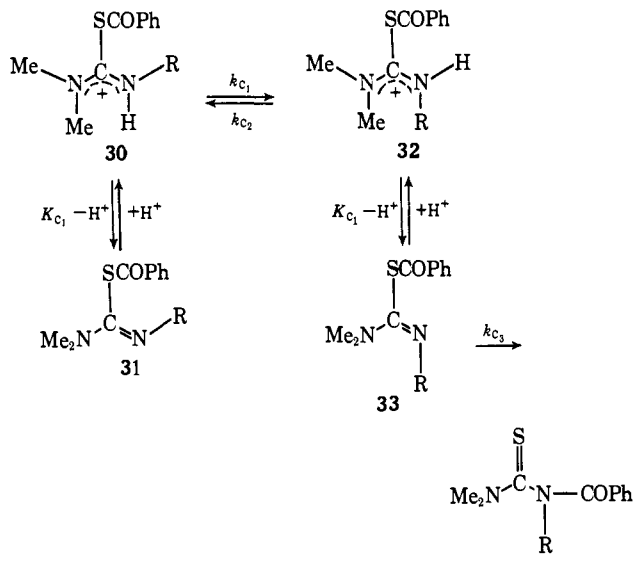
have detected hindered rotation about the C–S and C–N bonds. In the *S*-benzoylisothiouronium cations **3**–**10** a rather smaller C–S bond order would be expected than where R is alkyl or aryl since this would reduce the positive charge unfavorably placed α to the carbonyl group. There is, in fact, some evidence that this is so. In acid solution the dimethylamino methyl groups of **6** are nonequivalent (Table I), whereas those of **13** are equivalent. This suggests less double bond character in the C–N bonds of **13** than in those of **6** and thus presumably less C–S double bond character in **6** than in **13**. At all events, however, in the reactive (acyl transfer) free base form of the *S*-benzoylisothioureas, little C–S double bond character would be anticipated.

On the basis of the above discussion Scheme VI is presented to explain the kinetics of the acyl transfer reaction of **6** and **7**. Significant features of this scheme are the following.

Scheme VI



31–**33**a, R = Me
31–**33**b, R = *tert*-Bu

(a) The predominant species in acid and alkaline solution are **30** and **31**, respectively. This is reasonable because of the intense steric interaction of the 1,3 methyl groups trans to sulfur in **32** and **33**, particularly in the (presumed) planar cation **32**. This type of interaction has been suggested to account for the anomalous properties of 1,1,3,3-tetramethylurea and thiourea.[39]

(31) H. Kessler, *Angew. Chem., Int. Ed. Engl.*, 9, 219 (1970).
(32) M. Raban and E. Carlson, *J. Amer. Chem. Soc.*, 93, 685 (1971).
(33) N. P. Marullo and E. H. Wagener, *ibid.*, 88, 5034 (1966).
(34) W. E. Stewart and T. H. Siddall, III, *Chem. Rev.*, 70, 517 (1970).
(35) F. Vogtle, A. Mannschreck, and H. A. Staab, *Justus Leibig Ann. Chem.*, 708, 51 (1967).
(36) N. P. Marullo and E. H. Wagener, *Tetrahedron Lett.*, 2555 (1969).
(37) M. Raban, *Chem. Commun.*, 1415 (1970).
(38) V. J. Bauer, W. Fulmer, G. O. Morton, and S. R. Safir, *J. Amer. Chem. Soc.*, 90, 6846 (1968).
(39) M. J. Jansen, *Recl. Trav. Chim. Pays-Bas.*, 79, 454, 464 (1960).

(b) Isomerization by rotation in the cations is fast compared with isomerization by rotation or inversion in the free base species. Thus, the acyl transfer reaction, which must go *via* **33**, requires the presence of acid to enable isomerization of the predominant **31** form to **33** to occur by way of the protonated species. It is this requirement for acid which leads to the observed rate decrease (Figures 1a and b) at high pH where isomerization is rate determining.

Treatment of **32** and **33** as steady-state intermediates leads to eq 26 for the observed pseudo-first-order rate

$$k_s = \frac{a_H k_{c_1} k_{c_3} K_{c_2}/k_{c_2}}{a_H{}^2 + (K_{c_1} + k_{c_3}K_{c_2}/k_{c_2})a_H + k_{c_3}K_{c_1}K_{c_2}/k_{c_2}} \quad (26)$$

constant for acyl transfer. Comparison with the empirical eq 2 leads to the following equations

$$k_a K_a = k_{c_1} k_{c_3} K_{c_2}/k_{c_2} \quad (27)$$

$$K_a = K_{c_1} + k_{c_3} K_{c_2}/k_{c_2} \quad (28)$$

$$K_a K_b = k_{c_3} K_{c_1} K_{c_2}/k_{c_2} \quad (29)$$

These equations lead, using the constants of Table IV, to the following alternative (quadratic) solutions

	A	B
pK_{c_1} =	8.73	9.18
$k_{c_3}K_{c_2}/k_{c_2}$ =	6.45×10^{-10}	1.86×10^{-9}
k_{c_1} =	20	7

Of these A is preferred because of the glycinolysis results. The empirical equation here (10) indicates that the predominant reaction is attack of glycine on the protonated *S*-benzoylisothiourea. An apparent pK_a (pK_x) of 8.65 for the protonated isothiourea was required. If it is assumed, as seems likely, that nucleophiles would react at the ester functions of **30** and **32** at not greatly disparate rates, then such reactions must go largely *via* **30** and thus the apparent pK_a for the glycinolysis should be very close to pK_{c_1}. The agreement (A) is satisfactory.

The value obtained for the rate of isomerization of **30** to **32** (k_{c_1}) of 20 sec^{-1} ($\Delta G^{\ddagger}$ = 14.6 kcal/mol) is not an unreasonable one for such a system. If $K_{c_1} \simeq K_{c_2}$, then $k_{c_2} \simeq 0.4\ k_{c_3}$ (solution A), and if **30** is the favored species, then $k_{c_2} \gg k_{c_1}$; hence, $k_{c_3} \gg 20$ sec^{-1}.

Similar solutions can be obtained for **7**: pK_{c_1} = 8.63, $k_{c_3}K_c/k_{c_2} = 1.70 \times 10^{-10}$, and k_{c_1} = 50 sec^{-1}.

Now the results for **8** can be considered. Although both **6** and **8** are 1,1,3-trialkyl-substituted isothioureas the pH dependence for the acyl transfer reaction for **8** is that of the earlier considered type (Scheme I) rather than as for **6**. In terms of the mechanism proposed for **6** (Scheme VI), one must conclude that isomerization is fast in the case of **8**, *i.e.*, the barrier to rotation about the C–NH bond is much faster in **30b** than in **30a**. This is not entirely unreasonable. Rotational barriers in amides are known to fall when bulky substituents are present, either on the acyl carbon or on the nitrogen atom,[34] because of destabilization of the planar ground state with respect to the transition state for rotation. Decreased rigidity of the **8** system is perhaps indicated by the apparent equivalence of the dimethylamino methyl groups in the nuclear magnetic resonance spectrum of **8** (Table I) although simple coincidence of absorptions is at least as likely an explanation of this in view of the small chemical shift differences between the dimethylamino methyl groups of **6** and **7**. Rapid rotation almost certainly is responsible for the total equivalence of methyl groups in **10** where in the planar state severe steric interactions are impossible to avoid. This is analogous to the case of tetramethylthiourea[39] and has been observed in a variety of other tetraalkylurea and isourea systems.[27,28,38]

Scheme VI can then be modified by treating **30b** → **32b** as a fast preequilibrium (put $k_{c_1}/k_{c_2} = K_{c_3}$) and then eq 30 can be derived which is of the form of eq 1. The

$$k_s = \frac{k_{c_3}K_{c_3}K_{c_2}}{a_H(1 + K_{c_3}) + (K_{c_1} + K_{c_2}K_{c_3})} \quad (30)$$

empirical constant, k_{s_1} (see Results), for the acyl transfer reaction of **8** is thus given by eq 31 and the empirical

$$k_{s_1} = k_{c_3}K_{c_3}K_{c_2}/(K_{c_1} + K_{c_2}K_{c_3}) \quad (31)$$

dissociation constant K_a by eq 32. The scheme re-

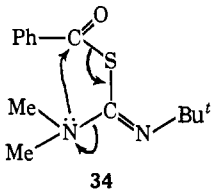
$$K_a = (K_{c_1} + K_{c_2}K_{c_2})/(1 + K_{c_3}) \quad (32)$$

quires $K_{c_3} \ll 1$ and $K_{c_1} \gg K_{c_2}K_{c_3}$ so that (from eq 31) $k_{c_3} \gg k_{s_1}$, *i.e.*, $\gg$7.38 sec^{-1}, and (from eq 32) $pK_{c_1} \simeq pK_a$ = 9.57.

An alternate means of the proposed rapid isomerization in compound **8** would be direct interconversion of the free base forms **31b** and **33b** by an inversion mechanism; bulky substituents decrease barriers to inversion as well as rotation.

The bulk of the *tert*-butyl group is thus considered to be the reason for the difference in pH dependence of the acyl transfer reaction between compounds **6** and **8**. The effects of this bulk are also seen elsewhere. The ultraviolet spectra of thioureas typically show strong absorption in the 230–240-nm range due to a π–π^* transition and a much weaker absorption band at higher wavelength from a (forbidden) n → π^* transition. Jansen[39] has argued that the position and intensity of the n → π^* bond can be correlated with the closeness to planarity of the thiourea. The greater the steric interactions between the nitrogen substituents in the planar conformation, the further from planarity will be the ground-state conformation and the more favorable will be the n → π^* transition. The classic example of this, mentioned previously in the discussion here, is 1,1,3,3-tetramethylthiourea. X-Ray crystallographic studies of this compound show it in fact to be nonplanar in the ground state (crystalline).[40,41] On the basis of the ultraviolet spectra, similar claims for distortions from planarity have been made for some *N*-acetylthioureas[42] and *N*-phenylthioureas.[43] The positions of the n → π^* transition in a series of 1,1-dimethyl-3-alkylthioureas are given in Table II, with that of 1,1,3,3,-tetramethylthiourea for comparison. The wavelength of the absorption increases with the bulk of the alkyl group, with the change being greatest by far between the 3-isopropyl and 3-*tert*-butyl derivatives. This can be interpreted as indicating the increasing steric interactions in these thioureas as the size of the

(40) Z. V. Zvonkova, L. I. Astakhova, and V. P. Glushkova, *Kristallografiya*, **5**, 547 (1960); *Chem.Abstr.*, **56**, 12399 (1962).
(41) It is thus unlikely that the cations **32a** and **32b** are completely planar.
(42) J. Sandstrom, *Acta Chem. Scand.*, **17**, 678 (1963).
(43) G. Isaksson and J. Sandstron, *ibid.*, **24**, 2565 (1970).



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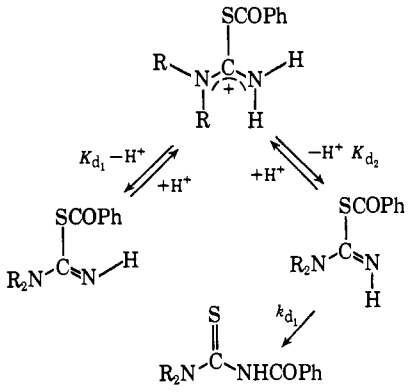
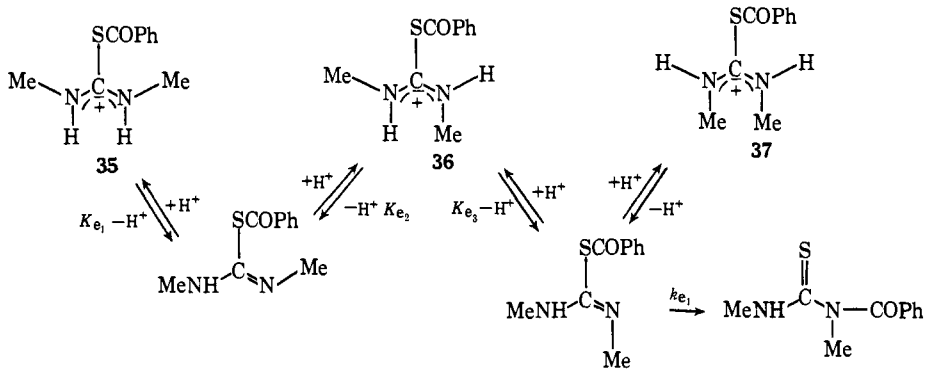
Scheme VII



Scheme VIII



alkyl group increases; these interactions then are particularly severe with the *tert*-butyl compound.

The strong influence of the *tert*-butyl group on the properties of **8** is also seen in the other reactions of this compound. The value of k_6 for **8**, interpreted as that for **6** *via* Scheme II, is 2.58×10^5 sec^{-1} M^{-1} which is 27 times that for **7** (Table VIII) and 50 times that for **6**. This suggests a steric acceleration for this reaction; possibly the spontaneous decomposition mechanism **18** is involved here.

More striking still is the reaction yielding *N*,*N*-dimethylbenzamide and *tert*-butyl isothiocyanate (the free base form of **8** breaks down to these products with a rate constant, k_{s_2}, of 8.0 sec^{-1}). This reaction is not seen at all in **6**, **7**, or **9** or in the lesser substituted compounds. The ground state of **8** must be so sterically crowded that even usually much less favorable reactions will occur if they lead to reduced strain. In this particular case, migration of the *S*-benzoyl group to the tertiary nitrogen has been forced (**34**). The reacting species here can, of course, be the favored isomer **31b**. Steric acceleration of unimolecular decompositions have previously been observed in *O*-alkylisoureas.[15]

Finally, it is useful to indicate that the intramolecular acyl transfer reactions of **3**, **4**, and **5** are probably more complex than Schemes I and II indicate, again because of possibilities of isomerization. For **3** and **5**, Scheme VII and eq 33 can be applied, and, for **4**, Scheme VIII and eq 34 can be applied.

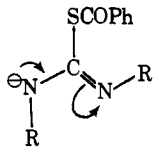
$$k_s = \frac{k_{d_1}K_{d_2}}{a_H + (K_{d_1} + K_{d_2})} \quad (33)$$

$$k_s = \frac{k_{e_1}K_{e_3}}{a_H(1 + K_{e_2}/K_{e_1}) + (K_{e_2} + K_{e_3})} \quad (34)$$

It can be safely assumed on the basis of previous discussion that **37** is by far the least stable of the protonated species of **4**, and eq 34 has been derived assuming it to occur in solution to a negligible extent with respect to **35** and **36**. The nuclear magnetic resonance spectrum of **4** (Table I) shows the methyl groups as a sharp singlet. Unless the chemical shifts of the methyl groups in **36** are, by coincidence, identical, which is certainly not impossible, then **35** must be the predominant species in acid solution (assuming rotation to be slow; pmr spectra of **4** at −20 and −50° in 30% H_2SO_4 gave no indication of any splitting of the methyl groups). Hammond and Neuman[25] have carried out pmr studies on the 1,3-dimethylacetamidinium cation. Here two methyl resonances are observed ($\Delta\nu$ = 5–10 Hz) which led them to conclude that rotation was hindered and that the asymmetric species analogous to **36** was the preferred one. It is not impossible, however, that **35** is the stablest cation of **4** since inspection of models suggests that the *C*-methyl group of acetamidine interacts sterically more strongly with the substituents on nitrogen than the bulkier, but more distantly so, PhCOS group.

A conclusion now does seem possible on the original problem with the S → N acyl migration, *viz.* the difference in kinetic behavior between **6** and **7** and the other *S*-benzoylisothioureas examined. The essential difference seems to be that all the compounds studied except **6**, **7**, and **8** can assume the reactive form of the isothiourea free base without the necessity of rotation or inversion about a carbon to nitrogen double or partially double bond. With the cyclic compounds **9**, **14**, **15**, and **1** the problem of isomerization does not exist, and with the acyclic compounds other than **6**, **7**, and **8** isomerization is possible by way of a series of rapid acid–base equilibria as in Schemes VII and VIII. Another possibility here, **38**, for suitably substituted derivatives is an isomerization at high pH *via* anions (*cf.* **20**). It is only in the acyclic trisubstituted compounds such as **6**, **7**, and **8** that these mechanisms are not possible. In such compounds if isomerization is necessary it must take place *via* rotation or inversion

and in cases where these processes are slow as in **6** and **7**, then the isomerization can be rate determining in the overall S → N acyl transfer reaction.



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This study has explored in depth the reactions in aqueous solution of a series of simple *S*-benzoylisothioureas. Three modes of reaction have been observed, hydrolysis of the thiol ester function yielding benzoic acid and the parent thioureas, displacement of thiolbenzoate, and a facile intramolecular 1,3 S → N acyl transfer reaction yielding *N*-benzoylthioureas. The relative extent of these reactions occurring at any given pH is very strongly dependent on the structure of the compound involved. Even apparently very small structural changes such as addition of or changes in an *N*-alkyl substituent often lead to great changes in the rates, relative and absolute, of the reactions observed. The reasons for this great structural dependence have been examined in detail. The conclusions have generally been more semiquantitative than quantitative because of the complexity of the systems involved, appreciation of which emerged slowly as the work progressed. For instance, very little attempt has been made to compare rate constants for the various compounds because of the large number of unknown quantities involved in defining the geometric isomer distributions and isomer interconversion rates which appear critical to the interpretation of the reactions of the acyclic species. No attempt has been made to examine electronic effects either, *e.g.*, use of electron-withdrawing substituents, etc., although great variation in the types and rates of reactions would be expected from such changes. Prediction of such variation is certainly possible on the basis of the data from this study.

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Intramolecular General Base and Intermolecular Nucleophilic Catalysis of Carbonate Ester Hydrolysis. Hydrolysis of Ethyl 2-Hydroxy-5-nitrophenyl Carbonate

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Abstract: The rates of hydrolysis of ethyl 2-hydroxy-5-nitrophenyl carbonate have been determined in H_2O at 30°. Two pH-independent regions are present in the pH–rate constant profile. The rate constant for the pH-independent reaction at higher pH is 50 times greater than that for reaction at lower pH. The former reaction is most likely a phenoxide ion catalyzed attack of H_2O at the ester carbonyl rather than a hydroxide ion catalyzed hydrolysis of the un-ionized ester. With azide and imidazole the rate constant for reaction with the ionized ester is considerably less than that for reaction with the un-ionized species, but the rate constants in the latter case are nearly the same as with ethyl 2-methoxy-5-nitrophenyl carbonate and ethyl 3-nitrophenyl carbonate. Thus a neighboring phenoxide ion greatly retards reaction with these nucleophiles. Hydroxide ion catalysis is also greatly reduced. However, morpholine catalysis displays little sensitivity to the nature of the leaving group in this series. Solvent isotope effects ($k_B^{H_2O}/k_B^{D_2O}$) close to unity were found for morpholine and pyrrolidine catalysis of the hydrolysis of the ionized species, and for imidazole-catalyzed hydrolysis of both ionized and un-ionized species. Nucleophilic catalysis is thereby indicated in all cases. *N*-Methylimidazole is a good catalyst for hydrolysis of the un-ionized compound, but catalysis of the hydrolysis of the ionized ester could not be detected. A likely possibility in hydrolysis of the ionized species is expulsion of the 4-nitrocatechol monoanion *via* a tetrahedral intermediate.

The presence of a neighboring hydroxyl group markedly accelerates the alkaline hydrolysis or methanolysis of aliphatic esters.[2,3] Esters possessing a neighboring phenolic hydroxyl group also hydrolyze with enhanced rates.[4-9] The most likely mechanism of this reaction has been considered to be a phenoxide ion general base catalyzed attack of water at the carbonyl of the ester.[4,5]

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