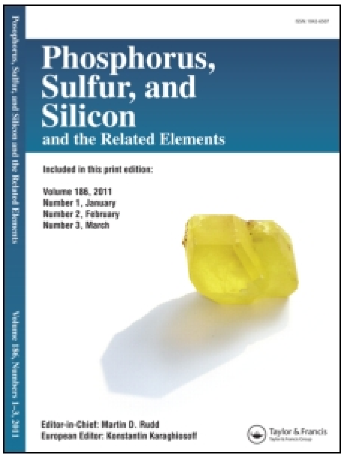

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

THE MECHANISM OF THE REACTION BETWEEN KETOXIMES AND PHENYL ISOTHIOCYANATE

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To cite this Article Hudson, R. F. and Dj-forudian, H.(1978) 'THE MECHANISM OF THE REACTION BETWEEN KETOXIMES AND PHENYL ISOTHIOCYANATE', Phosphorus, Sulfur, and Silicon and the Related Elements, 4: 1, 9 — 14

To link to this Article: DOI: 10.1080/03086647808079956

URL: http://dx.doi.org/10.1080/03086647808079956

Phosphorus and Sulfur
1978, Vol. 4, pp. 9–14

THE MECHANISM OF THE REACTION BETWEEN KETOXIMES AND PHENYL ISOTHIOCYANATE

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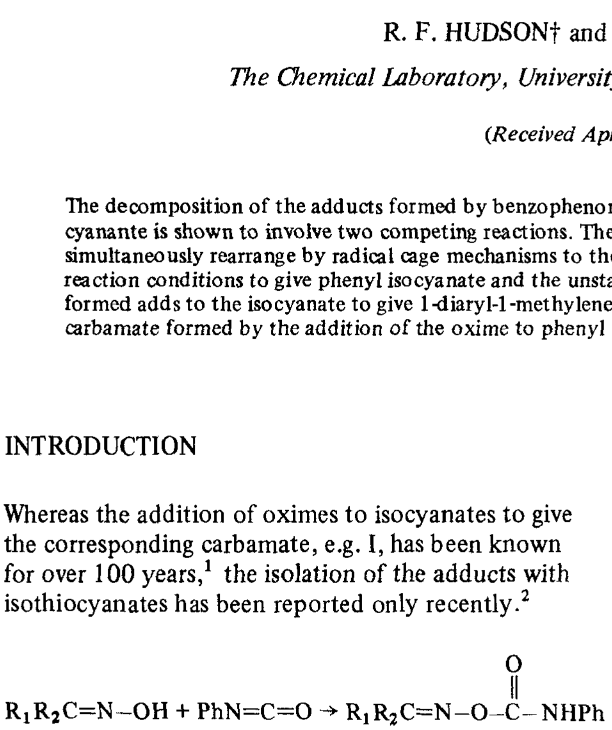
(*Received April 27, 1977*)

The decomposition of the adducts formed by benzophenone oxime and fluorenone 9-oxime with phenyl isothiocyanante is shown to involve two competing reactions. The adducts either dissociate to oxime and isothiocyanate or simultaneously rearrange by radical cage mechanisms to the thiolo-isomer. This latter product decomposes under the reaction conditions to give phenyl isocyanate and the unstable thioöxime which rapidly eliminates sulphur. The imine formed adds to the isocyanate to give 1-diaryl-1-methylene-3-phenyl urea, together with O-diarylimino-N-phenyl carbamate formed by the addition of the oxime to phenyl isocyanate.

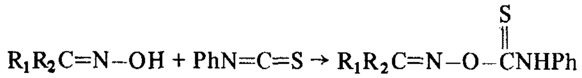
INTRODUCTION

Whereas the addition of oximes to isocyanates to give the corresponding carbamate, e.g. I, has been known for over 100 years,[1] the isolation of the adducts with isothiocyanates has been reported only recently.[2]



$$R_1R_2C{=}N{-}OH + PhN{=}C{=}O \rightarrow R_1R_2C{=}N{-}O{-}\overset{\overset{O}{\|}}{C}{-}NHPh$$

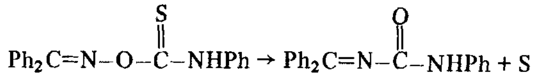
I



$$R_1R_2C{=}N{-}OH + PhN{=}C{=}S \rightarrow R_1R_2C{=}N{-}O{-}\overset{\overset{S}{\|}}{C}NHPh$$

These can be isolated by the reaction of the oxime salt with isothiocyanate followed by neutralization with ice-cold hydrochloric acid. These adducts are unstable and decompose in a complex manner, which is pertinent to the reaction between oximes and isothiocyanates.

In neutral solution at room temperature no reaction between oximes and isothiocyanates is observed, but on prolonged boiling in an inert solvent decomposition to sulphur and the carbamate I occurs.[3] However, we have shown[2] that the urea III is a major product of the decomposition of II with the carbamate, I, and other products formed in varying yields.



$$Ph_2C{=}N{-}O{-}\overset{\overset{S}{\|}}{C}{-}NHPh \rightarrow Ph_2C{=}N{-}\overset{\overset{O}{\|}}{C}{-}NHPh + S$$

II III

In some reactions between oximes and isothiocyanates, particularly when aldoximes are used, N-N-disubstituted ureas and thioureas are produced.[4] The removal of sulphur was at one time attributed to auto-oxidation, but this is now known not to be the case.

It is of interest, therefore, to investigate the mechanism of decomposition of II in solution, as this adduct is probably of fundamental importance in the oxime-isothiocyanate reaction.

RESULTS AND DISCUSSION

The reaction in chloroform (or in carbon tetrachloride) can be followed conveniently by ir spectroscopy over a period of 24 hr at 37°, when complex changes in the spectrum are observed (Figure 1). The rapid formation of isothiocyanate (ir peak at 2080 cm^{-1}) accompanies the decrease in the intensity of the peak at 1100 cm^{-1} due to the C=S group of II. Simultaneously, a strong peak at 1665 cm^{-1} corresponding to the carbonyl peak of IV is observed. At the same time, the intensity of the N–H band at 3300 cm^{-1} rapidly decreases and a new peak at 3360 cm^{-1} with a smaller one at 3400 cm^{-1} appear. These observations show that the adduct II decomposes initially by two simultaneous

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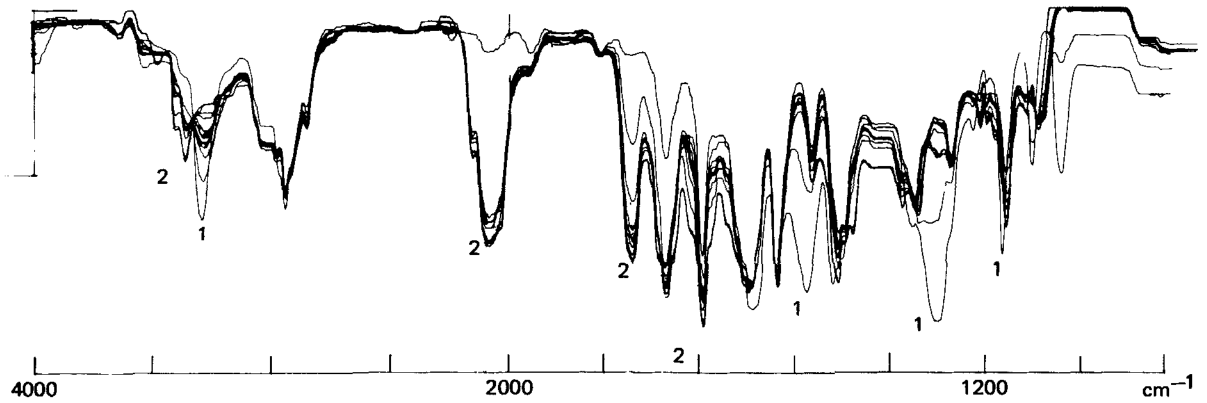
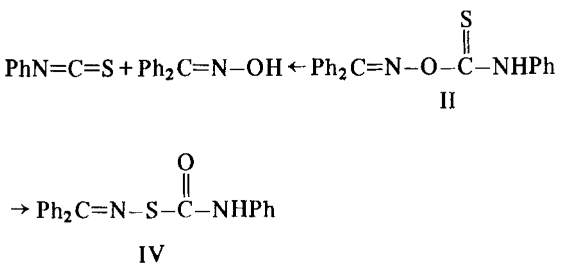


FIGURE 1 Time dependent ir spectrum of $Ph_2C{:}NOC(S)NHPh$ in chloroform at 37°. The initial spectrum is represented by (1) and the final spectrum (16 h) by (2).

reactions, the one involving dissociation, the other rearrangement,



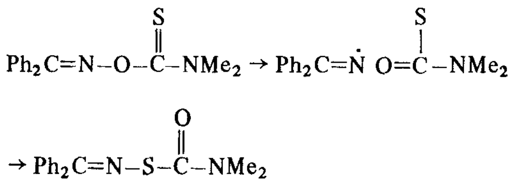
$$\mathrm{PhN{=}C{=}S + Ph_2C{=}N{-}OH \leftarrow Ph_2C{=}N{-}O{-}\overset{\overset{S}{\|}}{C}{-}NHPh}$$

II

$$\rightarrow \mathrm{Ph_2C{=}N{-}S{-}\overset{\overset{O}{\|}}{C}{-}NHPh}$$

IV

This rearrangement is similar to the rearrangement of O-methylenamino thiocarbamates,[5] which proceeds by a radical cage mechanism to give the isomer,



$$\mathrm{Ph_2C{=}N{-}O{-}\overset{\overset{S}{\|}}{C}{-}NMe_2 \rightarrow Ph_2C{=}\dot{N}\ \ O{=}\overset{\overset{S}{|}}{C}{-}NMe_2}$$

$$\rightarrow \mathrm{Ph_2C{=}N{-}S{-}\overset{\overset{O}{\|}}{C}{-}NMe_2}$$

In the present complex reaction, strong esr signals corresponding to both iminyl and iminoxy radicals are found to persist in the initial stages of the reaction. Moreover at higher temperatures (65°) CIDNP signals are observed in the ^{13}Cnmr spectrum showing enhanced absorption of the C_1 atom of the phenyl ring of IV and emission due to the carbon atom of the C=N group (Figure 2). No other enhancements were observed although the aromatic region is complicated by the presence of two kinds of phenyl group, the one attached to carbon and the other to nitrogen. With the known g value of 2.003 for the diphenyl iminyl radical[6] and assuming a value of >2.01 for the PhNHCOS Kaptein's rules[8] for the net polarization Γ_{ne} one can be applied.

$$\Gamma_{ne} = \mu \epsilon \Delta g A_i$$

For a singlet precursor μ is negative, and the coupling constants for C=N and C-1 are negative and positive respectively.[7] The following sign equations lead to a positive value for ϵ, as required for cage recombination of a geminate radical pair.

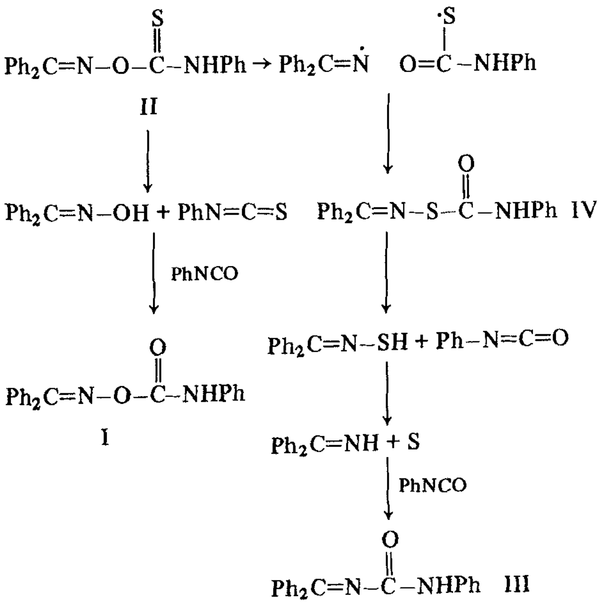
C=N: sign product ≡ – + – – ≡ –(E)
C-1: sign product ≡ – + –+ ≡ +(A)

Similar results were obtained for the rearrangement of the acetophenone oxime derivative (Figure 3). Here a weak absorption corresponding to the methyl group is observed, and several additional weak polarizations could not be assigned with certainty.

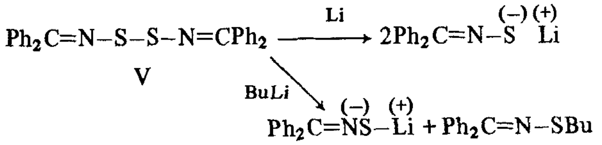
We conclude, therefore, that the thiono-thiolo rearrangement of the adduct II occurs, at least in part, by a radical cage mechanism, and that the final products isolated are formed in subsequent polar reactions, or alternatively in reactions involving radical and neutral unpolarized molecules.

Further examination of the change in the ir spectrum with time (Figure 1) shows that a peak centred at 1740 cm^{-1} corresponding to O-diphenylimino-N-phenyl carbamate, I, and a second peak at 1668 cm^{-1} corresponding to 1-phenyl-1-methylene-3-phenylurea, III, continue to grow throughout the reaction. It is clear that the latter increases more rapidly than the former as the reaction proceeds, and the peak at 1665 cm^{-1} due to IV decreases. A small peak at 2240 cm^{-1} due to phenyl isocyanate grows and decays as the reaction proceeds. Some decomposition to carbonyl sulphide is detected by the appearance of a shoulder at 2025 cm^{-1}.

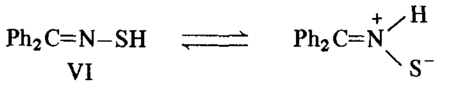
These observations lead to the following scheme for the overall reaction.

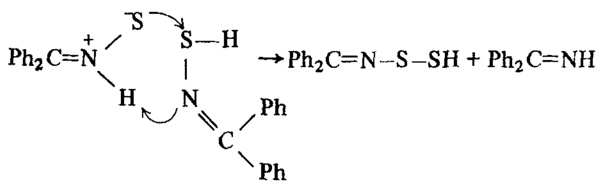


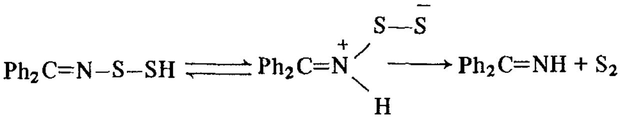
According to this scheme, the rearranged product undergoes an elimination reaction to isocyanate and thioöxime. Thioöximes are unknown in the free state although their salts have been prepared recently as transients,[9] by the action of lithium or butyl lithium on the disulphide, V.



Neutralization at low temperatures gives the neutral thioöxime VI which rapidly decomposes with the deposition of sulphur. We suggest that this is an important reaction in the present context, and suggest the following mechanism,







Imine is known to react exothermically with isocyanate to give 1-diphenyl-1-methylene 3-phenyl-urea.[10]

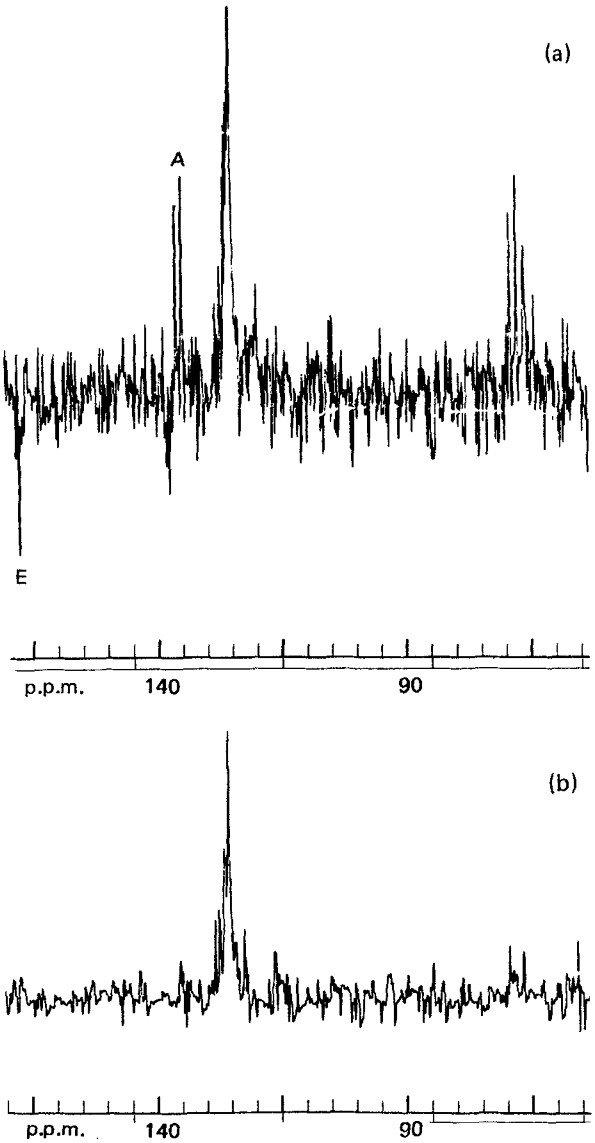


FIGURE 2(a) ^{13}Carbon nmr spectrum of Ph_2C:NSC(O)NHPh (10% w/v in $CDCl_3$) at 65° after 1 min 15 sec. Emission (*E*) for the imino carbon atom at 116 ppm and enhanced absorption (*A*) for the C_1 carbon atom of the benzene ring at 137 ppm.
FIGURE 2(b) ^{13}Carbon nmr spectrum of Ph_2C:NSC(O)NHPh (10% w/v in $CDCl_3$) at 65° after 3 min 5 sec.

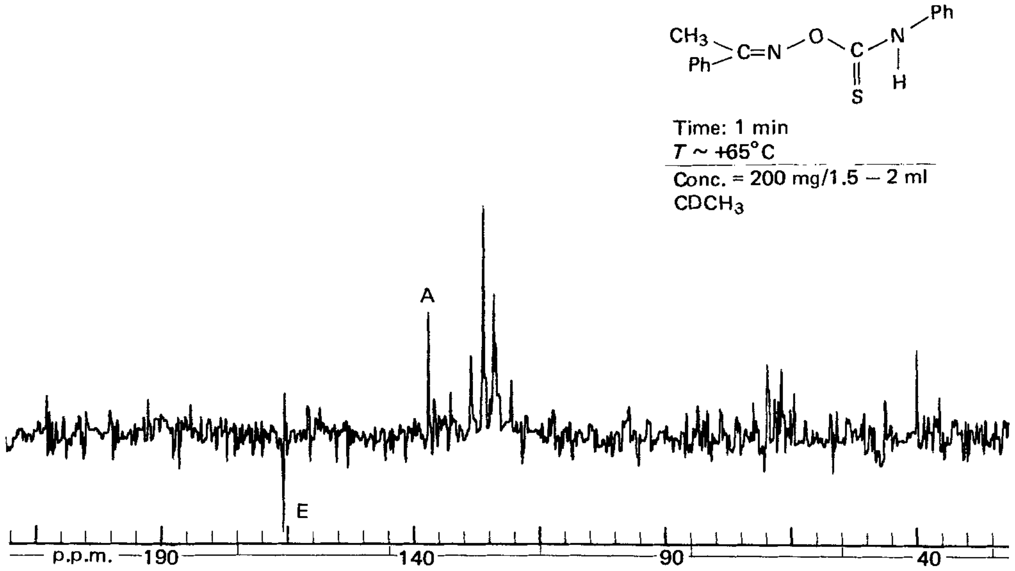


FIGURE 3 ^{13}Carbon nmr spectrum of Ph(Me)C:NSC(O)NHPh (10% in $CDCl_3$) at 65° after 1 min. Emission (*E*) for the imino carbon atom at 164 ppm and enhanced absorption (*A*) for the C_1 atom of the benzene ring at 139 ppm.

In the initial stages of the reaction the isocyanate reacts preferentially with oxime generated rapidly by the back reaction. This is also a rapid process, and we find that the addition is essentially complete within 1-2 min at room temperature when 0.1N solutions in chloroform were mixed.

The intermediate formed by the addition of di-*p*-tolylketoxime to phenyl isothiocyanate rearranges rapidly as shown by the disappearance of the ir peak at 1080 cm^{-1} (C=S) and appearance of the characteristic C=O peak at 1660 cm^{-1}. After 10 min absorption due to phenyl isocyanate (2240 cm^{-1}) was observed, but this disappears as the reaction proceeds. The rearranged product could not be isolated in the pure form as it rapidly decomposes to give 1-di-*p*-tolyl-1-methylene-3-phenylurea in 70% yield, with a minor yield of O-di-*p*-tolylimino-N-phenyl carbamate.

p-Nitrobenzophenone-α-oxime and phenyl isothiocyanate give a similar unstable adduct which decomposes in the course of purification. Again the urea derivative is the major product, but examination of the ir spectra shows the formation of carbonyl sulphide, phenyl isocyanate and phenyl isothiocyanate.

Examination of the ir spectra during the course of the reaction showed that the back reaction is much less predominant than in the case of the adducts formed

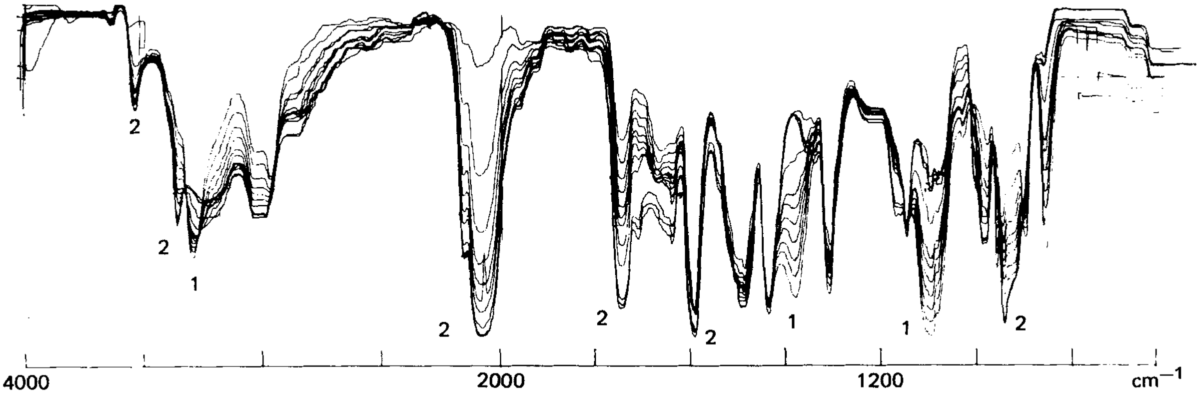
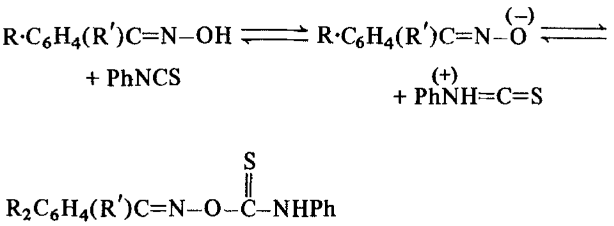


FIGURE 4 Time dependent ir spectrum of $C_{12}H_3C$:NOC(S)NHPh in chloroform at 37°. The initial spectrum represented by (1) and the final spectrum (19 h) by (2).

from benzophenone and di-*p*-tolylketoxime. This indicates that the equilibrium is favoured by an increase in acidity of the oxime, in accordance with an addition mechanism of the following kind,



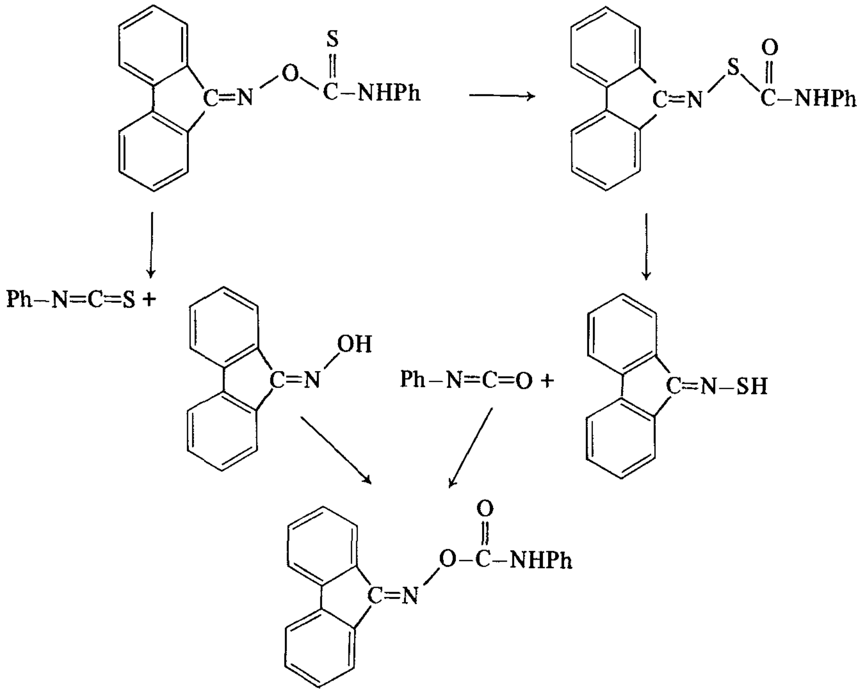
$$R{\cdot}C_6H_4(R')C{=}N{-}OH \rightleftharpoons R{\cdot}C_6H_4(R')C{=}N{-}\overset{(-)}{O} \rightleftharpoons$$

$$+\ PhNCS \qquad\qquad +\ Ph\overset{(+)}{N}H{=}C{=}S$$

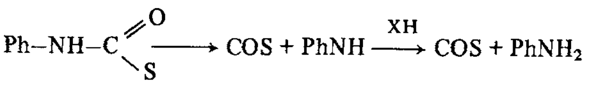
$$R_2C_6H_4(R')C{=}N{-}O{-}\overset{\overset{S}{\|}}{C}{-}NHPh$$

The adduct formed between fluorenone-9-oxime and phenyl isothiocyanate decomposes in chloroform, but both processes are significantly slower than in the rearrangement of the benzophenone oxime analogue (Figure 4). The main product in this reaction is the carbamate and not the urea derivative, which suggests that the rearrangement proceeds more slowly than the back reaction. The spectral change in the 1600-1700 cm^{-1} corresponding to the carbamate grows much more rapidly than that of the urea, which is in agreement with a slow rearrangement. Under these conditions, the isocyanate formed is rapidly removed by the oxime produced in a large excess by the disproportionation of the initial adduct.

The major reaction can therefore be represented by the following scheme.



The origin of the minor products requires some explanation. As mentioned above both iminyl and iminoxy radicals are detected by esr-spectroscopy, and these spectra must arise from radicals which have escaped from the radical cage. Fragmentation leads to carbonyl sulphide, which is observed in the ir spectra, and a reactive radical which would rapidly extract hydrogen to give aniline.



$$Ph{-}NH{-}C\genfrac{}{}{0pt}{}{\nearrow O}{\searrow S} \longrightarrow COS + PhNH \xrightarrow{XH} COS + PhNH_2$$

This then adds to isocyanate and isothiocyanate to give the substituted urea and thiourea respectively.

Although some of the steps in these complex decompositions are speculative, we feel that this work goes a long way in explaining the formation of a wide range of unexpected products in the formally simple reaction of oximes and isothiocyanates. It is highly probable that reactions of this kind also occur in reactions of other hydroxylamine derivatives with isothiocyanates and related thiocarbonyl compounds.

EXPERIMENTAL

Preparation of O-Methyleneamino Thiocarbamates[2]

These were prepared by the action of the sodium salt of the appropriate oxime on phenyl isothiocyanate in dry DMF at

−10°, followed by treatment in a large excess of ice-cold water or dilute acid. The precipitated solid was re-crystallized from benzene-petroleum ether (40–60°) mixtures, to give: O-diphenylmethyleneamino phenylthiocarbamate, II, m.p. 64–66°; O-phenylmethylmethyleneamino phenyl thiocarbamate, VII, m.p. 66° and O-fluorenyl-9-methyleneamino phenylthiocarbamate, VIII, m.p. 87–88°.

Reaction of II and VIII in Chloroform

A solution of II (0.66 g) in chloroform (10 ml) was introduced into a 25 ml flask which was immersed in a thermostat at 37°. Samples were removed at known times and the ir spectrum taken on a Perkin-Elmer 257 infrared spectrometer using 2 ml cells. The reaction was followed by the changes in absorption at the following frequencies

3360 cm^{-1}–NH group of II
3290 cm^{-1}–NH group of IV
2080 cm^{-1}–PhNCS
1735 cm^{-1}–C=O group of I
1665 cm^{-1}–C=O group of IV
1668 cm^{-1}–C=O group of III

Similar experiments were performed over a 19 hr period with the fluorenone compound (0.33 g) in 5 ml of chloroform.

Reaction of di-p-Tolylketoxime with Phenyl Isothiocyanate

The sodium salt of the ketoxime (5 g) was added to a solution of phenyl isothiocyanate (2.7 g) in DMF (60 ml) at −10°. The reaction mixture was then poured into 200 ml of an ice-water mixture, which was then acidified with dilute hydrochloric acid. The gum-like product was filtered and dissolved in benzene. The ir spectrum showed absorption at 1080 cm^{-1} (C=S), 955 cm^{-1} (>N–O) and 3280 cm^{-1} (N–H). An increasing C=O band at 1660 cm^{-1} and a band at 3290 cm^{-1} (N–H) showed that rearrangement was occurring in the solution. After 10 min a peak at 2240 cm^{-1} showed the presence of phenyl isocyanate.

The impure solid was dissolved in chloroform and the ir spectrum followed. Rearrangement continued for a period of 0.5 hr with the appearance of a strong peak at 1670 cm^{-1} corresponding to 1-di-*p*-tolyl-1-methylene-3-phenyl urea. This was obtained in 70% yield, m.p. 183–185°.
Found: C, 80.30; H, 6.86; N, 8.36. $C_{22}H_{20}N_2O$ requires C, 80.46; H, 6.14; N, 8.53%. This compound is unstable in air, rapidly hydrolysing to phenylurea. This accounts for the high analytical figure for hydrogen.

In water the rearrangement proceeds to give O-di-*p*-tolylimino-N-phenyl carbamate, m.p. 140–142° (decomp.) identified by the ir spectrum with absorption at 1735 cm^{-1} (C=O) and 3360 cm^{-1} (N–H). Found: C, 76.62; H, 5.57; N, 8.17. $C_{22}H_{20}N_2O_2$ requires C, 76.72; H, 5.82; N, 8.13%.

The Reaction of p-Nitrobenzophenone-α-oxime with Phenyl Isothiocyanate

The sodium salt of the oxime (5.2 g) was added to phenyl isothiocyanate (2.7 g) in DMF (50 ml) at −10°, and the solution stirred for 1 hr. The mixture was added to 2 l of an ice-water mixture which was then acidified. The solid was filtered, dissolved in benzene and precipitated with petroleum ether (40–60°). Rearrangement of the initial adduct, identified by the ir absorption at 1100 cm^{-1} (C=S) and 3300 cm^{-1} (N–H) occurred with the formation of carbonyl sulphide, phenyl isocyanate and 1-phenyl-1-*p*-nitrophenyl-1-methylene-3-phenyl urea, isolated as the mono-hydrate, m.p. 90–93° in 30% yield. Found: C, 65.66; H, 4.85; N, 11.37. $C_{20}H_{17}N_3O_4$ requires C, 66.11; H, 4.72; N, 11.56%.

Reaction between Benzophenone Oxime and Phenyl Isocyanate

Benzophenone oxime (0.197 g) and phenyl isocyanate (0.119 g) in chloroform (10 ml) were allowed to react at room temperature. The reaction was followed by measuring the change in intensity of the absorption at 2240 cm^{-1} (N=C=O) and at 1740 cm^{-1} (C=O). The reaction was almost complete after 1 min.

CIDNP Studies[7]

Solutions of II and of the acetophenone analogue VII (*ca.* 200 mg) in deuterochloroform (2 ml) were heated separately in the probe of a JEOL PS 100 nmr spectrometer heated to 65°. The ^{13}C spectra were taken using FT after 1 min, 2.5 min and compared with the normal spectra of the product III.

ACKNOWLEDGEMENTS

We thank Dr. K. A. F. Record for helpful discussions and Dr. D. O. Smith for taking the NMR spectra.

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