STRUCTURAL PROBLEMSPOSED BY THE REACTIONS
OF THIOCYANATE WITH MALONYL CHLORIDE

A Thesis presented to the University of Surrey in partial
fulfilment of the requirements for the degree of Doctor
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Sciences

by

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ABSTRACT

Malonyl Chloride reacts with alkyl and aryl thiocyanates yielding 2-alkyl-(or aryl) thio-7-chloro-4,5-dioxopyrano[3,4-j]-3-oxazines (I). These react stepwise with amines, undergoing replacement of the thio group and then of the chloro substituent. Next, the pyrone ring is opened and finally the oxazine ring, to yield N-substituted β-aminoglutacondiamides having an α-carboxyureido side chain. The intermediate 2-7-diamino-4,5-dioxopyrano[3,4-j]-I,3-oxazines (some of which are tautomeric) suffer oxazine ring scission with amine hydrochloride and yield substituted 4,6-diaminopyran-2-one-3-carboxyureides. The parent product (I) with amine hydrochloride retains the sulphur group and yields 4,6 dianinopyrone-3-carboxythiourethananes. However, the reactions of the parent product (I) with water and alcohol gave several quite unexpected products. From the reaction of compounds (I) with water (1 mol) at 80°C the 6-Amino-3-thioester-2 pyrones (2) were obtained. Whilst in the presence of hydrogen chloride, 4-chloro-6-N-(substituted) thiocarboxyamido 2-pyrones resulted. Boiling water (2 mols) with compounds (I) gave 4-chloro-2,6-dihydroxypyrindina, also obtained similarly from the compounds (2). 4-Chloro-2,6-dihydroxypyrindina-3-carboxylic esters arose when compounds (I) or (2) were refluxed with alcohols. With alcohols at ambient temperature the compounds (I) underwent replacement of the S-alkyl group by alkoxyl, but under reflux with 1 mol of alcohol two isomers C7H2ClNO(SR)OR were formed. The structures of these and other products were elucidated by chemical and physical means, especially 1H and 13C NMR and mass spectrometry. Possible reaction mechanisms are discussed and some use has been made of specific carbon-13 labelling.
TO MY WIFE SAMIRA
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THEORETICAL

PART I
Reinvestigation of the interaction between malonyl chloride and acetone, which claimed by Komninos to give 3,5-diketo-5 chloro-2,2-dimethyl-4,5-dioxopyranos-3,4,3-oxazines, was undertaken by Davis and Elvidge. They found neither of the above compounds was formed, but that the product was more complicated. They established beyond doubt that the product was a bicyclic heterocycle, 7-chloro-2,2-dimethyl-4,5-dioxopyranos-3,4,3-oxazines, formed by interaction of two mols. of malonyl chloride and one mol. of acetone:

\[ \text{RCOR}^1 + 2\text{CH}_2(\text{COCl})_2 \rightarrow \text{RCOR}^1 + 3\text{HCl} \]

The reaction was found to be a general one for the simple aliphatic and aromatic ketones.

Davis and Elvidge had extended this reaction and found that malonyl chloride reacted with benzo-, aceto- and naphtho-nitriles at 100° to give, 2-substituted-7-chloro-4,5-dioxopyranos-3,4,3-oxazines, products which had an analogous structure of the type (2).

Butt, Elvidge and Foster also investigated the reaction of isocyanates with malonyl chloride. This produced bicyclic heterocycles which were proved to be 3-substituted-7-chloro-3,4-dihydro-2,4,5-trioxopyranos-3,4,3-oxazines (3).
Evidence was obtained indicating that the reaction proceeded in two stages. In the first stage the ketones, nitriles, or isocyanates, as very weak bases induced a self condensation of malonyl chloride to 6-chloro-4-hydroxy-2-oxopyran-3-carbonyl chloride (4).

In the second stage of the reaction, this acid chloride (4) reacted with one molecule of the ketone, nitrile or isocyanate to produce the bicyclic heterocyclic products of the type (1), (2) and (3), respectively.

That this mechanism for the production of the bicyclic heterocycles was a probable one, was indicated by the fact that the pyrone acid (5) separated as an intermediate in the reaction. Later, the pyrone acid (5) was prepared by an independent route and was converted to the pyrone acid chloride (4) which when treated with ketone, nitrile, or isocyanate, gave the same products (1), (2) and (3), respectively, as before. The chemical behaviour of these compounds were studied. It was established that the chlorine atom at position 7 in the bicyclic heterocyclic compounds of type (1), (2) and (3) was very reactive and could be replaced by primary and secondary amines to produce 7-aminoproducts (6), which could react further with primary and secondary amines, with cleavage of the pyrone ring to produce products of the type (7).
$2 \text{CH}_2(\text{COCl})_2$
Further degradation of the products (7) with primary and secondary amines was studied. The degradation of the 7-chloro-pyrono products (1), (2), and (3) with alcohol was examined and it was found that the 7-chlorine atom was also replaced by alcohol. Then the alcohol reacted further and cleaved the pyrone ring, and gave products of the type (8).

Davis and Elvidge found that weakly enolic ethylacetoacetate and ethylpyruvate with malonyl chloride readily produced pyronodioxins. On the other hand, the unsaturated oxoester \( \text{C}_2\text{H}_5\text{O}_2\text{C} = \text{CH} = \text{CH} \text{COCH(CO}_2\text{C}_2\text{H}_5)_2 \) failed to react with malonyl chloride to produce a pyronodioxin, this unsaturated oxoester evidently being insufficiently basic to induce the self condensation of malonyl chloride to pyrone acid chloride.
Davis and Elvidge also found that the 1,3-diketone, acetyl acetone, afforded a chlorine-free compound, isomeric with dehydro acetic acid, whilst a 1,4-diketone, acetonyle acetone, converted malonyl chloride vigorously into malonic acid.

Davis and Elvidge (loc. cit.) showed that an aliphatic aldehyde could induce the self-condensation of malonyl chloride, but that the second stage of the reaction to pyronodioxin appeared not to take place. In contrast, benzaldehyde reacted with malonyl chloride to yield the expected chloropyronodioxin, whilst other aromatic aldehydes condensed with the methylene group yielding α,β- unsaturated acids.

Davis, Elvidge and Foster discovered in the case of the nitrile-malonyl chloride reaction, that if the nitrile contained a cyano-methylene group (-CH₂CN), the final product depended mainly on the reaction conditions. They found that such nitriles yielded at room temperature 3-substituted-2-chloro-4,6-dihydroxy pyridines (9) with slow evolution of hydrogen chloride.

Several products of the formula (9) were prepared (R = -CH₃, -(CH₂)₂Cl - CO₂C₂H₅, -C₆H₅) and their structure was determined by chemical degradation.

A mechanism of the formation of the compounds (9) has been suggested and is written as follows:
\[
RCH_2 \cdot \overset{\text{CH}_2\text{CO}_2\text{Cl}}{\text{Cl}} \quad \overset{\text{RCH}_2}{\text{C}} \quad \overset{\text{N}}{\text{C}} \quad \overset{\text{Cl}}{\text{CH}_2\text{CO}_2\text{Cl}}
\]

\[
RCH_2\text{C(}\text{Cl}) : \overset{\text{N}}{\text{C}} \quad \overset{\text{OH}}{\text{C}} \quad \overset{\text{Cl}}{\text{CHCOCl}}
\]

\[
RCH_2\text{C(}\text{Cl}) : \overset{\text{N}}{\text{C}} \quad \overset{\text{OH}}{\text{C}} \quad \overset{\text{Cl}}{\text{CHCOCl}}
\]

(a)
As a first step, the nitrile reacted with malonyl chloride to form an open chain intermediate (a) which in its enol form underwent cyclisation to give the final product (9) with elimination of hydrogen-chloride.

Later, Elvidge and Zaidi found that chloroacetonitrile with malonyl chloride at room temperature yielded 2,3-dichloro-4,6-dihydroxy pyridine (9, R = Cl) together with an unexpected product, 4-chloro-2-chloromethyl-6-pyrimidone (10, R = -CH₂Cl). Further examples of this new synthesis of 2-substituted-4-chloro-6-pyrimidones (10) were obtained with fluoro- and bromo-acetonitrile, α-bromopropionitrile and acetonitrile. Propio- and butyro-nitrile each gave a mixture of pyridine (9, R = Me, C₂H₅, respectively) and pyrimidine product (10, R = C₂H₅ and pr, respectively) whilst various other nitriles gave only pyridine products. They also obtained the fully substituted pyrimidones from fluoroacetonitrile and chloro malonyl chloride, and from dibromoacetonitrile with bromo malonyl chloride.

Some novel halogen transfer reactions were also encountered. The structure of these pyrimidines was determined by chemical transformation into a known compound.

They suggested a mechanism for the formation of the pyrimidine products as a result of ¹³C labelled malonyl chloride. It seemed that the pyrimidine synthesis, like the pyridine synthesis, must involve as a first step acylation of the nitrile by malonyl chloride to give (a).

At first, completion of the synthesis was envisaged as involving an exchange between (a) and a second molecule of nitrile to give acid chloride and the cyanoentity (b), cycloisomerisation of which would yield the pyrimidone (10). However, cyanoacetyl chloride failed to yield any
pyrimidine with fluoro- or chloro-acetonitrile or with either of these nitriles mixed with corresponding acid chloride, so routes through (b) were unlikely. An alternative was that an initial di-acylation product (c) might undergo rearrangement to (d) from which the pyrimidon (10) would arise straightforwardly, but no reasonable mechanism for the rearrangement could be envisaged.

The second proposal, unlike the first, implied that all three carbon atoms of malonyl chloride were incorporated into pyrimidone ring. By treating fluoroacetonitrile with malonyl chloride labelled with $^{14}C$ in both carbonyl groups, this implication was established. The various observations may be accommodated as in the scheme shown. Acylation of 2 mol. of nitrile would yield (c). This might be expected to enolise more readily than an acid chloride, and so through cyclisation resulting from this capacity, as in (e), to an entity which may be regarded as an azapyrylium salt (f), and by nucleophilic attack on this by chloride, the entity (g) could arise. Cyclisation would then lead to the pyrimidone (10) and acid chloride.

$$R^2 = CH_2CO.N:CCl.R$$

where R comes from

- (a) $R^2 = CO.Cl$
- (b) $R^2 = CN$
- (c) $R^2 = CO.N:CCl.R^1$
- (d) $R^2 = CCl:N.COR^1$
Ziegler and his co-worker have also reported the formation of some heterocyclic compounds from malonyl chloride.

They reported formation of derivatives of 4-hydroxy-2-pyridone.

They also reported the reaction of malonyl chloride and substituted malonyl chloride with carbodimides.

Ziegler and Kleineberg also showed that anils with a methyl or methylene group in the α-position to the (C = N) bond reacted with malonyl chloride yielding N-aryl-4-hydroxy-2-pyridones.

They also studied the reaction of substituted malonyl chloride
with nitriles and isocyanates. Benzonitrile and substituted benzonitriles reacted with benzyl-malonyl chloride yielding 6-chloro-5-benzyl-2-phenyl-1,3-oxazines (11).

\[
\begin{align*}
\text{(II)} & \quad \text{PhCH}_2 \quad \text{Ph} \\
\end{align*}
\]

Similarly, phenyl isocyanates and their substituted derivatives reacted with benzylmalonyl chloride producing 6-chloro-5-benzyl-3-phenyl-2,4-dioxo-dihydro-1,3-oxazine (12).

\[
\begin{align*}
\text{(I2)} & \quad \text{PhCH}_2 \quad \text{Ph} \\
\end{align*}
\]

Ziegler et al.\textsuperscript{14} studied the reaction of ketoxime O-alkyl ethers with monosubstituted malonyl chlorides and they obtained derivatives of 1-alkoxy and 4-hydroxy-2-oxopyridines.

They also studied\textsuperscript{15} the reaction of monosubstituted malonyl chlorides with oxime ethers of cyclic ketones.

Ziegler et al\textsuperscript{16} studied the reaction of monosubstituted malonyl chlorides with disubstituted hydrazones of cyclic ketones and they obtained, 1-dialkylamino- or 1-diarylamino-4-hydroxy-5,6-polymethylene-2-oxopyridines.
CHAPTER I

REACTIONS OF MALONYL CHLORIDE WITH SIMPLE

ALKYL- AND ARYL-THIOCYANATES
The reactions of malonyl chloride with thiocyanates have been investigated and the structures of the products elucidated by chemical means and by making use of spectroscopic methods \( \text{I.r., u.v., n.m.r., and m.s.} \).

The first thiocyanate to be treated with malonyl chloride was phenylthiocyanate.

It was found that 1 mol. of phenylthiocyanate reacted with 2 mols. of malonyl chloride at 100 and a product with an empirical formula \( \text{C}_{12}\text{H}_6\text{ClNO}_4\text{S} \) was formed, with evolution of hydrogen chloride gas. The mass spectrum of the product showed that the molecular weight was 307 A \((\text{P+2})\) peak indicated the presence of one chlorine atom. The presence of an odd number of nitrogen atoms were also apparent from the odd molecular ion. Thus the reaction could be written as:-

\[
\text{CH}_2(\text{COCI})_2 + \text{Ph SCN} \rightarrow \text{C}_{12}\text{H}_6\text{ClNO}_4\text{S} + 3\text{HCl} \quad (13, \text{R = Ph}).
\]

Other thiocyanates (ethyl, benzyl and p-chlorobenzyl) were also interacted with malonyl chloride and it was found they behaved in an analogous manner forming the chloro-compounds \((13)\).

It was found later that the chloro-product \((13, \text{R = Ph})\) could be prepared by the reaction of phenyl thiocyanate with 6-chloro-4-hydroxy-2-oxopyran-3-carbonyl chloride \((4)\) (which was prepared by the action of warm thiony chloride on 6-chloro-4-hydroxy-2-oxopyran-3-carboxylic acid \((5)\)) as follows:-

\[
\text{Ph SCN} \rightarrow \text{SOCI}_2 \rightarrow C_{12}H_6ClNO_4S + \text{HCl} \quad (13, \text{R = Ph})
\]

\[
\text{Cl} \quad \text{OH} \quad \text{Cl}
\]

\((5)\)

\[
\text{Cl} \quad \text{OH} \quad \text{Cl}
\]

\((4)\)
The formation of the chloro-product by this route indicated the presence of one pyrone ring in the molecule.

By simple analogy with the mechanism of the reactions of malonyl chloride with ketones, with nitriles at 100°, and with isocyanates at 100°, a molecule of phenylthiocyanate, after inducing the formation of the pyrone acid chloride (4), would be expected to react with it to produce the 7-chloro-2-phenylmercapto-4,5-dioxopyrones-1,3-oxazine (13, R = Ph) as follows:

\[
2 \text{CH}_2(\text{COCl})_2 + 2\text{HCl} \rightarrow \begin{array}{c}
\text{OH} \\
\text{Cl}
\end{array}
\]

\[
\begin{array}{c}
\text{Cl} \\
\text{O} \\
\text{N}
\end{array}
\]

The structure of the 7-chloro-2-mercapto products (13) were supported by the infra-red absorptions as shown in Table (I).

**TABLE I**
(Product 13, R = Ph)

<table>
<thead>
<tr>
<th>Absorption max. cm(^{-1})</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1775 sh</td>
<td>(\text{C}=\text{O})</td>
</tr>
<tr>
<td>1745 s</td>
<td>(\text{C}=\text{O})</td>
</tr>
<tr>
<td>1590 s</td>
<td>(\text{C}=\text{N})</td>
</tr>
<tr>
<td>1540 w )</td>
<td>(\text{C}=\text{C})</td>
</tr>
<tr>
<td>1515 s )</td>
<td>(\text{C}=\text{C})</td>
</tr>
</tbody>
</table>
The ultra violet light absorption properties of the 7-chloro-2-mercaptop products (13) are recorded in Table (II): these products are characterised by absorption in the region 341-347 nm.

<table>
<thead>
<tr>
<th>Products (R)</th>
<th>λ&lt;sub&gt;max&lt;/sub&gt; (CHCl₃) nm</th>
<th>ε x 10⁻³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>347</td>
<td>14.8</td>
</tr>
<tr>
<td></td>
<td>279.5</td>
<td>10.7</td>
</tr>
<tr>
<td>PhCH₂</td>
<td>346</td>
<td>13.9</td>
</tr>
<tr>
<td></td>
<td>280</td>
<td>9.8</td>
</tr>
<tr>
<td>p-Cl-C₆H₄CH₂</td>
<td>341.5</td>
<td>17.0</td>
</tr>
<tr>
<td></td>
<td>278.5</td>
<td>15.0</td>
</tr>
<tr>
<td>C₆H₅</td>
<td>344</td>
<td>15.9</td>
</tr>
<tr>
<td></td>
<td>280</td>
<td>14.8</td>
</tr>
</tbody>
</table>

The n.m.r. spectra of these products were also studied: the results, recorded in Table (III), also supported the structure (13). Thus from these observations it was concluded that the chloro-products also have the structure (13).
TABLE III
N.M.R. spectra of the 7-chloro-2-mercapto compounds (13) (5-10% in CDCl₃)

<table>
<thead>
<tr>
<th>R</th>
<th>ppm</th>
<th>Intensity</th>
<th>Multiplicity</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph-</td>
<td>2.42</td>
<td>5</td>
<td>s</td>
<td>Ph</td>
</tr>
<tr>
<td></td>
<td>3.67</td>
<td>1</td>
<td>s</td>
<td>8 - H</td>
</tr>
<tr>
<td>PhCH₂-</td>
<td>2.52</td>
<td>5</td>
<td>s</td>
<td>Ph</td>
</tr>
<tr>
<td></td>
<td>3.62</td>
<td>1</td>
<td>s</td>
<td>8 - H</td>
</tr>
<tr>
<td></td>
<td>5.58</td>
<td>2</td>
<td>s</td>
<td>CH₂</td>
</tr>
<tr>
<td>p-Cl-C₆H₄CH₂-</td>
<td>2.8</td>
<td>4</td>
<td>s</td>
<td>C₆H₄</td>
</tr>
<tr>
<td></td>
<td>3.63</td>
<td>1</td>
<td>s</td>
<td>8 - H</td>
</tr>
<tr>
<td></td>
<td>5.73</td>
<td>2</td>
<td>s</td>
<td>CH₂</td>
</tr>
<tr>
<td>C₂H₅-</td>
<td>3.7</td>
<td>1</td>
<td>s</td>
<td>8 - H</td>
</tr>
<tr>
<td></td>
<td>6.8</td>
<td>2</td>
<td>q, J = 7Hz</td>
<td>CH₂, of C₂H₅S</td>
</tr>
<tr>
<td></td>
<td>8.58</td>
<td>3</td>
<td>t, J = 7Hz</td>
<td>CH₂, of C₂H₅</td>
</tr>
</tbody>
</table>
CHAPTER II

FORMATION OF 2-AMINO-7-CHLORO-4,5-DIOXOPYRANO[3,4-e]\textit{J}-

-1,3-OXAZINES (14)
Elvidge and his co-workers\textsuperscript{3,7,17} found that the chlorine atom in the chloropyrono products (1, 2 and 3) was very reactive towards primary and secondary amines and that it could be replaced to form the aminopyrono products of structure (6), as mentioned in the introduction, but the 7-chloro-2-mercapto-pyrono-oxazines (13) were found to react in a different way with amines.

It was found on treating the 7-chloro-2-ethyl mercapto compound (13, \( R = \text{C}_2\text{H}_5 \)) in dry chloroform with one mol. of dry morpholine (dropwise with stirring) that an exothermic reaction took place, with evolution of ethylmercaptan \((\text{C}_2\text{H}_5\text{SH})\).

The colourless crystalline product (80\%) had \( m/e 284 \) \( \text{M}^+ \) and 286 \((p + 2)\), which according to the nitrogen rule established the presence of an even number of nitrogen atoms. The percentages of the intensities of the \((p + 2)\) peak with respect to the parent peak were 24.5 to 73.2, very close to the calculated values (24.4, 75.5) for the compound containing one chlorine atom. The product had the composition \( \text{C}_{11}\text{H}_9\text{ClN}_2\text{O}_5 \).

The same product was also obtained from the reactions of one mol. of dry morpholine with each of the following - the 7-chloro-2-benzylmercapto, phenylmercapto and p-chloro-benzylmercapto - compounds (13, \( R = \text{PhCH}_2, \text{Ph} \) and \( p-\text{Cl-C}_6\text{H}_4\text{CH}_2 \) - respectively). Thus the morpholine residue had replaced the mercapto residue \((2 - \text{SR})\) to give 7-chloro-2-morpholino-4,5-dioxopyrano \( \square_{3,4}-\cdot-\square_{1,3}-\text{oxazinc} \) \((14, \text{R}^1\text{R}^2 = \square_{\text{CH}_2\text{CH}_2,0\text{CH}_2\text{CH}_2})\). That the mercapto group \((2 - \text{SR})\) in the 7-chloro-2-mercapto compounds (13) was more reactive towards amines than the 7-chloro atom was not expected in view of the high reactivity of the latter in the previous cases and in the 7-chloro-pyrono products (1, 2 and 3).
A mechanism for the formation of the 7-chloro-2-morpholino product (14h) could be written as follows:

\[
\begin{align*}
(I3) & \quad R = \text{C}_2\text{H}_5, \text{Ph}, \text{PhCH}_2 \quad \text{and} \quad P = \text{Cl} - \text{C}_6\text{H}_4\text{CH}_2 \\
\end{align*}
\]

The \(^1\)H n.m.r. spectrum of the product showed signals at \(\delta 6.20\) (c, \(2 \times \text{CH}_2\), of the morpholine residue) and \(\delta 3.95\) (s, 8 - H) which confirmed the structure (14h).

The infra-red spectrum of the 7-chloro-2-morpholino product (14h) also supported the structure (14) (Table IV).
TABLE IV

I.R. spectrum (Nujol)

<table>
<thead>
<tr>
<th>Absorption max. cm$^{-1}$</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>3090 w</td>
<td>CH</td>
</tr>
<tr>
<td>1785 s</td>
<td>5- C=O</td>
</tr>
<tr>
<td>1740 s</td>
<td>4- C=O</td>
</tr>
<tr>
<td>1584 s</td>
<td>C=N</td>
</tr>
<tr>
<td>1620 s )</td>
<td></td>
</tr>
<tr>
<td>1574 s )</td>
<td>C=C</td>
</tr>
<tr>
<td>1535 s )</td>
<td></td>
</tr>
<tr>
<td>1520 s )</td>
<td></td>
</tr>
</tbody>
</table>

The formation of 2-amino-7-chloro products (14) from treatment of the 7-chloro-2-mercapto compound (13) with one mol. of amine was found to be a general reaction, ammonia, primary, secondary, aliphatic and aromatic amines, all displacing the thio substituent.

\[
\begin{array}{c}
\text{Cl} \\
\text{NR}^1 R^2
\end{array}
\]

(14)

a, $R^1 = R^2 = H$
b, $R^1 = H, R^2 = C_2H_5$
c, $R^1 = H, R^2 = CH_3(CH_2)_3$
d, $R^1 = H, R^2 = CH_3(CH_2)_7$
e, $R^1 = H, R^2 = Ph$
f, $R^1 = H, R^2 = PhCH_2$
g, $R^1 R^2 = CH_2CH_2$
h, $R^1 R^2 = CH_2CH_2CH_2$
i, $R^1 = H, R^1 = (CH_3)_2CH$
Hence, the primary mode of the reaction was independent of the amine or the nature of the 2-thio group.

It was observed that the 2-amino-7-chloro products (14) were stable towards water and alcohols. The 2-amino products (14) were recovered after being refluxed with an excess of water and ethyl alcohol, respectively, in dioxan for 1½ hours. These -2-amino-7-chloro compounds (14) showed characteristic absorption in the u.v. near 340 and 295 nm (Table V).

<table>
<thead>
<tr>
<th>TABLE V</th>
</tr>
</thead>
<tbody>
<tr>
<td>U.V. absorption in (CH$_3$CN)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Compound 14</th>
<th>$\lambda_{\text{max}}$ nm</th>
<th>$\epsilon \times 10^{-3}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>a,</td>
<td>291</td>
<td>11.6</td>
</tr>
<tr>
<td></td>
<td>333.5</td>
<td>16.8</td>
</tr>
<tr>
<td>c,</td>
<td>294</td>
<td>13.8</td>
</tr>
<tr>
<td></td>
<td>336.5</td>
<td>16.9</td>
</tr>
<tr>
<td>d,</td>
<td>294.5</td>
<td>13.0</td>
</tr>
<tr>
<td></td>
<td>338</td>
<td>16.8</td>
</tr>
<tr>
<td>e,</td>
<td>296</td>
<td>7.8</td>
</tr>
<tr>
<td></td>
<td>347</td>
<td>12.7</td>
</tr>
<tr>
<td>f,</td>
<td>293</td>
<td>15.4</td>
</tr>
<tr>
<td></td>
<td>338</td>
<td>18.6</td>
</tr>
<tr>
<td>g,</td>
<td>298</td>
<td>7.6</td>
</tr>
<tr>
<td></td>
<td>341</td>
<td>12.5</td>
</tr>
<tr>
<td>h,</td>
<td>297</td>
<td>12.5</td>
</tr>
<tr>
<td></td>
<td>340</td>
<td>20.3</td>
</tr>
</tbody>
</table>
The i.r. spectra of the 2-amino-7-chloro products (14) derived from primary amines showed the expected carbonyl absorption in the 1770-1750 cm\(^{-1}\) region (Table VI), but in the NH stretching region showed two sets of bands, indicating tautomerism as follows:

![Diagram of tautomerism](image)

<table>
<thead>
<tr>
<th>Compound (14)</th>
<th>Absorption max. cm(^{-1})</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>c</td>
<td>3295 m</td>
<td>NH</td>
</tr>
<tr>
<td></td>
<td>3150 m</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3080 w</td>
<td>CH</td>
</tr>
<tr>
<td></td>
<td>1770 sh</td>
<td>5= C=O</td>
</tr>
<tr>
<td></td>
<td>1735 s</td>
<td>4= C=O</td>
</tr>
<tr>
<td></td>
<td>1580</td>
<td>C=N</td>
</tr>
<tr>
<td></td>
<td>1626</td>
<td>C=C</td>
</tr>
<tr>
<td></td>
<td>1530</td>
<td></td>
</tr>
</tbody>
</table>

/contd...
TABLE VI (continued)

<table>
<thead>
<tr>
<th>Compound (14)</th>
<th>Absorption max. cm$^{-1}$</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>e</td>
<td>3326 w )</td>
<td>NH</td>
</tr>
<tr>
<td></td>
<td>3220 w )</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3100 w</td>
<td>CH</td>
</tr>
<tr>
<td></td>
<td>1760 m</td>
<td>$\nu_C=O$</td>
</tr>
<tr>
<td></td>
<td>1730 s</td>
<td>$\delta_C=O$</td>
</tr>
<tr>
<td></td>
<td>1590 m</td>
<td>C=N</td>
</tr>
<tr>
<td></td>
<td>1655 s )</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1610 w )</td>
<td>C=C</td>
</tr>
<tr>
<td></td>
<td>1536 m )</td>
<td></td>
</tr>
<tr>
<td>f</td>
<td>3250 m )</td>
<td>NH</td>
</tr>
<tr>
<td></td>
<td>3150 w )</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3090 w</td>
<td>CH</td>
</tr>
<tr>
<td></td>
<td>1775 s</td>
<td>$\nu_C=O$</td>
</tr>
<tr>
<td></td>
<td>1715 s</td>
<td>$\delta_C=O$</td>
</tr>
<tr>
<td></td>
<td>1580 s</td>
<td>C=N</td>
</tr>
<tr>
<td></td>
<td>1630 m )</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1610 m )</td>
<td>C=C</td>
</tr>
<tr>
<td></td>
<td>1550 w )</td>
<td></td>
</tr>
<tr>
<td>a</td>
<td>3360 m )</td>
<td>NH</td>
</tr>
<tr>
<td></td>
<td>3330 w )</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3230 w )</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3170 w )</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1750 m</td>
<td>$\nu_C=O$</td>
</tr>
<tr>
<td></td>
<td>1710 s</td>
<td>$\delta_C=O$</td>
</tr>
<tr>
<td></td>
<td>1578 m</td>
<td>C=N</td>
</tr>
<tr>
<td></td>
<td>165 s )</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1550 s )</td>
<td>C=C</td>
</tr>
<tr>
<td></td>
<td>1500 m )</td>
<td></td>
</tr>
</tbody>
</table>
The tautomerism was confirmed for solutions in deuteriochloroform by the $^1H$ n.m.r. spectra of the 2-butylamino and 2-octylamino-7-chloro compounds (14c and d) (Figures 1 and 2) which showed two singlets (total intensity one proton) from the lone ring proton H - 8, and two broadened lines (again totalling one proton) attributable to NH in each tautomer.

In other solvents there was less indication of the tautomerism, for example the 7-chloro-2-octylamino-product (14d) in dry dioxan showed two singlets (total intensity one proton) from the lone ring proton H - 8, but only one broadened line attributable to NH.

These features were also found in the $^1H$ n.m.r. spectra of the 7-chloro-2-ethylamino product (14b) in d$_6$ DMSO and in the spectra of the 2-benzylamino product (14f) in acetone and in acetonitrile.

It was also noticed in the $^1H$ n.m.r. spectra of the 2-amino-7-chloro products (14, $R$ = H) derived from primary amines that there was coupling between the methylene group adjacent to the NH in the 2-NH-CH$_2$-R group. For instance, the methylene group of the 2-benzylamino-7-chloro product (14f) appeared as a doublet (J 6 Hz) in acetone and in acetonitrile.

It was also found that the methylene groups of the 2-butylamino- and 2-octylamino-7-chloro products (14c and d) appeared as quartets (J 6.8 Hz) (Figures 1 and 2) in deuteriochloroform, and also that the NH signal was two triplets (J 6.8 Hz). The quartet changed to a triplet when the solution of the 2-butylamino-7-chloro product (14c) was shaken with D$_2$O and the triplets from the NH groups disappeared (Figure 3).

In the case of the 7-chloro-2-ethylamino product (14b) in d$_6$ DMSO there was no coupling between the NH and the methylene group adjacent to it. This could be due to the fast exchange between the proton on the NH group and the water which was present in the d$_6$ DMSO.
The 1H n.m.r. spectrum of 2-butylamino-7-chloro-compound (1k&c) in CDCl₃.
Fig. 2  The $^1$H n.m.r. spectrum of 7-chloro-2-octylamino product (I4d) in CDCl$_3$
Fig. 3  The $^1H$ n.m.r. spectrum of 2-butylamino-7-chloro-compound (I4c) in CDCl$_3$ after the addition of D$_2$O
CHAPTER III

FURTHER DEGRADATION OF THE 2-MERCAPTO-7-CHLORO-
PYRANO-OXAZINES AND THEIR DERIVATIVES WITH AMINES
It was found that secondary and primary amines could displace the 7-chloro atom in the 2-amino-7-chloro products (14) to give 2,7-diamino products (15).

Thus the 7-chloro-2-morpholino compound (14h), when dissolved in dry chloroform and boiled with two molecular proportions of dry morpholine, gave morpholine hydrochloride and the 2,7-dimorpholino-pyrone-oxazine derivative (15a). This had the correct composition and mass spectrum.

The same product was also obtained by treating the 7-chloro-2-ethyl mercapto derivative (13, $R = C_2H_5$), in dry chloroform, with three mols of dry morpholine.

The infrared spectrum of the 2,7-dimorpholino derivative showed the expected carbonyl absorptions in the 1700-1800 cm$^{-1}$ region as indicated in Table VII.
TABLE VII

I.R. absorption (Nujol)

<table>
<thead>
<tr>
<th>Compound (15a)</th>
<th>Absorption cm(^{-1})</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3060 w</td>
<td>CH</td>
</tr>
<tr>
<td></td>
<td>1764 m</td>
<td>5- C=O</td>
</tr>
<tr>
<td></td>
<td>1714 s</td>
<td>4- C=O</td>
</tr>
<tr>
<td></td>
<td>1580 m</td>
<td>C=N</td>
</tr>
<tr>
<td></td>
<td>1621 m</td>
<td>C=C</td>
</tr>
<tr>
<td></td>
<td>1514 s</td>
<td></td>
</tr>
</tbody>
</table>

The \(^1\)H n.m.r. spectrum of the 2,7-dimorpholino derivative (15a) showed resonances at \(\delta 4.82 (\zeta, 8 - H)\), \(6.15 (\zeta, 6 \times \text{CH}_2)\), and \(6.82 (\varepsilon, \text{CH}_2\varepsilon, \varepsilon, \text{CH}_2)\) aff the 7-morpholino), which confirmed the structure (15a). The increase in the chemical shift of the proton of the 8-position, from \(\delta 3.9\) in the 7-chloro-2-morpholino derivative (14h) to \(\delta 4.82\) in the 2,7-dimorpholino derivative (15a), was an expected result of replacing the 7-chloro group by a morpholino residue. The position of the signal from the \((\text{CH}_2\varepsilon, \text{CH}_2)\) group in the 2-morpholino residue in compounds (14h and 15a), which should be at a higher field, coincided with the signal from the \(\text{CH}_2\varepsilon\varepsilon, \text{CH}_2\) protons. The paramagnetic shift was probably caused by the adjacent C=N group.

The 2-butylamino-7-morpholino derivative (15b) was similarly obtained by boiling the 2-butylamino-7-chloro product (14c) with two mols. of dry morpholine in dry chloroform.
The 2,7-dibenzylamino derivative (15C·) was obtained from the 7-chloro-2-ethyl mercapto compound (12, R = C₂H₅) and three mols of dry benzylamine or from the 2-benzylamino-7-chloro product (14·) with two mols of dry benzylamine. The yield was poor and the product was found to be mixed with further degradation products (which will be discussed later).

The formation of the 2,7-diamino derivative (15) from treatment of the 2-amino-7-chloro compound (14) with amine could be written as follows:

\[
\begin{align*}
&\text{(14)} \\
&\text{(15)}
\end{align*}
\]

\[
\begin{align*}
(a) & \quad R¹R² = R³R⁴ = \underbrace{CH₂}₀₂CH₂₂ \\
(b) & \quad R¹ = H, R² = B ; R³R⁴ = \underbrace{CH₂}₀₂CH₂₂ \\
(c) & \quad R¹R³ = H, R²R⁴ = PhCH₂-
\end{align*}
\]

It was found from the \(^1\)H n.m.r. spectrum of the 2-butylamino-7-morpholino compound (15b·) in (CDCl₃) (Table VIII) that this compound existed in two tautomeric forms:

\[
\begin{align*}
&\text{(15b)}
\end{align*}
\]
Thus there were two signals (total intensity one proton) from the lone ring proton $H - 8$, and two broadened lines (again totalling one proton) attributable to NH in each tautomer.

The 2,7-dibenzylamino compound $(15_c)$ also showed tautomerism. In the $^1H$ n.m.r. spectrum in $d_6$ DMSO the NH of the 7-NHCH$_2$Ph group appeared as a triplet signal (coupled to the adjacent CH$_2$), whilst at lower field there were two fractional signals, a broadened one from the 2-NHCH$_2$Ph group proton together with a singlet from the ring NH of the tautomer, their relative intensities being $0.72: 0.28$.

<table>
<thead>
<tr>
<th>TABLE VIII</th>
</tr>
</thead>
</table>

$^1H$ n.m.r. of the 2,7-diamino compounds $(15)$

<table>
<thead>
<tr>
<th>Compound $(15)$</th>
<th>Line Positions</th>
<th>Intensity</th>
<th>Multiplicity</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>in $(CDCl_3)$</td>
<td>1.09 and 3.8 br</td>
<td>1</td>
<td>s</td>
<td>NH from each tautomer</td>
</tr>
<tr>
<td></td>
<td>4.78 and</td>
<td>1</td>
<td>s, s</td>
<td>3 - H</td>
</tr>
<tr>
<td></td>
<td>6.15</td>
<td>4</td>
<td>c</td>
<td>CH$_2$OCH$_2$</td>
</tr>
<tr>
<td></td>
<td>6.85</td>
<td>4</td>
<td>c</td>
<td>CH$_2$NCH$_2$</td>
</tr>
<tr>
<td></td>
<td>6.53</td>
<td>2</td>
<td>$q$, J6Hz</td>
<td>CH$_2$N of BuNH</td>
</tr>
<tr>
<td></td>
<td>8.8 - 8.1</td>
<td>4</td>
<td>c</td>
<td>2 x CH$_2$ of Bu</td>
</tr>
<tr>
<td></td>
<td>9.05</td>
<td>3</td>
<td>$t$, J6Hz</td>
<td>me</td>
</tr>
<tr>
<td>in $(CD_3)_{2}$SO$_7$</td>
<td>-1.10</td>
<td>72%</td>
<td>1</td>
<td>s</td>
</tr>
<tr>
<td></td>
<td>-0.85 br</td>
<td>28%</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.21 br</td>
<td>1</td>
<td>$t$, J7Hz</td>
<td>7NH</td>
</tr>
<tr>
<td></td>
<td>2.7</td>
<td>10</td>
<td>e</td>
<td>2 x Ph</td>
</tr>
<tr>
<td></td>
<td>4.85</td>
<td>1</td>
<td>s</td>
<td>8 - H</td>
</tr>
<tr>
<td></td>
<td>5.57</td>
<td>4</td>
<td>br</td>
<td>2 x CH$_2$</td>
</tr>
</tbody>
</table>
The diamino-pyrano-oxazines (15) were distinguishable from the 2-amino- and 2-mercapto compounds (12 and 14) by their light absorption near 288 and 324 nm (Table IX).

### Table IX

<table>
<thead>
<tr>
<th>Compound (15)</th>
<th>$\lambda_{\text{max}}, \text{nm}$</th>
<th>$E \times 10^{-3}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>281</td>
<td>7.9</td>
</tr>
<tr>
<td></td>
<td>325</td>
<td>20.9</td>
</tr>
<tr>
<td>b</td>
<td>287</td>
<td>7.7</td>
</tr>
<tr>
<td></td>
<td>323</td>
<td>15.5</td>
</tr>
</tbody>
</table>

On attempting to recrystallize the 2-butylamino-7-morpholino derivative (15b) from ethanol, both the rings reacted with the solvent and the glutaconic ester amide (16) was obtained.

The nature of the substituents on the bicyclic system thus profoundly effect its reactivity, the amino-chloro compounds (14) being unchanged after 1.5 hours refluxing with ethanol.

The formation of the glutaconic ester amide (16) could be explained as below: first the alcohol attacked the pyrone ring and gave the oxazine derivative (a) which underwent further reaction with another mole of ethyl alcohol at the 5,6-double bond to produce the final product (16):-
The above mechanism was supported by the previous work of this kind. The structure of the glutaconic ester amide (16) was confirmed by $^1$H n.m.r. (Table X). The infrared absorption of the compound (16) also supported the structure (Table XI).

When the 2,7-dimorpholino derivative (15a) was boiled in chloroform with an excess of morpholine for $2\frac{1}{2}$ hours, the β-morpholinoglutcondimorpholide was obtained. Its structure was indicated by the composition, mass spectrum and $^1$H n.m.r. (Table XII) characteristics.
### TABLE X

\(^1\)H n.m.r. of compound (16) in (CDCl\(_3\))

<table>
<thead>
<tr>
<th>Line Positions</th>
<th>Intensity</th>
<th>Multiplicity</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>-0.35 br</td>
<td>1</td>
<td>s</td>
<td>CO•NH•CO</td>
</tr>
<tr>
<td>1.3 br</td>
<td>1</td>
<td>t, J 5.6Hz</td>
<td>NH of BuNH</td>
</tr>
<tr>
<td>5.78, 5.83</td>
<td>4</td>
<td>q, q, J 6.8Hz</td>
<td>2 x CH(_2)O of C(_2)H(_5)</td>
</tr>
<tr>
<td>6.15</td>
<td>2</td>
<td>c</td>
<td>CH(_2)N of BuN</td>
</tr>
<tr>
<td>6.3</td>
<td>2</td>
<td>s</td>
<td>4 - H(_2)</td>
</tr>
<tr>
<td>6.77</td>
<td>4</td>
<td>c, c</td>
<td>CH(_2)NCH(_2)</td>
</tr>
<tr>
<td>8.3 - 8.9</td>
<td>4</td>
<td>c</td>
<td>2 x CH(_2) of Bu</td>
</tr>
<tr>
<td>8.69</td>
<td>3</td>
<td>t, J 6.8Hz</td>
<td>Me of EtO•CO•O</td>
</tr>
<tr>
<td>8.75</td>
<td>3</td>
<td>t, J 6.8Hz</td>
<td>Me of 3 - OC(_2)H(_5)</td>
</tr>
<tr>
<td>9.09</td>
<td>3</td>
<td>c</td>
<td>Me of Bu</td>
</tr>
</tbody>
</table>

### TABLE XI

I.R. results of the compound (16) in Nujol

<table>
<thead>
<tr>
<th>Absorption cm(^{-1})</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>3320 s</td>
<td>NH</td>
</tr>
<tr>
<td>1740 s</td>
<td>C=O of the ester</td>
</tr>
<tr>
<td>1698 s</td>
<td>I,5- C=O</td>
</tr>
<tr>
<td>1670 m</td>
<td>C=O of the amide</td>
</tr>
<tr>
<td>1630 s</td>
<td>NH deformation</td>
</tr>
<tr>
<td>1540 br</td>
<td>C=C</td>
</tr>
</tbody>
</table>
TABLE XII

$^1$H n.m.r. at compound (17) in (CDCl$_3$)

<table>
<thead>
<tr>
<th>Line Position</th>
<th>Intensity</th>
<th>Multiplicity</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.88</td>
<td>1</td>
<td>s</td>
<td>$\gamma$ - CH</td>
</tr>
<tr>
<td>5.05</td>
<td>2</td>
<td>s</td>
<td>$\alpha$ - CH$_2$</td>
</tr>
<tr>
<td>6.37</td>
<td>20</td>
<td>c</td>
<td>10 x CH$_2$ of</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>morpholine</td>
</tr>
<tr>
<td>6.87</td>
<td>4</td>
<td>c</td>
<td>CH$_2$N.CH$_2$</td>
</tr>
</tbody>
</table>

Thus the pyrone ring has been opened, as expected, but an arylureido chain, which should have derived from opening of the oxazine ring, had been lost. This was attributed to traces of water in the morpholine used. The formation of product (17) could be explained as below:

First, 1 mol. of morpholine had attacked the pyrano ring of the 2,7-dimorpholino-derivative to give the expected oxazine derivative (a) which underwent attack by the water at the 5-position to give another intermediate (b). This was evidently followed by hydrolysis of the side chain and decarboxylation to give the acetone-1,3-dicarboxymorpholide (c). Normal condensation of the acetone-1,3-dicarboxymorpholide product (c) with morpholine then provided the end product (17).
(Where \( R \) is morpholine)
In previous reactions involving acetone-carboxamides conditions had not been so vigorous as in this reaction to cause the replacement of the enolic hydroxyl by amine.

The oxazine ring in the intermediate (a) could have been attacked by morpholine at the 5-position to give the disubstituted glutamidomorpholide (c) which might then have suffered by hydrolysis of the side chain and decarboxylation to provide the end product (17). However, the side chain amide in compounds of this kind showed stability towards water.

The product (17) was also obtained by boiling in chloroform the 7-chloro-2-ethylmercapto derivative (13, R = C₆H₅) with an excess of morpholine and similarly from the 7-chloro-2-morpholino-derivative (14h).
CHAPTER IV

THE FORMATION OF THE 4,6-DIAMINOPYRONE DERIVATIVES
(18) AND (19)
It was realised that if a 7-chloro-pyranoxazine derivative (12) or (14) was heated with three or two molecular proportions of amines, respectively under conditions such that the diamino product (15) and the amine-hydrochloride by-product both remained in solution in the reaction medium, then the oxazine ring was cleaved preferentially so that the product was a pyrone derivative (18). Possibly, hydrogen chloride-addition or proton-assisted amine-addition to the 4a,8a-double bond initiated the specific ring-opening. Thus the formation of pyrone derivatives by this route could be depicted as:-

\[ \begin{align*}
\text{Cl} & \\
\text{O} & \\
\text{NH} & \\
\text{R}^2 & \\
\text{R}^3 & \\
\text{R}^4 & \\
\text{NH}_2 & \\
2 \text{R}^3 \text{R}^4 \text{NH}_2 & \\
\rightarrow & \\
\text{R}^3 \text{R}^4 \text{NH}_3 \text{Cl} & \\
\rightarrow & \\
\text{R}^3 \text{R}^4 \text{NH}_2 & + \text{HCl}
\end{align*} \]
In this way, 7-chloro-2-morpholino-pyran-oxazine (14h) was converted by benzylamine in boiling chloroform into the 4,6-dibenzylamino-pyrone derivative (18c) which absorbed strongly in the u.v. near 311 nm.

In dimethylsulphoxide the 2-amino-7-chloro compound (14a) with benzylamine gave the 4,6-dibenzylaminopyrone-3-carboxyureide (18a).

Furthermore, the 2-benzylamino-7-chloro compound (14f) in dioxan with benzylamine provided the benzylureido homologue (18b). This last product was also obtained direct from the 7-chloro-2-ethylthio compound (13, R = C$_2$H$_5$) with three molecular proportions of benzylamine in dioxan, a marked but now understandable contrast to the same reaction in chloroform which had yielded the 2,7-dibenzylaminopyrano-oxazine (15c).

These products showed a characteristic light absorption in the 311 and 250 nm regions.

The i.r. spectra (Table XIII) of the pyrone derivatives (18) indicated that the 2-pyrene carbonyl group was hydrogen-bonded, as expected from analogous derivatives. Indeed double hydrogen-bonding, as in structure (19) was strongly indicated by the $^1$H n.m.r. spectra (Table XIV), which showed two signals from NH protons at rather low field.

![Diagram](image)
### TABLE XIII

**I.R. spectra of the pyrono derivative (18) (Nujol)**

<table>
<thead>
<tr>
<th>Compound (18)</th>
<th>Absorption $\lambda_{\text{max}}$ cm$^{-1}$</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>3400 m )</td>
<td>NH</td>
</tr>
<tr>
<td></td>
<td>3230 m )</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3080 sh</td>
<td>CH</td>
</tr>
<tr>
<td></td>
<td>1690 sh</td>
<td>2- C=O H-bonded</td>
</tr>
<tr>
<td></td>
<td>1660 sh</td>
<td>C=O remote in the 3-substituent</td>
</tr>
<tr>
<td></td>
<td>1646 sh</td>
<td>C=O at 3-position H-bonded</td>
</tr>
<tr>
<td></td>
<td>1618 w )</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1590 w )</td>
<td>C=C</td>
</tr>
<tr>
<td></td>
<td>1555 br )</td>
<td></td>
</tr>
</tbody>
</table>
TABLE XIV

$^1$H n.m.r. results of compound (18)

<table>
<thead>
<tr>
<th>Compound (18)</th>
<th>Line Position</th>
<th>Intensity</th>
<th>Multiplicity</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>a in (d$_6$ DMSO)</td>
<td>-0.88</td>
<td>1</td>
<td>s</td>
<td>CO NH CO bonded</td>
</tr>
<tr>
<td></td>
<td>-0.4</td>
<td>1</td>
<td>br</td>
<td>4 - NH H-bonded</td>
</tr>
<tr>
<td></td>
<td>1.30</td>
<td>1</td>
<td>br</td>
<td>6 - NH</td>
</tr>
<tr>
<td></td>
<td>2.5</td>
<td>2</td>
<td>br</td>
<td>NH$_2$</td>
</tr>
<tr>
<td></td>
<td>2.73</td>
<td>10</td>
<td>s</td>
<td>2 x Ph</td>
</tr>
<tr>
<td></td>
<td>4.9</td>
<td>2</td>
<td>s</td>
<td>5 - H</td>
</tr>
<tr>
<td></td>
<td>5.61</td>
<td>4</td>
<td>c</td>
<td>2 x CH$_2$ overlapped</td>
</tr>
<tr>
<td>c in (CDCl$_3$)</td>
<td>-1.15 br</td>
<td>1</td>
<td>s</td>
<td>CO NH CO bonded</td>
</tr>
<tr>
<td></td>
<td>-0.58 br</td>
<td>1</td>
<td>t, J 6Hz</td>
<td>4 - NH bonded</td>
</tr>
<tr>
<td></td>
<td>1.15 br</td>
<td>1</td>
<td>t, J 6Hz</td>
<td>NH remote at 3 position</td>
</tr>
<tr>
<td></td>
<td>3.24 br</td>
<td>1</td>
<td>t, J 6Hz</td>
<td>6 - NH</td>
</tr>
<tr>
<td></td>
<td>2.53 - 3.0</td>
<td>15</td>
<td>c</td>
<td>3 x Ph</td>
</tr>
<tr>
<td></td>
<td>5.28</td>
<td>1</td>
<td>s</td>
<td>5 - H</td>
</tr>
<tr>
<td></td>
<td>5.52 and 5.72</td>
<td>6</td>
<td>d,d,d, J 6Hz</td>
<td>3 x CH$_2$</td>
</tr>
</tbody>
</table>

It was also noticed in the $^1$H n.m.r. spectrum of compound (18b) in (CDCl$_3$) that there was coupling between the methylene group adjacent to the
NH in the NHCH$_2$Ph group ($J$ 6Hz), but again this coupling disappeared in d$_6$ DMSO as had been noticed for compound (18a) (Table XIV).

Yet other examples of the selectivity which could now be exercised were provided by the interactions of the 2-benzyl- and 2-ethyl-thio-7-chloro compounds (13, R=PhCH$_2$ and C$_2$H$_5$ respectively) with aniline-hydrochloride in dioxan solution.

There was attack at the 8a-position with opening of the oxazine ring as well as displacement of the chloro substituent by aniline, to yield 4,6-dianilino-pyran-3-one-3-carboxythiourethanes (20a and b). The alkylthio groups remained unaffected, in strong contrast to their preferential displacement by free aniline.

It is possible that the aniline first attacks the oxazine ring at the 8a-position, with proton-assistance, to give the 4-anilino-6-chloropyrano derivative (a) by analogy with the formation of the 4,6-dibenzylamino-pyrano derivative (I3):-

\[
\begin{align*}
\text{PhNH}_2\text{Cl} & \xrightarrow{\text{HCl}} \text{PhNH}_2 + \text{HCl} \\
\text{HCl} & \xrightarrow{\text{H}^+ + \text{Cl}^-} \\
\end{align*}
\]

\[
\begin{align*}
\text{(I3)} & \xrightarrow{\text{H}^+} \text{Cl} - \text{HNPh} - \text{O} - \text{SR} - \text{HNPh} - \text{O} - \text{SR} - \text{Cl} + \text{H}^+ \\
\text{(a)} & \xrightarrow{\text{H}^+} \text{Cl} - \text{NPh} - \text{O} - \text{SR} - \text{NPh} - \text{O} - \text{SR} - \text{Cl} + \text{H}^+ \\
\end{align*}
\]
Then secondly, that aniline replaces the chlorine in (a) to provide the final product (20):

(a) $R=\text{PhCH}_2$

(b) $R=\text{C}_2\text{H}_5$

The $-\text{SR}$ group remained unaffected with aniline hydrochloride, but the chlorine had been replaced, which indicated the stability of the $-\text{SR}$ group towards amine hydrochloride in the type of compound (a). Indeed the $-\text{SR}$ group was unaffected by free amine in this kind of compound (alcohol product), which will be discussed later in Part II.

The pyrone structure of these products (20) was confirmed by the u.v. absorption in the 327 and 251 nm regions.

The i.r. spectra of the pyrone derivative (20) also indicated that the 2-pyrene carbonyl group was hydrogen-bonded. Indeed double hydrogen-bonding by analogy with the compound (19), as in structure (21), was strongly
indicated by the $^1$H n.m.r. spectra (Table XV) which showed two signals from NH protons at rather low field:

![Chemical Structure](image)

### (21)

#### TABLE XV

$^1$H n.m.r. spectra at compound (20) in (CDCl$_3$)

<table>
<thead>
<tr>
<th>Compound (20)</th>
<th>Line position</th>
<th>Intensity</th>
<th>Multiplicity</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>-2.11 br</td>
<td>1</td>
<td>s</td>
<td>NH at 3-position bonded</td>
</tr>
<tr>
<td></td>
<td>-1.3 br</td>
<td>1</td>
<td>s</td>
<td>4-NH bonded</td>
</tr>
<tr>
<td></td>
<td>-0.57 br</td>
<td>1</td>
<td>s</td>
<td>6 - NH</td>
</tr>
<tr>
<td></td>
<td>2.3 - 3.0</td>
<td>15</td>
<td>c</td>
<td>3 x Ph</td>
</tr>
<tr>
<td></td>
<td>4.09</td>
<td>1</td>
<td>s</td>
<td>5 - H</td>
</tr>
<tr>
<td></td>
<td>5.85</td>
<td>2</td>
<td>s</td>
<td>CH$_2$ of PhCH$_2$</td>
</tr>
<tr>
<td>b</td>
<td>-2.17 br</td>
<td>1</td>
<td>s</td>
<td>NH at 3-position bonded</td>
</tr>
<tr>
<td></td>
<td>-1.35 br</td>
<td>1</td>
<td>s</td>
<td>4- NH bonded</td>
</tr>
<tr>
<td></td>
<td>-0.62 br</td>
<td>1</td>
<td>s</td>
<td>6 - NH</td>
</tr>
<tr>
<td></td>
<td>2.75</td>
<td>10</td>
<td>c</td>
<td>2 x Ph</td>
</tr>
<tr>
<td></td>
<td>4.04</td>
<td>1</td>
<td>s</td>
<td>5 - H</td>
</tr>
<tr>
<td></td>
<td>7.05</td>
<td>2</td>
<td>q, $\frac{J}{7,1}$Hz</td>
<td>CH$_2$ of C$_2$H$_5$</td>
</tr>
<tr>
<td></td>
<td>8.68</td>
<td>3</td>
<td>q, $\frac{J}{7,1}$Hz</td>
<td>Me</td>
</tr>
</tbody>
</table>
CHAPTER V

THE FORMATION OF THE 1,3-OXAZINE PRODUCT (22)
The foregoing results, and previous experience, suggested that by heating the 2-benzylthio compound (13, \( R = \text{PhCH}_2 \)) in chloroform with 4 molecular proportions of dry benzylamine, one more than required to yield the 2,7-dibenzylamino-pyrano-oxazine (15c)-cleavage of the pyrone ring would, additionally, be affected. This occurred and the 2-benzylamino-1,3-oxazinedicarboxybenzylamide derivative (22) was obtained, but in poor yield. The major product was the disubstituted glutacondibenzyllamide (23b)(This product will be discussed later).

The loss of the pyrone ring was confirmed by the hypsochromic shift in light absorption to 222 nm.

The structure of the product (22) was confirmed by the \(^1\text{H n.m.r.}\) spectrum (Table XVI) as well by its composition and mass spectrum m/e 482).
<table>
<thead>
<tr>
<th>Line Position</th>
<th>Intensity</th>
<th>Multiplicity</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.26 br</td>
<td>1</td>
<td>s</td>
<td>NH at 5</td>
</tr>
<tr>
<td>0.83 br</td>
<td>1</td>
<td>s</td>
<td>NH at 6</td>
</tr>
<tr>
<td>1.45 br</td>
<td>1</td>
<td>s</td>
<td>2 - NH</td>
</tr>
<tr>
<td>2.7</td>
<td>15</td>
<td>c</td>
<td>3 x Ph</td>
</tr>
<tr>
<td>5.85 - 5.47</td>
<td>6</td>
<td>c</td>
<td>3 x CH₂</td>
</tr>
<tr>
<td>6.06</td>
<td>2</td>
<td>s</td>
<td>6 - CH₂</td>
</tr>
</tbody>
</table>

The lower NH which has been assigned for the NH at 5-position was because of the hydrogen-bonding with 4-C=O, and the next up is the amide NH at 6-position.
CHAPTER VI

THE FORMATION OF THE DISUBSTITUTED GLUTACONDIAMIDE DERIVATIVES (23)
When the 2-butylamino-7-morpholino compound (15b) was treated with two molecular portions of dry morpholine in boiling chloroform, the expected disubstituted glutacondiamide (23a) was produced, this structure being supported by the $^1$H n.m.r. spectrum (Table XVII) (the coupling between the NH and adjacent CH$_2$-protons of the butylamine residue facilitated a complete assignment) and mass spectrum m/e 495).

**TABLE XVII**

$^1$H n.m.r. spectra of the disubstituted glutacondiamide (23a)

<table>
<thead>
<tr>
<th>Line Position</th>
<th>Intensity</th>
<th>Multiplicity</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.77 br</td>
<td>1</td>
<td>s</td>
<td>CO-NH-CO</td>
</tr>
<tr>
<td>1.63 br</td>
<td>1</td>
<td>t</td>
<td>NH of NHB$_4$</td>
</tr>
<tr>
<td>6.35</td>
<td>24</td>
<td>c</td>
<td>12 x CH$_2$ 2,4-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-morpholine, CH$_2$OCH$_2$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>of 3 morpholine and</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-CH$_2$ and NCH$_2$ of Bu</td>
</tr>
<tr>
<td>6.7</td>
<td>4</td>
<td>c</td>
<td>CH$_2$NCH$_2$ of 3-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-morpholine</td>
</tr>
<tr>
<td>8.2 - 8.9</td>
<td>4</td>
<td>c</td>
<td>CH$_2$CH$_2$ of Bu</td>
</tr>
<tr>
<td>9008</td>
<td>3</td>
<td>t</td>
<td>ca, Me</td>
</tr>
</tbody>
</table>

The formation of the disubstituted glutacondiamide (23a) could be explained as follows.
The first molecule of morpholine presumably attacked the pyrone ring to produce the 1,3-oxazine (a) (as before) and then the second molecule of the morpholine attacked the oxazine ring of the 6-position to provide the final product (23a):

![Chemical Diagram]

(23a)

Analogously, the 7-chloro-2-ethylthio compound (13, R = C₂H₅) with five molecular proportions of dry benzylamine in boiling chloroform yielded the disubstituted glutacondibenzylamide (23b). This product was also obtained from the 2-benzylamino-7-chloro compound (14f) with four molecular proportions of dry benzylamine.
When the 1,3-oxazine derivative (22) and the 4,6-disubstituted pyrone derivative (18b) were treated with one molecular proportion of benzylamine the disubstituted glutacondibenzyllamide (23b) was also obtained (see the following reaction scheme).

\[(23) \quad (a) \quad R^1 = H, \quad R^2 = Bu, \quad R^3R^4 = (CH_2)_2O(CH_2)_2 \]

\[(b) \quad R^1 = R^3 = H, \quad R^2 = R^4 = PhCH_2 \]
Further degradation of the disubstituted glutacondibenzylamide (23b) with benzylamine

This compound (23b) was treated with an excess of benzylamine in boiling dioxan. After the solvent and excess of benzylamine had been removed, the residue was washed with ethanol. Evaporation of the washings afforded malondibenzylamide (24), m.p. and mixed m.p. 140° (with an authentic sample). The nature of the product was confirmed by its composition and I.R. and $^1H$ n.m.r. spectral characteristics.

Crystallization of the foregoing residue from ethanol afforded the acylureide product (25). The structure of this product was likewise confirmed by its composition and mass spectrum (m/e 325).

The reaction can be represented as follows:

![Chemical structure diagram]

The $^1H$ n.m.r. spectrum of compound (25) (Table XVIII) provided good evidence for the structure.
TABLE XVIII

\[^1H\] NMR spectrum of compound (25) in d\(_6\) DMSO

<table>
<thead>
<tr>
<th>Line Position</th>
<th>Intensity</th>
<th>Multiplicity</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.41 br</td>
<td>1</td>
<td>s</td>
<td>CO-NH-CO</td>
</tr>
<tr>
<td>1.36 br and 1.45 br</td>
<td>1,1</td>
<td>t,t, (J = 5.1\text{Hz})</td>
<td>2 x NH of PhCHNH</td>
</tr>
<tr>
<td>2.7</td>
<td>10</td>
<td>s</td>
<td>2 x Ph</td>
</tr>
<tr>
<td>5.62 and 5.72</td>
<td>2 + 2</td>
<td>d,d, (J = 5.1\text{Hz})</td>
<td>2 x CH(_2) of PhCH(_2)</td>
</tr>
<tr>
<td>6.69</td>
<td>2</td>
<td>s</td>
<td>CO-CH(_2)-CO</td>
</tr>
</tbody>
</table>

Malondibenzylamide (24) were obtained, mixed with a poor yield of N,N-dibenzylurea (26) (m.p. 169°C lit. 169°C, m/e 240) when the disubstituted glutacodibenzylamide (23b) was heated under reflux with benzylamine.

Proof of the formation of compound (26) comes from the i.r. absorption \(\lambda_{(\text{max.})} at 3350\text{s (NH), and 1625 and 1590 (CONH deformation) cm}^{-1}\).

The same compound (26) was also obtained, mixed with malondibenzylamide (24), from the acylureide (25) and boiling benzylamine, as follows:-

\[
\begin{align*}
\text{CO-NHCH}_2\text{Ph} & \quad \rightarrow \quad \text{CH}_2(\text{CONHCH}_2\text{Ph})_2 \\
\text{CO-NH}_2\text{CO-NHCH}_2\text{Ph} & \quad + \quad \text{PhCH}_2\text{NH}_2 \\
& \quad \rightarrow \quad \text{CO(NHCH}_2\text{Ph})_2
\end{align*}
\]
PART II

REACTIONS OF THE 7-CHLORO-2-MERCAPTO PYRANO-
OXAZINE (13) WITH WATER AND ALCOHOLS
Davis and Elvidge examined the reaction of the 7-chloro-pyrano compound (1) with water and alcohol. They found that when the compound (1, \( R = R' = \text{Ph} \)) was boiled with water it gave carbondioxide (38\% of 3 mols.), hydrogen chloride (1 mol.), acetone (1 mol.) and one mole of diphenyl ketone. But when the compound (1, \( R = R' = \text{Ph} \)) was treated with one mol. of water in dioxan at room temperature, it gave the diphenyl ketone together with the 6-chloro-4-hydroxy-pyrano acid (5). They also found (loc. cit.) by boiling the compound (1, \( R = R' = \text{Ph} \)) with 3 mols. of ethanol, that triethyl acetone-1,1,3-tricarboxylate (27) was formed together with one mol. of diphenyl ketone.

The product (27) was also obtained by boiling the 7-chloro-pyrano-oxazine (2) with three moles of ethanol. The reaction of compound (2) with water at room temperature gave product (28). The reaction of methanol with compound (2) at room temperature unexpectedly gave the 7-hydroxy-pyrano-oxazine (29) (50\%) and some of the methyl ester corresponding to product (27).
Butt has found that when the 7-chloro-pyrano compound (3) was refluxed with an excess of water, 3 moles of carbon dioxide were evolved with one mole of hydrogen chloride. He also obtained acetone-1,1,3-tricarbethoxy-late (27) together with diethylmalonate (30) when compound (3) was refluxed with an excess of ethanol.
CHAPTER VII

THE FORMATION OF 4-CHLORO-2,6-DIHYDROXYPYRIDINE (31)
AND SOME OF ITS DERIVATIVES.
The Reactions of the 7-chloro-2-mercapto-pyrano-oxazine (I3) with water

When the 7-chloro-2-ethylmercapto compound (I3, R = C₂H₅) was treated with two molecular proportions of water in dioxan under reflux for two and a half hours, evolution of carbon dioxide and ethyl mercaptan was noticed. A solid product was isolated after the reaction solvent had been removed.

It was found that the solid product gave a molecular ion with m/e 145 and a p + 2 peak which indicated the presence of one atom of chlorine. The odd molecular weight indicated the presence of an odd number of nitrogen atoms. This together with the elementary composition, showed that the product had the molecular formula C₅H₅ClNO₂.

The reaction can be written as follows:

$$\text{Cl} - \text{C₂H₅SH} \xrightarrow{2\text{H}_₂\text{O}} \text{C₅H₅ClNO₂} + \text{C₂H₅SH} + \text{CO}_₂$$

(31)

(13, R=C₂H₅)

This product was found to be 4-chloro-2,6-dihydroxy-pyridine (31) from two experiments. First, by treating the product (31) with phosphorus oxychloride in a sealed tube, 2,4,6-trichloro-pyridine (32) was obtained (m.p. 32°, Lit. m.p. 33°) with m/e 181 and p + 2, p + 4 and p + 6 peaks confirming the presence of three chlorine atoms.

It followed therefore that the precursor (31) was a chloro-dihydroxy pyridine having the functional groups in the 2-, 4- and 6-positions only. To determine the position of the chlorine atom a hydrogenolysis experiment was done. This gave glutarimide (33) (m_p. 154°, Lit. m.p. 154° - 155°) with m/e 113, which demonstrated that the chlorine atom in the product (31) had been at position 4.
The 4-chloro-2,6-dihydroxy pyridine was also obtained from each of the 7-chloro-2-mercapto compounds (13, \( R = \text{Ph and PhCH}_2 \)) by treating them with two molecular proportions of water.

\[
\begin{align*}
\text{(13)} & \quad \text{Cl} \quad \text{Cl} \\
\text{Cl} & \quad \text{N} \quad \text{Cl} \\
\text{Cl} & \quad \text{N} \quad \text{Cl} \\
\text{Cl} & \quad \text{N} \quad \text{Cl} \\
\end{align*}
\]

The 4-chloro-2,6-dihydroxy pyridine could exist in more than one tautomeric form by analogy with 2,6-dihydroxy pyridine.\(^{26}\)
Now Spinner and White\textsuperscript{27} compared the ultra-violet absorption of 2-methoxypyridine and of 1-methyl-2-pyridone with that of 2-hydroxypyridine itself and found that the last two compounds were similar and had maxima at considerably longer wavelengths than 2-methoxypyridine. This showed that the hydroxy-tautomer (a) was not favoured, the pyridone form (b) predominating.
They also found that 2,6-dihydroxypyridine in neutral shows u.v. absorption at 332 and 234 nm., which indicated clearly that it is predominately in the 2-pyridone lactam form and not the dihydroxy form. By analogy, 4-chloro-2,6-dihydroxypyridine (31) which absorbs at 316 and 235 nm., also exists predominately as the 2-pyridone tautomer.

Mason showed by infrared spectroscopy that 2-hydroxypyridine existed predominately in the amide form in the solid state and in solution (which, respectively, showed strong carbonyl absorption at 1650 and 1659 cm$^{-1}$).

Spinner and White also showed by infrared spectroscopy that 2,6-dihydroxypyridine existed predominately in the 2-pyridone form in the solid state (Table XIX). The similar absorption shown by the 4-chloro-2,6-dihydroxypyridine (31) in turn shows that this exists predominately in the amide form in the solid state (Table XIX).

<table>
<thead>
<tr>
<th>TABLE XIX</th>
</tr>
</thead>
<tbody>
<tr>
<td>I.R. Spectrum</td>
</tr>
<tr>
<td>$\nu_{\text{max}, \text{cm}^{-1}}$</td>
</tr>
<tr>
<td>Structure</td>
</tr>
<tr>
<td>(a)</td>
</tr>
<tr>
<td>(b)</td>
</tr>
</tbody>
</table>

a, in potassium chloride disc.  
b, in Nujol.
The breadth of the infrared absorptions from solid 2,6-dihydroxypyridine was taken by Spinner and White to indicate strong hydrogen bonding.

Treatment of 4-chloro-2,6-dihydroxypyridine with diazomethane (in excess) gave a mixture of 4-chloro-2,6-dimethoxypyridine (34) (45%) and 4-chloro-6-methoxy-1-methylpyridine-2(1H)-one (34a) (45%).

\[ \text{Cl} \quad \overset{\text{CH}_2\text{N}_2}{\longrightarrow} \quad \text{Cl} \]

\[ \text{(31)} \quad \text{(34a)} \quad \text{(34)} \]

The light absorption of the former compound (34) in Table XX was similar to that of 2,6-diethoxypyridine (\( \lambda_{\text{max}} = 217, 277 \text{ nm} \), see ref. 27), whereas that of the latter compound (34a) was similar to that of the 4-chloro-2,6-dihydroxypyridine (31). Clearly, compound (31) exists predominately in the pyridone form.

**TABLE XX**

U.V. spectra in 96% ethanol

<table>
<thead>
<tr>
<th>Compound</th>
<th>( \lambda_{\text{max}} ) nm</th>
<th>( \varepsilon \times 10^{-3} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>34a</td>
<td>308</td>
<td>8.0</td>
</tr>
<tr>
<td></td>
<td>233</td>
<td>4.18</td>
</tr>
<tr>
<td>34</td>
<td>278</td>
<td>11.21</td>
</tr>
<tr>
<td></td>
<td>130</td>
<td>6.34</td>
</tr>
</tbody>
</table>
Table XXI gives infrared data for those compounds which support the previous conclusions.

**TABLE XXI**
I.R. (Nujol)

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>$\gamma_{\text{max}}$ cm$^{-1}$</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>(34a)</td>
<td>3060 w</td>
<td>CH</td>
</tr>
<tr>
<td></td>
<td>1658 s</td>
<td>2- C=O</td>
</tr>
<tr>
<td></td>
<td>1582 m)</td>
<td>C=C</td>
</tr>
<tr>
<td></td>
<td>1542 ( )</td>
<td></td>
</tr>
<tr>
<td>(34)</td>
<td>3090 w</td>
<td>CH</td>
</tr>
<tr>
<td></td>
<td>1592 s)</td>
<td>C=C and C=N</td>
</tr>
<tr>
<td></td>
<td>1585 s)</td>
<td></td>
</tr>
</tbody>
</table>

The $^1$H n.m.r. spectra of the 4-chloro-pyridone (34a) and 4-chloro-2,6-dimethoxypyridine (34) are recorded in Table XXII.
TABLE XXII

Proton magnetic resonance data for the products (34a) and (34)

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>Line Positions</th>
<th>Intensity</th>
<th>Multiplicity</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>(34a) in CDCl₃</td>
<td>3.76</td>
<td>1</td>
<td>d, J 2 Hz</td>
<td>5-H</td>
</tr>
<tr>
<td></td>
<td>4.43</td>
<td>1</td>
<td>d, J 2 Hz</td>
<td>3-H</td>
</tr>
<tr>
<td></td>
<td>6.10</td>
<td>3</td>
<td>s</td>
<td>6-O-Me</td>
</tr>
<tr>
<td></td>
<td>6.60</td>
<td>3</td>
<td>s</td>
<td>1-N-Me</td>
</tr>
<tr>
<td>(34) in CCl₄</td>
<td>3.73</td>
<td>2</td>
<td>s</td>
<td>3,5-H</td>
</tr>
<tr>
<td></td>
<td>6.13</td>
<td>6</td>
<td>s</td>
<td>2,6-O-Me</td>
</tr>
</tbody>
</table>

The assignments of the chemical shift of 3.76 to 5-H and 4.43 to 3-H in compound (34a) had been made by comparison with compound (34) where the substituents at the 2- and 6-position are both methoxyl groups, and the chemical shift of the equivalent 3- and 5-protons is 3.76. That this comparison was in fact misleading was found by using the shift reagent Eu(fod)₃, which was added progressively (see Fig. 4). From the progressive changes in the chemical shift (down-field) for the various protons it was apparent that the most affected protons were those of the N-CH₃ group and the low-field one of the 3- or 5-protons. This last was necessarily the one closest to the place of attachment of the reagent, i.e. the 3-H, near the 2-carbonyl (Fig. 4, curves 2 and 4). Therefore, 3-H has the shift 3.76 and 5-H has the shift 4.43.
The chemical shift of the methoxy group protons in compound (34a) was assigned by comparison with the chemical shift of the same group in compound (34). Therefore the signal at 6.6 in compound (34a) is assigned to the N-CH₃ protons. Their shift is similar to that of the N-CH₃ protons of N-methyl-2-pyridone. Good evidence for the assigning of N-CH₃ at 6.6 comes from running the spectrum of compound (34a) by FT n.m.r. (Bruker WH 90) (Fig. 4a). The spectrum showed a broader signal at 6.6 than at 6.1. The former signal is therefore to be assigned to the N-CH₃ group, the protons in this group being relaxed relative to those in the OMe group by the adjacent nitrogen quadrupole nucleus.

The ¹H n.m.r. spectrum of 4-chloro-2,6-dihydroxypyridine (31) showed a signal at 4.2 and one at the low field of 0.2 (in D₆ DMSO). This spectrum suggests that the compound (31) exists in the form (31a). But as mentioned before, it has been proved by using u.v. and i.r. that 2,6-dihydroxypyridine exists in the pyridone form. Therefore compound (31) is very likely to undergo rapid tautomerism (b) ⇌ (c), so that the 2 ring protons are made equivalent and the OH and NH signals have coalesced.
Fig. (4), (a) $^1$H.n.m.r spectra of compound (3a); (b) and (c) the $^1$H.n.m.r. spectra after the addition of Eu(fod)
CHAPTER VIII

THE FORMATION OF 6-AMINO-4-CHLORO-2-PYRANO DERIVATIVES (35) AND 4-CHLORO-2,6-DIHYDROXYPYRIDINE-3-CARBOXYLIC ESTERS (44)
As discussed before (Chapter 7), reaction of the 7-chloro-2-mercapto compound (13) with two molecular proportions of water in refluxing dioxan gave, unexpectedly, 4-chloro-2,6-dihydroxypyridine (31). Therefore an attempt was made to obtain an intermediate product using milder reaction conditions. To achieve this, the reaction was done with the 7-chloro-2-ethyl-mercapto compound (13, R = C₂H₅) using one molecular proportion of water at the same concentration in dioxan at 80 - 85° for one and a half hours. The product was a crystalline solid, C₆H₆ClNO₂S, as indicated by analysis and the mass spectrum. Thus the reaction could be written as follows:—

\[
\text{Cl} \quad \text{SR} \quad \xrightarrow{\text{C₆H₆ClNO₂S + CO₂}} \quad (35a)
\]

(13, R=C₂H₅)

From the u.v. absorption (Table XXII), this product was evidently a pyrone.

Similarly, the 7-chloro-2-mercapto compounds (13, R = PhCH₂ and p-Cl-C₆H₄CH₂) were converted into corresponding pyrones. These were eventually found to have the structure (35).

(35)

a, R = C₂H₅
b, R = PhCH₂
c, R = p-Cl-C₆H₄CH₂
That these compounds had longer wavelength absorption (330-340 nm region) than 6-chloro-3-carboxy-4-hydroxy-2-pyrone, but similar absorption to the 7-aminopyrano-dioxins suggested that they might be aminopyrones.

**TABLE XXII**

Light absorption of compound (35)

<table>
<thead>
<tr>
<th>Compound 35</th>
<th>$\lambda_{max}$ nm</th>
<th>$\varepsilon \times 10^{-3}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(CH$_3$CN)</td>
<td>297</td>
<td>12.8</td>
</tr>
<tr>
<td></td>
<td>337.5</td>
<td>14.76</td>
</tr>
<tr>
<td>(b)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(CH$_3$CN)</td>
<td>302.5</td>
<td>13.8</td>
</tr>
<tr>
<td></td>
<td>343</td>
<td>17.6</td>
</tr>
<tr>
<td>(c)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(CHCl$_3$)</td>
<td>308</td>
<td>18.6</td>
</tr>
<tr>
<td></td>
<td>331</td>
<td>20.9</td>
</tr>
</tbody>
</table>

In the infrared, the new compounds as Nujol mulls (fig. 5) showed maxima at 3275 and 3140 cm$^{-1}$ for an NH$_2$ group, at 1720 cm$^{-1}$ for the 2- C=O, and at 1625 sh for the carbonyl of a thiolester function. The solution spectrum (in CHCl$_3$) of compound (35b) showed a change in the 2- C=O absorption to 1750 cm$^{-1}$ which indicated that intermolecular hydrogen bonding as in (36) in the solid, had been broken in solution.
Only a very limited amount of data are available on thiol esters, but ClavK and J0 Wons31 had found for a number of simple open-chain thiol esters that the carbonyl frequencies occurred at 1675 cm\(^{-1}\), but the effect of hydrogen bonding to the carbonyl had not been investigated. Consequently it was necessary to prepare ethylthioanthranilate (37)\(^{32}\) (b.p. 172\(^{\circ}\)/15 mm., n\(_D\) 25 = 1.638. L.t. b.p. 172\(^{\circ}\)/15 mm., n\(_D\) 25 = 1.634) as a model for the compounds (35). Ethyl thioanthranilate (as a liquid (Fig. 6) showed bands at 3500 and 3400 cm\(^{-1}\) from the \(\text{NH}_2\) group and very weak absorption at 1730 cm\(^{-1}\). The carbonyl absorption was at 1645 cm\(^{-1}\). Rather clearer was the solution spectrum (Fig. 7), and comparison with the spectrum of ethylanthranilate\(^{33}\) (Fig. 8) was helpful. It thus became clear that the 1645 cm\(^{-1}\) peak (Figures 5 and 6) was from the bonded
carbonyl of the thiol ester in compound (37).

\[
\text{(37)}
\]

It was noticed that the NH\textsubscript{2} absorption in compound (35) (Fig. 5 and Table XXIV) was at a lower wavenumber than in compound (37) (Fig. 6). This shift in position is probably characteristic of β-aminopyrones. Thus the NH\textsubscript{2} group in compound (35) has absorption at a similar wavenumber to the NH of 6-N-methyl- or 6-N-ethyl-3,4-diphenyl-2-pyrone\textsuperscript{34} (38) (Table XXIV) which absorbs at 3270 cm\textsuperscript{-1}.

\[
\text{(38)}
\]

a, R = Me-

b, R = C\textsubscript{2}H\textsubscript{5}
<table>
<thead>
<tr>
<th>Compound No.</th>
<th>( \nu_{\text{max.}} \text{ (cm}^{-1}) )</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>35a (Nujol)</td>
<td>3275 m) 3140 m) 1720 s 1625 sh 1610 m) 1595 s) 1550 m)</td>
<td>NH(_2), 2-C=O hydrogen bonded C=O of thiol-ester</td>
</tr>
<tr>
<td>32b (KBr)</td>
<td>3270 1695 1605 ) 1595 )</td>
<td>NH 2-C=O C=C</td>
</tr>
<tr>
<td>37 (Liquid)</td>
<td>3500 m) 3400 m) 2980 w 1645 s 1728 w) 1620 s) 1590 s) 1560 m)</td>
<td>NH(_2), C=O of the thiol-ester C=C</td>
</tr>
<tr>
<td>Ethylanthra-nilate (Liquid)</td>
<td>3497 m) 3378 m) 2967 w 1695 s 1695 s) 1590 s) 1565 m)</td>
<td>NH(_2), C=O of the ester C=C</td>
</tr>
</tbody>
</table>
The infrared spectra of compounds (35) could not be explained on the basis of the isomeric 4-chloro-2,6-dihydroxypyridine (3-thiolester structures (39).

![Diagram of compounds](image)

Fig. 5 - I.R. spectrum of compound (35a) (Nujol)
Fig. 6 - I.R. spectrum of ethylthidanthranlate (as a liquid).

Fig. 7 - Solution I.R. spectrum of ethylthidanthranlate
Fig. 8 - I.R. spectrum of ethyl anthranilate (as liquid)
The 
characteristics of the compound (35) are recorded in Table XXV. The ring-proton chemical shift is reasonable for an aminopyrone, but at too high a field for a pyridone such as (39).

<table>
<thead>
<tr>
<th>Line Position</th>
<th>Intensity</th>
<th>Multiplicity</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.77 b</td>
<td>2</td>
<td>s</td>
<td>NH₂</td>
</tr>
<tr>
<td>4.30</td>
<td>1</td>
<td>s</td>
<td>3-NH</td>
</tr>
<tr>
<td>7.07</td>
<td>2</td>
<td>q, J 7.6Hz</td>
<td>CH₂ of C₂H₅</td>
</tr>
<tr>
<td>8.77</td>
<td>3</td>
<td>t, J 5.6Hz</td>
<td>CH₃</td>
</tr>
</tbody>
</table>

Chemical evidence in support of the structure (35), which ruled out structure (39) was the reaction of compound (35a) with an excess of benzylamine at room temperature. This produced ethyl-4-benzyl carbamoyl-3-benzylamino-2-carbamoyl but-2-enthiolate (40), C₂₂H₂₆N₀₃S₂. The mass spectrum of the compound (40) showed the expected molecular ion with m/e 411. Ring-opening of the pyrone (35a) had therefore occurred together with replacement of the chlorine atom by benzylamine.
There were no direct indications as to whether these processes occurred simultaneously, or consecutively and in which order. However, in previous work\textsuperscript{1,2,3} on the chloro-pyrone compounds (1, 2, 3) it was found that the chlorine atom is more reactive towards amines than the pyrone ring. Hence the above scheme is probably correct.

The $^1$H n.m.r. spectrum of compound (40) afforded the data recorded in Table XXVI. This supported the structure.
### TABLE XXVI

$^1$H n.m.r. spectra of compound (40)
in (CDCl$_3$)

<table>
<thead>
<tr>
<th>Line Position ($\delta$)</th>
<th>Intensity</th>
<th>Multiplicity</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>-1.01 and 1.53</td>
<td>2</td>
<td>br</td>
<td>2 x NH</td>
</tr>
<tr>
<td>4.05</td>
<td>2</td>
<td>br</td>
<td>2 x NH</td>
</tr>
<tr>
<td>2.74</td>
<td>10</td>
<td>s</td>
<td>2 x Ph</td>
</tr>
<tr>
<td>5.26 and 5.60</td>
<td>4</td>
<td>d, d, $J$ 6Hz</td>
<td>2 x CH$_2$ of PhCH$_2$</td>
</tr>
<tr>
<td>6.61</td>
<td>2</td>
<td>s</td>
<td>4-CH$_2$</td>
</tr>
<tr>
<td>7.12</td>
<td>2</td>
<td>q, $J$ 6.8Hz</td>
<td>CH$_2$ of C$_2$H$_5$S</td>
</tr>
<tr>
<td>8.74</td>
<td>3</td>
<td>t, $J$ 6.8Hz</td>
<td>CH$_3$</td>
</tr>
</tbody>
</table>

The infrared spectrum of compound (40) (Fig. 9) showed strong NH absorption at 3410, 3330 and 3200 cm$^{-1}$, a band at 1632 cm$^{-1}$ from the hydrogen-bonded amido-carbonyl group and a shoulder at 1645 cm$^{-1}$ from the hydrogen-bonded carbonyl of the thiol-ester, indicating the form (41).
Fig. 9 - I.R. spectrum of compound (41) (Nujol)
Reaction of the 6-amino-4-chloro-2-pyrone (35) with water

When the compound (35) was refluxed with water in dioxan for two and a half hours, 4-chloro-2,6-dihydroxypyridine (31) was obtained, identified by m.p., and mixed m.p., and i.r. and mass spectrum, with the product prepared from the 7-chloro-2-mercapto compound (13) which had m.p. 218° (decomp.), and m/e 145.

\[
\begin{align*}
\text{RS} & \quad \text{Cl} \\
\text{NH}_2 & \quad \text{O} \\
\text{C}=\text{O} & \quad \rightarrow \\
\text{HO} & \quad \text{NH} \\
\text{Cl} & \quad \text{+ RSH + CO}_2
\end{align*}
\]

(35a) and (35b)

(31)

The formation of compound (31) from (35) could be explained as follows:

First the water hydrolysed the thiol-ester giving the corresponding pyrone acid (a) with liberation of RSH. Then the mercaptan opened the pyrone ring which gave the glutaric amide-thiol-ester derivative (b), the open chain intermediate (b) could cyclise followed by decarboxylation, or decarboxylation could occur before the cyclisation, to give the 2,6-dihydroxypyridine (31).
It was found by Errera\(^\text{36}\) that the 2,6-dihydroxypyridine derivative (42) could be prepared by refluxing a glutarconic dinitrile in dilute hydrochloric acid or in ethyl alcohol,\(^\text{37}\) or by treating the corresponding amide ester at 190°.\(^\text{38}\)
Hence the formation of compound (31) from compound (35) was supported.

Reaction of the 6-amino-4-chloro-2-pyrano derivative (35) with absolute ethyl alcohol:

The reaction was done in dioxan under reflux for two and a half hours. The product was found to be 4-chloro-2,6-dihydroxy-3-ethoxy-carbonylpyridine (44a).
The formation of compound (44a) from (35a) could be explained as below.

First the exchange of the thiol-ester group took place with liberation of ethyl mercaptan. Ring opening and cyclisation could then be expected as discussed before in respect of the formation of compound (31) from compound (35).

Compound (44) was also obtained directly from the 7-chloro-2-mercapto compound (13) by refluxing it with absolute ethyl or methyl alcohol in dioxan for two and a half hours.
The light absorption of compounds (44) were measured and compared with the light absorption of compounds (35) (Fig. 10) which were pyrones structure. This comparison supported the structure of the compounds (44) as pyridine type and not pyrone, e.g. (45).
The infrared spectrum was in good agreement with the structure (44) and did not fit structure (45). There was no NH$_2$ absorption, as in compound (35), and no pyrone carbonyl absorption. The spectrum was more like that of 2-chloro-2,4-dihydroxy-3-ethoxycarbonyl pyridine (46) (Table XXVII).

![Structure](image)

### TABLE XXVII

I.R. spectra of compounds (44) and (46)

<table>
<thead>
<tr>
<th>Structure</th>
<th>NH/OH</th>
<th>C=O</th>
<th>C=C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3230-2630 br</td>
<td>1657s</td>
<td>1600m</td>
</tr>
<tr>
<td></td>
<td>3200-2560 br</td>
<td>1670s</td>
<td>1600m</td>
</tr>
<tr>
<td></td>
<td>3200-2550 br</td>
<td>1665s</td>
<td>1600m</td>
</tr>
<tr>
<td></td>
<td>3200-2630 br</td>
<td>1653sh</td>
<td>1580sh</td>
</tr>
<tr>
<td></td>
<td>3200-2560 br</td>
<td>1656sh</td>
<td>1580sh</td>
</tr>
<tr>
<td></td>
<td>3200-2550 br</td>
<td>1656</td>
<td>1580sh</td>
</tr>
</tbody>
</table>

The infrared spectrum of compound (44) indicated a strong hydrogen bonding to the carbonyl group of the ester.
Previous findings on the 2,6-dihydroxypyridine compounds suggested that the compound (44) could exist in two forms, the dihydroxypyridine form (44a) and the hydroxypyridone form (44β). The ultra-violet absorption (Fig. 10) showed that compound (44) resembled compounds (31), (34a) and (34) and so existed predominantly in the pyridone form (44β).

The \(^1\text{H} \text{n.m.r.}\) spectrum of compound 44 gave the data shown in Table XXVIII which agreed with the suggested structure.

### TABLE XXVIII

\(^1\text{H} \text{n.m.r.}\) spectrum of compound (44)

in \(d_6\) DMSO

<table>
<thead>
<tr>
<th>Compound</th>
<th>Line Position</th>
<th>Intensity</th>
<th>Multiplicity</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(\ell)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a</td>
<td>1.75</td>
<td>2</td>
<td>br</td>
<td>NH/OH and OH</td>
</tr>
<tr>
<td></td>
<td>4.25</td>
<td>1</td>
<td>s</td>
<td>5-H</td>
</tr>
<tr>
<td></td>
<td>5.78</td>
<td>2</td>
<td>q, (J=6.8\text{Hz})</td>
<td>(\text{CH}_2) of (\text{C}_2\text{H}_5)-0</td>
</tr>
<tr>
<td></td>
<td>8.7</td>
<td>3</td>
<td>t, (J=6.8\text{Hz})</td>
<td>(\text{CH}_3)</td>
</tr>
<tr>
<td>b</td>
<td>1.2</td>
<td>2</td>
<td>br</td>
<td>NH/OH and (-\text{OH})</td>
</tr>
<tr>
<td></td>
<td>4.2</td>
<td>1</td>
<td>s</td>
<td>5-H</td>
</tr>
<tr>
<td></td>
<td>6.25</td>
<td>3</td>
<td>s</td>
<td>(\text{CH}_3)</td>
</tr>
</tbody>
</table>
Fig. 10  u.v. spectra of compounds (35a---), (44b ----), (31 xxx), (34a - - - -) and (38 .. .. .. ..)
Reaction of the 4-chloro-2,6-dihydroxy-3-ethoxycarbonylpyridine (44) with benzylamine

The reaction was done in dry dioxan with an excess of benzylamine under reflux. The product was found to be 4-benzylamino-2,6-dihydroxy-3-ethoxycarbonylpyridine (47), not an open-chain glutaric diamide derivative (40) as obtained from the pyrone (35) when treated with benzylamine. Therefore the compound (44) has the pyridine structure not a pyrone structure.

It was found by Thorpe\textsuperscript{38} that the 2,6-dihydroxypyridine ring is stable towards amines and even strong alkali (it is stable when it fused with sodium hydroxide).

\[
\begin{align*}
\text{Cl} & \quad \text{CO}_2\text{C}_2\text{H}_5 \\
\text{HO} & \quad \text{PhCH}_2\text{NH}_2 \\
\text{OH} & \\
\end{align*}
\]

(44) \quad \text{PhCH}_2\text{NH}_2 \quad \text{Cl} \quad \text{CO}_2\text{C}_2\text{H}_5 \\

(47)

The $^1$H n.m.r. spectrum of compound (47) (Table XXIX) confirmed that only one mole of the benzylamine had interacted replacing the chlorine atom. In the benzylamino derivative (47) the 5-H signal had moved to $\tau$ 4.98 from $\tau$ 4.02 in compound (44), a shift of +0.78 ppm which agrees with the replacement of chlorine by amine (0.7).\textsuperscript{51}
**TABLE XXIX**

$^1$H n.m.r. spectrum of compound (47) in $d_6$ DMSO

<table>
<thead>
<tr>
<th>Line Position</th>
<th>Intensity</th>
<th>Multiplicity</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.80</td>
<td>3</td>
<td>br</td>
<td>NH/OH</td>
</tr>
<tr>
<td>2.90</td>
<td>5</td>
<td>s</td>
<td>Ph</td>
</tr>
<tr>
<td>4.98</td>
<td>1</td>
<td>s</td>
<td>5-H</td>
</tr>
<tr>
<td>5.95</td>
<td>2</td>
<td>q, J 7Hz</td>
<td>$\text{CH}_2$ of $\text{C}_2\text{H}_5$</td>
</tr>
<tr>
<td>5.99</td>
<td>2</td>
<td>s</td>
<td>$\text{CH}_2$ of PhCH$_2$</td>
</tr>
<tr>
<td>8.82</td>
<td>3</td>
<td>t, J 7Hz</td>
<td>CH$_3$</td>
</tr>
</tbody>
</table>

The infrared spectrum of compound (47) (Table XXX) also supported the structure, which does not show much difference from the spectrum of compound (44).

**TABLE XXX**

I.R. spectra of compound (47) (Nujol)

<table>
<thead>
<tr>
<th>$\nu_{\text{max}}$ cm$^{-1}$</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>3450 b</td>
<td>H$_2$O</td>
</tr>
<tr>
<td>3110 w</td>
<td>NH of PhCH$_2$NH</td>
</tr>
<tr>
<td>3180-2600</td>
<td>NH/OH hydrogen-bonded</td>
</tr>
<tr>
<td>1660 s (b)</td>
<td>C=O hydrogen-bonded of the ester</td>
</tr>
<tr>
<td>1640 s (b)</td>
<td>C=O of the pyridone</td>
</tr>
<tr>
<td>1600 m)</td>
<td>C=C</td>
</tr>
<tr>
<td>1555 m)</td>
<td></td>
</tr>
</tbody>
</table>
Compound (47) had light absorption (Fig. 11) similar to the light absorption of compound (44) (Fig. 10), again supporting the structure.

The hydrolysis of compound (44) with hydrochloric acid

An attempt was made to hydrolyse 4-chloro-2,6-dihydroxy-3-ethoxy-carbonylpyridine (44) with 2N-hydrochloric acid by refluxing for two and a half hours in dioxane. 4-Chloro-2,6-dihydroxypyridine was obtained, together with some of the unreacted starting material.

\[
\begin{align*}
\text{Cl} & \quad \text{CO}_2 \text{R}^1 \\
\text{HO} & \quad \text{N} \\
\text{HO} & \quad \text{OH} \\
(44) & \\
\end{align*}
\]

\[
\begin{align*}
\text{H}_2\text{O} & \quad \rightarrow \\
\text{Cl} & \quad \text{CO}_2 \uparrow + \text{R}^1\text{OH} \\
\text{HO} & \quad \text{N} \\
\text{HO} & \quad \text{OH} \\
(31) & \\
\end{align*}
\]
CHAPTER IX

FORMATION OF THE 6-N-ACYL-4-HALO-2-PYRONE (48) and (49)

AND SOME OF ITS REACTIONS
Yet another unexpected pyrone product was obtained by treating the 7-chloro-2-mercapto compound (13, $R = C_2H_5$) with two mols of water in dry dioxan at 80° for one and a half hours and by passing dry hydrogen chloride through the reaction mixture. The product gave a molecular ion with m/e 233 and an isotopic p + 2 peak which indicated the presence of one chlorine atom and a molecular formula, $C_{8}H_{8}ClNO_{3}S$. The product was therefore isomeric with compound (35a). Further evidence led to the pyrone structure (48a).

\[ \text{(13, } R = C_2H_5) \xrightarrow{\text{reaction}} \text{(48a)} \]

The above reaction was carried out also with 2-benzyl mercapto-7-chloro-compound (13, $R = PhCH_2$) and the corresponding pyrone product (48b) was obtained.

\[ \text{(48b)} \]

In the first experiment, dry hydrogen bromide was used instead of hydrogen chloride and the 4-bromo derivative (49) was obtained.

\[ \text{(49)} \]
The pyrone type of structure for compounds (48) and (49) was supported by their chemical properties and by spectroscopic information. In the ultra-violet (Table XXXI), compounds (48) showed absorption at longer wave-lengths than the N-(ethylthiocarbonyl) 2-pyridone (50) (335 nm). However, compounds (48) absorb in a similar region to the 6-amino-4-chloro-3-ethylthiocarbonyl-2-pyrene (35).

![Pyrene Structure](image_url)

**TABLE XXXI**

<table>
<thead>
<tr>
<th>Compounds</th>
<th>( \lambda_{\text{max}} ) nm</th>
<th>( \varepsilon \times 10^{-3} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>242.5</td>
<td>9.24</td>
</tr>
<tr>
<td></td>
<td>341</td>
<td>14.7</td>
</tr>
<tr>
<td></td>
<td>380</td>
<td>4.8</td>
</tr>
<tr>
<td>b</td>
<td>241</td>
<td>9.02</td>
</tr>
<tr>
<td></td>
<td>341</td>
<td>15.26</td>
</tr>
<tr>
<td></td>
<td>378</td>
<td>2.46</td>
</tr>
</tbody>
</table>

The infrared of compounds (48) were also recorded (Table XXXII). The assignment of the band at 1713 cm\(^{-1}\) to the 2-C=O was supported by
the corresponding assignment for compound (38)\textsuperscript{34} which absorbs at 1695 cm\textsuperscript{-1} (KBr). This absorption of the 2-C=O in compounds (48) moved to 1750 cm\textsuperscript{-1} when the NH group had been methylated (the methylation products will be discussed later). This indicated intermolecular hydrogen bonding of the 2-C=O group to the NH. The assignment of the band at 1691 cm\textsuperscript{-1} in compound (48) to the carbonyl group of the NH\textsubscript{2}CO\textsubscript{2}H\textsubscript{2} group was made by analogy with compound (50)\textsuperscript{39} which absorbs at 1695 cm\textsuperscript{-1} and 1667 cm\textsuperscript{-1} where the latter is most likely to be the pyridone-2-carbonyl absorption.

TABLE XXXII
Infrared absorption of compounds (48) (Nujol)

<table>
<thead>
<tr>
<th>Compound</th>
<th>(\nu\text{ cm}^{-1})</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3180 w)</td>
<td>NH</td>
</tr>
<tr>
<td></td>
<td>3120 w)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1713 s</td>
<td>2-C=O, hydrogen bonded</td>
</tr>
<tr>
<td></td>
<td>1691 s</td>
<td>C=O of NH\textsubscript{2}CO\textsubscript{2}H\textsubscript{2}</td>
</tr>
<tr>
<td></td>
<td>1617 m)</td>
<td>C=C</td>
</tr>
<tr>
<td></td>
<td>1550 b)</td>
<td></td>
</tr>
<tr>
<td>b</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3180 w)</td>
<td>NH</td>
</tr>
<tr>
<td></td>
<td>3135 w)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1713 s</td>
<td>2-C=O, hydrogen bonded</td>
</tr>
<tr>
<td></td>
<td>1690 s</td>
<td>C=O of NH\textsubscript{2}CO\textsubscript{2}Ph</td>
</tr>
<tr>
<td></td>
<td>1622 m)</td>
<td>C=C</td>
</tr>
<tr>
<td></td>
<td>1617 m)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1555 s)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1542 s)</td>
<td></td>
</tr>
</tbody>
</table>
The $^1$H n.m.r. spectra of compounds (48) yielded the data recorded in Table XXXIII.

### TABLE XXXIII

$^1$H n.m.r. characteristics of compounds (48)
in d$_6$ DMSO

<table>
<thead>
<tr>
<th>Compound</th>
<th>Line Position</th>
<th>Intensity</th>
<th>Multiplicity</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>-1.91</td>
<td>1</td>
<td>br</td>
<td>NH</td>
</tr>
<tr>
<td></td>
<td>3.31 and 3.81</td>
<td>1,1</td>
<td>d,d, $\ddot{J}$ 1.7Hz</td>
<td>3,5-H</td>
</tr>
<tr>
<td></td>
<td>7.11</td>
<td>2</td>
<td>q, $\ddot{J}$ 7Hz</td>
<td>$\text{CH}_2$ of $\text{C}_2\text{H}_5$-</td>
</tr>
<tr>
<td></td>
<td>8.79</td>
<td>3</td>
<td>t, $\ddot{J}$ 7Hz</td>
<td>$\text{CH}_3$</td>
</tr>
<tr>
<td>b</td>
<td>-2.10</td>
<td>1</td>
<td>br</td>
<td>NH</td>
</tr>
<tr>
<td></td>
<td>2.69</td>
<td>5</td>
<td>s</td>
<td>Ph</td>
</tr>
<tr>
<td></td>
<td>3.34 and 3.83</td>
<td>1,1</td>
<td>d,d, $\ddot{J}$ 1.7Hz</td>
<td>3,5-H</td>
</tr>
<tr>
<td></td>
<td>5.85</td>
<td>2</td>
<td>s</td>
<td>$\text{CH}_2$ of $\text{PhCH}_2$</td>
</tr>
</tbody>
</table>

Reactions of compounds (48) with diazomethane

The reaction was done in diethyl ether with an excess of diazomethane and yielded the 6-N-methyl-4-chloro-2-pyrone derivatives (51).
It was noticed from infrared measurement (Table XXXIV) that the 2-\text{C=O} absorption had shifted to a higher wavenumber with respect to compounds (48) (from 1713 to 1750 cm$^{-1}$) and that the absorption of the side chain carbonyl had moved to a lower wavenumber (from 1691 to 1678 cm$^{-1}$).

TABLE XXXIV

I.R. absorption of compounds (51) in Nujol

<table>
<thead>
<tr>
<th>Compound</th>
<th>$v_{\text{max}}$ cm$^{-1}$</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3080 w</td>
<td>CH</td>
</tr>
<tr>
<td></td>
<td>1750 s</td>
<td>2-\text{C=O}</td>
</tr>
<tr>
<td></td>
<td>1678 s</td>
<td>C=O of \text{NCO}SC\text{H}_5</td>
</tr>
<tr>
<td></td>
<td>1609 m)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1590 m)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1535 s)</td>
<td>C=C</td>
</tr>
<tr>
<td></td>
<td>1522 s)</td>
<td></td>
</tr>
<tr>
<td>b</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3060 sh</td>
<td>CH</td>
</tr>
<tr>
<td></td>
<td>1736 s</td>
<td>2-\text{C=O}</td>
</tr>
<tr>
<td></td>
<td>1678 s</td>
<td>C=O of \text{NCO}SC\text{H}_5 Ph</td>
</tr>
<tr>
<td></td>
<td>1640 w)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1610 sh)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1600 m)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1535 s)</td>
<td>C=C</td>
</tr>
<tr>
<td></td>
<td>1522 s)</td>
<td></td>
</tr>
</tbody>
</table>
The $^1$H n.m.r. spectra of compounds (54) (Table XXXV) agreed with the structure; the N-Me signal was at $\tau$ 6.61 (in CCl$_4$).

### TABLE XXXV

$^1$H n.m.r. spectra of compounds (51) in CCl$_4$

<table>
<thead>
<tr>
<th>Compound</th>
<th>Line Position</th>
<th>Intensity</th>
<th>Multiplicity</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>3.30 and 4.02</td>
<td>1,1</td>
<td>d, d, $\chi$ 1.7Hz</td>
<td>3,5-H</td>
</tr>
<tr>
<td></td>
<td>6.61</td>
<td>3</td>
<td>s</td>
<td>N-CH$_3$</td>
</tr>
<tr>
<td></td>
<td>7.06</td>
<td>2</td>
<td>q, $\chi$ 7Hz</td>
<td>CH$_2$ of C$_2$H$_5$S</td>
</tr>
<tr>
<td></td>
<td>8.68</td>
<td>3</td>
<td>t, $\chi$ 7Hz</td>
<td>CH$_3$</td>
</tr>
<tr>
<td>b</td>
<td>2.76</td>
<td>5</td>
<td>s</td>
<td>Ph</td>
</tr>
<tr>
<td></td>
<td>3.29 and 4.01</td>
<td>1,1</td>
<td>d, d, $\chi$ 1.7Hz</td>
<td>3,5-H</td>
</tr>
<tr>
<td></td>
<td>5.86</td>
<td>2</td>
<td>s</td>
<td>CH$_2$- of PhCH$_2$</td>
</tr>
<tr>
<td></td>
<td>6.61</td>
<td>3</td>
<td>s</td>
<td>N-CH$_3$</td>
</tr>
</tbody>
</table>

To assign the chemical shift of the 3,5-protons in compounds (51), the Eu (fod)$_3$ reagent was added progressively to the solution of compound (51a) in CDCl$_3$. From the progressive change in the chemical shift (down-field), it was apparent that the most affected proton was the upfield one of the 3- and 5- protons (see fig. 12). This was necessarily the one closest to
the place of the attachment of the reagent i.e. the 3-H, near the 2-carbonyl. Therefore the 3-proton has the shift $\Delta\delta_{4.03}$. It was also noticed from the progressive changes (down-field) for the N-Methyl protons and the CH$_2$ of the C$_2$H$_5$S and the 5-H that the Eu(fod)$_3$ was attached to the carbonyl of the 6-CH$_3$-NCO$_2$SC$_2$H$_5$ group.

(51)
Fig. 12.  
(a) $^1$H n.m.r. spectrum of compound (51a)  
(b), (c) and (d) the $^1$H n.m.r. spectra after the addition of Bi(Iod)₃
It was initially believed that compound (48) had a pyridine structure and hence that the acyl group should be on the N- or O- atom as in (53) or (54). In fact, compound (48) when reacted with an excess of diazomethane gave an N-methyl derivative (51) indicating that the acyl group was necessarily attached to oxygen. The O-ethylthio carbonyl-4-chloro-pyridine (54) was then prepared by acylating 4-chloro-2,6-dihydroxypyridine (see Chapter XI). Comparison of the product with compound (48) showed that they were different.

This observation lent support to the pyrone structure for compounds (48).

\[ \text{(54)} \]

\[ \text{(53)} \]
Another piece of evidence for the compounds (48) being pyrones was their hydrolysis with hydrochloric acid in acetic acid to an open chain compound (55).

\[
\begin{align*}
\text{(48)} & \quad \overset{\text{HCl}}{\longrightarrow} \quad \text{(55)} \\
\end{align*}
\]

\[a, R = \text{C}_2\text{H}_5 \]
\[b, R = \text{PhCH}_2 \]

The compounds (55) were also prepared directly from the 7-chloro-2-mercapto compounds (13). This reaction was done in acetone with an excess of water, at room temperature for three days.

The infrared spectra of compounds (55) (Table XXXVI) show typical aliphatic carboxylic acid carbonyl absorption at 1725 cm\(^{-1}\).
### TABLE XXXVI

**I.R. Spectrum of compound (55b) (Nujol)**

<table>
<thead>
<tr>
<th>( \nu_{\text{max}}, \text{cm}^{-1} )</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>3300 - 2700 br</td>
<td>OH</td>
</tr>
<tr>
<td>3180 w)</td>
<td>NH</td>
</tr>
<tr>
<td>3080 w)</td>
<td></td>
</tr>
<tr>
<td>1725 s</td>
<td>C=O of the -COOH</td>
</tr>
<tr>
<td>1678 s</td>
<td>C=O of NH CO SCH Ph</td>
</tr>
<tr>
<td>1635 sh (br)</td>
<td>C=O of =C-CONH</td>
</tr>
<tr>
<td>1625 s</td>
<td>C=C</td>
</tr>
<tr>
<td>1580 w)</td>
<td></td>
</tr>
</tbody>
</table>

The \( ^1H \) n.m.r. spectra of compound (55) was also in agreement with the structure.

### TABLE XXXVII

**\( ^1H \) n.m.r. spectra of compounds (55) in \( d_6 \) DMSO**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Line Position</th>
<th>Intensity</th>
<th>Multiplicity</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>1.41</td>
<td>1</td>
<td>s</td>
<td>OH</td>
</tr>
<tr>
<td></td>
<td>1.80</td>
<td>1</td>
<td>br</td>
<td>NH</td>
</tr>
<tr>
<td></td>
<td>3.72</td>
<td>1</td>
<td>s</td>
<td>2-H</td>
</tr>
<tr>
<td></td>
<td>5.85</td>
<td>2</td>
<td>s</td>
<td>4-H(_2)</td>
</tr>
<tr>
<td></td>
<td>7.11</td>
<td>2</td>
<td>q, ( J ) 7Hz</td>
<td>( CH_2 ) of ( C_2H_5S^- )</td>
</tr>
<tr>
<td></td>
<td>8.70</td>
<td>3</td>
<td>t, ( J ) 7Hz</td>
<td>( CH_3 )</td>
</tr>
<tr>
<td>b</td>
<td>-1.66</td>
<td>1</td>
<td>s</td>
<td>O-H</td>
</tr>
<tr>
<td></td>
<td>2.71</td>
<td>6</td>
<td>s</td>
<td>Ph and NH</td>
</tr>
<tr>
<td></td>
<td>3.74</td>
<td>1</td>
<td>s</td>
<td>2-H</td>
</tr>
<tr>
<td></td>
<td>5.87</td>
<td>2</td>
<td>s</td>
<td>4-H(_2)</td>
</tr>
<tr>
<td></td>
<td>5.93</td>
<td>2</td>
<td>s</td>
<td>( CH_2 ) of PhCH(_2)</td>
</tr>
</tbody>
</table>
The esterification of compounds (55) with diazomethane gave the corresponding methyl esters (56).

![Chemical structures](image)

\( a, \text{ } R = \text{C}_2\text{H}_5 \)
\( b, \text{ } R = \text{PhCH}_2 \)

The infrared spectrum of compound (56a) is given in Table XXXVIII.

**TABLE XXXVIII**

<table>
<thead>
<tr>
<th>( \nu_{\text{max}} \text{ cm}^{-1} )</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>3270 m)</td>
<td>NH</td>
</tr>
<tr>
<td>3180 m)</td>
<td></td>
</tr>
<tr>
<td>1715 s</td>
<td>C=O of the ester</td>
</tr>
<tr>
<td>1675 m</td>
<td>C=O of ( \text{NHCO-SC}_2\text{H}_5 )</td>
</tr>
<tr>
<td>1635 m</td>
<td>C=O of =C-CONH</td>
</tr>
<tr>
<td>1525 s</td>
<td>C=C</td>
</tr>
</tbody>
</table>

\( ^1H \) nuclear spectra of compounds (56) are recorded in Table XXXIX and again there is good agreement with the proposed structure.
TABLE XXXIX

$^1$H n.m.r. spectrum of compound (56a) in CDCl$_3$

<table>
<thead>
<tr>
<th>Line Position</th>
<th>Intensity</th>
<th>Multiplicity</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.01</td>
<td>1</td>
<td>br</td>
<td>NH</td>
</tr>
<tr>
<td>3.68</td>
<td>1</td>
<td>s</td>
<td>2-H</td>
</tr>
<tr>
<td>5.90</td>
<td>2</td>
<td>s</td>
<td>4-H$_2$</td>
</tr>
<tr>
<td>6.25</td>
<td>3</td>
<td>s</td>
<td>CH$_3$-O</td>
</tr>
<tr>
<td>7.08</td>
<td>2</td>
<td>q, J 7Hz</td>
<td>CH$_2$ of C$_2$H$_5$S-</td>
</tr>
<tr>
<td>8.69</td>
<td>3</td>
<td>t, J 7Hz</td>
<td>CH$_3$ of C$_2$H$_5$S-</td>
</tr>
</tbody>
</table>
CHAPTER X

REACTIONS OF 4-CHLORO-2,6-DIHYDROXYPYRIDINE (31)

WITH ETHYL- AND ETHYLTHIO-CHLORO-FORMATE
The reaction of ethylthio-chloro-formate with 4,6-dihydroxypyridine (31) was carried out in dry dioxan under reflux at 140° for three hours. It was found that the product was the O-acyl 4-chloro-hydroxy-pyridine (54).

\[
\begin{align*}
\text{Cl} & \quad \text{HO} \\
\text{N} & \quad \text{S} \text{CO}_2 \text{H}
\end{align*}
\]

(31)

\[
\text{Cl} \quad \text{C}_2\text{H}_5\text{CO}_2\text{Cl}
\]

(54)

This structure (54) was supported by examining the reaction of compound (54) with an excess of diazomethane in the n.m.r. tube. This gave a mixture of N-methyl (57) and O-methyl (58) derivatives (see \textsuperscript{1}H n.m.r. spectra, Fig. 13).

\[
\begin{align*}
\text{Cl} & \quad \text{Cl} \\
\text{C}_2\text{H}_5\text{S} & \quad \text{C}_2\text{H}_5\text{S} \quad \text{C}_2\text{H}_5
\end{align*}
\]

(54)

\[
\begin{align*}
\text{Cl} & \quad \text{Cl} \\
\text{N} & \quad \text{C}_2\text{H}_5\text{CO}_2\text{Cl}
\end{align*}
\]

(59)

The reaction of ethyl-chloro-formate with 4-chloro-2,6-dihydroxy-pyridine (31) was also carried out as above. The corresponding O-acyl product was obtained (59).
Figure 13. $^1$H n.m.r. spectra of the mixture of compounds (57) and (58) in CDCl$_3$
The infrared absorption of compounds (54) and (59) are recorded in Tables XL and Fig. 14). Compound (54) showed carbonyl absorption from the -O-CSC₂H₅ group at 1730 cm⁻¹ which agrees with that found in compound (60) (1724 cm⁻¹).

![Chemical Structure](60)

The infrared absorption shown by compound (59) in Nujol was virtually unchanged in solution (CHCl₃). A shoulder at 1650 cm⁻¹ in Nujol appeared at 1660 cm⁻¹ in CHCl₃ solution, indicating the presence of the pyridone form.

**TABLE XL**

Infrared spectrum of compound (59) (Nujol)

<table>
<thead>
<tr>
<th>( \nu_{max} \ cm^{-1} )</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>3300-2600 br</td>
<td>NH/OH</td>
</tr>
<tr>
<td>1735 s) 1710 sh)</td>
<td>C=O of O-CSC₂H₅</td>
</tr>
<tr>
<td>1645 sh</td>
<td>C=O of the pyridone form</td>
</tr>
<tr>
<td>1625 s) 1575 s)</td>
<td>C=C</td>
</tr>
</tbody>
</table>
Fig. 14. I.R. spectrum of compound (54) (Nujol)
The $^1H$ n.m.r. spectra of compounds (54) and (59) (Table XLI) confirmed the structures.

TABLE XLI

$^1H$ n.m.r. spectra of compound (54) and (59) in CDCl$_3$

<table>
<thead>
<tr>
<th>Compound</th>
<th>Line Position</th>
<th>Intensity</th>
<th>Multiplicity</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>54</td>
<td>-1.79 br</td>
<td>1</td>
<td>s</td>
<td>NH/OH</td>
</tr>
<tr>
<td></td>
<td>3.31</td>
<td>2</td>
<td>AB quartet</td>
<td>3,5-H</td>
</tr>
<tr>
<td></td>
<td>7.04</td>
<td>2</td>
<td>q, J 7Hz</td>
<td>CH$_2$ of C$_2$H$_5$S</td>
</tr>
<tr>
<td></td>
<td>8.63</td>
<td>3</td>
<td>t, J 7Hz</td>
<td>CH$_3$</td>
</tr>
<tr>
<td>59</td>
<td>-1.23 br</td>
<td>1</td>
<td>s</td>
<td>NH/OH</td>
</tr>
<tr>
<td></td>
<td>3.29 and 3.35</td>
<td>2</td>
<td>AB quartet</td>
<td>3,5-H</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>J = 1.7Hz</td>
<td>CH$_2$ of C$_2$H$_5$O-</td>
</tr>
<tr>
<td></td>
<td>5.65</td>
<td>2</td>
<td>q, J = 7Hz</td>
<td>CH$_2$ of C$_2$H$_5$O-</td>
</tr>
<tr>
<td></td>
<td>8.58</td>
<td>3</td>
<td>t, J = 7Hz</td>
<td>CH$_3$</td>
</tr>
</tbody>
</table>

It was clear (see Chapters VII and VIII) that 2-hydroxypyridine and 2,6-dihydroxypyridine exist predominantly in the pyridone form because they show reasonably intense carbonyl absorption at 1635 - 1660 cm$^{-1}$. Together with the 4-chloro-2,6-dihydroxypyridine they showed light absorption at 310 - 320 nm. However, compounds (54) and (59) in non polar solvents (dioxan, CH$_3$CN and CCl$_4$) showed absorption at 273 - 277 nm, with some indication of a maximum in the region 300 - 310 nm. The main band at
273 nm, compared with the absorption of 4-chloro-2,6-dimethoxypyridine (34) at 277 nm. In polar solvents (alcohol and CHCl₃), however, compounds (54) and (59) showed an increase in the intensity of the longer wavelength band, which had also moved to slightly longer wavelengths. This suggested an increase in the percentage of the pyridone form in the above solvents.

It was also noticed from the ¹H n.m.r. that compounds (54) and (59) gave different AB quartets for the 3,5- H in different solvents (Fig.15 showed ¹H n.m.r. spectrum of compound 54 in d₆DMSO).
Fig. 15. $^1$H n.m.r. spectrum of compound (54) in $d_6$DMSO
CHAPTER XI

REACTIONS OF THE 7-CHLORO-2-ETHYL MERCAPO

COMPOUND (13, \( R = \text{C}_2\text{H}_5 \)) WITH AN EXCESS OF ETHYL ALCOHOL

AT ROOM TEMPERATURE
The 7-chloro-2-ethyl-mercapto compound (13, R=C₂H₅) was dissolved in dry chloroform and mixed with an excess of absolute ethyl alcohol. After four days, the reaction mixture was evaporated under reduced pressure, and the residue was treated with petroleum ether (b.p. 40-60) and crystallized from carbon tetrachloride to give colourless needles of the 7-chloro-2-ethoxy-pyranoxazine (62) (62.5%). There was a small residue insoluble in carbon tetrachloride, which crystallized from acetonitrile, and thus gave the 6-chloro-4-hydroxy-2-pyran-3-amide (63) (6%).

The ¹H n.m.r. spectrum of compound (62) (Table XLII) supported the structure.

<table>
<thead>
<tr>
<th>Line Position</th>
<th>Intensity</th>
<th>Multiplicity</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.73</td>
<td>1</td>
<td>s</td>
<td>8-H</td>
</tr>
<tr>
<td>5.37</td>
<td>2</td>
<td>q, J 7Hz</td>
<td>CH₂ of C₂H₅⁻</td>
</tr>
<tr>
<td>8.51</td>
<td>3</td>
<td>t, J 7Hz</td>
<td>CH₃</td>
</tr>
</tbody>
</table>
Further evidence came from the infrared spectrum of compound (62) (Table XLIII) which showed a band at 1778 cm$^{-1}$ from the 2-carbonyl group of the pyrone ring and at 1590 cm$^{-1}$ for C=N similarly to the thioanalogue (13).

**TABLE XLIII**

<table>
<thead>
<tr>
<th>$\gamma_{\text{max}}$ cm$^{-1}$</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>3050 sh</td>
<td>CH</td>
</tr>
<tr>
<td>1778 m</td>
<td>2- C=O</td>
</tr>
<tr>
<td>1745 s</td>
<td>4- C=O</td>
</tr>
<tr>
<td>1590 s</td>
<td>C=N</td>
</tr>
<tr>
<td>1608 s)</td>
<td></td>
</tr>
<tr>
<td>1540 s)</td>
<td>C=C</td>
</tr>
<tr>
<td>1510 m)</td>
<td></td>
</tr>
</tbody>
</table>

Compound (62) showed light absorption maxima at 275, 282.5 and 322 nm. The shorter wave-length as compared with the thioanalogue (13, C$_2$H$_5$) (342 nm) was in accord with the change from a thio- to an oxy-substituent.

The formation of compound (62) could be written as below:

![Chemical Reaction Diagram](image-url)
It was found that the other product (63) had m/e 189 M⁺ with an isotopic p + 2 peak which indicated the presence of one chlorine atom. According to the nitrogen rule, the product (63) had an odd number of nitrogen atoms in its constitution. Combustion analysis gave the empirical formula C₆H₄ClNO₄, which was then also the molecular formula.

The ultraviolet spectrum of compound (63) (330 and 272 nm.) suggested a pyrone structure and ruled out the pyridone structure (63a).

\[
\begin{array}{c}
\text{Cl} \\
\text{HO} \\
\text{N} \\
\text{OH}
\end{array}
\]

(63a)

The structure (63a) was also ruled out by the infrared spectrum which showed two bands for NH₂ at 3360 and 3220 cm⁻¹. The product (63) was not soluble in a 5% solution of sodium bicarbonate, which indicated that the product was not an acid. The ¹H n.m.r. spectrum of product (63) showed a signal at 7.4±0 (d, DMSO) which is at rather a high field for the product (63) to have the 6-chloro-4-hydroxy-2-pyrone-amide structure. It appeared that the 6-amino-4-chloro-3-carboxylic-2-pyrone structure (63b) would better accommodate the n.m.r. observation. However, as has been

\[
\begin{array}{c}
\text{H₂N} \\
\text{Cl} \\
\text{O} \\
\text{CO₂H}
\end{array}
\]

(63b)

pointed out the product (63) was not acidic. Moreover it gave a purple colour with alcoholic ferric chloride, which supported the structure (63). The pyrone structure for compound (63) did not accommodate the ¹H n.m.r.
absorption, further investigation is needed to elucidate the structure.

The formation of compound (63) is presumably due to the presence of water in the reaction mixture. This could attack the 7-chloro-2-ethyl mercapto compound (13; R=C₆H₅), or the 7-chloro-2-ethoxy compound (62), and give the intermediate (a) which would then react further with water to give the final product (63).

\[
\begin{align*}
(13) & \quad X = S \\
(62) & \quad X = O \\
(a) & \quad \text{+ RH} \\
(63) & \quad \text{+ CO}_2^- 
\end{align*}
\]
CHAPTER XII

REACTIONS OF THE 7-CHLORO-2-MERCAPTO-COMPOUNDS (13)

WITH ONE OR TWO MOLS. OF ALCOHOL
Reactions of 7-chloro-2-mercapto compounds (13) with one mol. of alcohol

The reaction was performed in dry dioxan under reflux for two and a half hours and a solid was then obtained after the reaction mixture had been evaporated under reduced pressure. From carbon tetrachloride (charcoal), colourless crystalline product (64) was isolated (40%) and another product (65) (20%) was obtained by evaporating the carbon tetrachloride filtrate.

These products (64) and (65) were found to be isomers.

\[
\begin{align*}
\text{(13)} & \quad \text{(64)} \\
a, R = R^1 = \text{C}_2\text{H}_5 & \quad a) R = R^1 = \text{C}_2\text{H}_5 \\
b, R = \text{Ph}, R^1 = \text{C}_2\text{H}_5 & \quad b) R = \text{C}_2\text{H}_5, R^1 = \text{CH}_3 \\
c, R = \text{PhCH}_2, R^1 = \text{C}_2\text{H}_5 & \\
d, R = \text{C}_2\text{H}_5, R^1 = \text{CH}_3
\end{align*}
\]

Ultraviolet measurements suggested that the compounds (64) (Table XLIV) had a pyrone structure.
TABLE XLIV

U.V. absorptions for compounds (64) in CH$_3$CN

<table>
<thead>
<tr>
<th>Compounds</th>
<th>$\lambda_{\text{max}}$ nm</th>
<th>$\varepsilon \times 10^{-3}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>347.5</td>
<td>17.0</td>
</tr>
<tr>
<td>b</td>
<td>356</td>
<td>16.4</td>
</tr>
<tr>
<td>c</td>
<td>372</td>
<td>17.9</td>
</tr>
<tr>
<td>d</td>
<td>346.5</td>
<td>11.5</td>
</tr>
</tbody>
</table>
The $^1$H n.m.r. spectral characteristics of compounds (64) are listed in Table XLVI. The pyrone ring-proton has an unusually low-field shift which is not in agreement with the proposed structure.

**TABLE XLVI.**

$^1$H n.m.r. spectra of compounds (64) in CDCl$_3$

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Line Position $^c$</th>
<th>Intensity</th>
<th>Multiplicity</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>-1.69 br</td>
<td>1</td>
<td>s</td>
<td>NH</td>
</tr>
<tr>
<td></td>
<td>3.14</td>
<td>1</td>
<td>s</td>
<td>5-H</td>
</tr>
<tr>
<td></td>
<td>5.71</td>
<td>2</td>
<td>q, $^J$ 7Hz</td>
<td>CH$_2$ of C$_2$H$_5$-</td>
</tr>
<tr>
<td></td>
<td>6.94</td>
<td>2</td>
<td>q, $^J$ 7Hz</td>
<td>CH$_2$ of C$_2$H$_5$S-</td>
</tr>
<tr>
<td></td>
<td>8.67</td>
<td>6</td>
<td>t, $^J$ 7Hz</td>
<td>2 x CH$_3$</td>
</tr>
<tr>
<td>b</td>
<td>-1.97 br</td>
<td>1</td>
<td>s</td>
<td>NH</td>
</tr>
<tr>
<td></td>
<td>2.71</td>
<td>5</td>
<td>c</td>
<td>Ph</td>
</tr>
<tr>
<td></td>
<td>3.12</td>
<td>1</td>
<td>s</td>
<td>5-H</td>
</tr>
<tr>
<td></td>
<td>5.72</td>
<td>2</td>
<td>q, $^J$ 7Hz</td>
<td>CH$_2$ of C$_2$H$_5$-</td>
</tr>
<tr>
<td></td>
<td>5.70</td>
<td>2</td>
<td>s</td>
<td>CH$_2$ of PhCH$_2$</td>
</tr>
<tr>
<td></td>
<td>8.71</td>
<td>3</td>
<td>t, $^J$ 7Hz</td>
<td>CH$_3$</td>
</tr>
<tr>
<td>c</td>
<td>-1.39</td>
<td>1</td>
<td>s</td>
<td>NH</td>
</tr>
<tr>
<td></td>
<td>3.12</td>
<td>1</td>
<td>s</td>
<td>5-H</td>
</tr>
<tr>
<td></td>
<td>6.18</td>
<td>3</td>
<td>s</td>
<td>CH$_3$O-</td>
</tr>
<tr>
<td></td>
<td>6.96</td>
<td>2</td>
<td>q, $^J$ 7Hz</td>
<td>CH$_2$ of C$_2$H$_5$S-</td>
</tr>
<tr>
<td></td>
<td>8.66</td>
<td>3</td>
<td>t, $^J$ 7Hz</td>
<td>CH$_3$</td>
</tr>
</tbody>
</table>
The formation of compounds (64) may occur as below:

\[
\begin{align*}
\text{U} & \quad \text{SRCl} \\
(64) & \quad + \quad \text{H}^+ \\
\end{align*}
\]

The compounds (64) were stable towards water and alcohol: no reaction took place on refluxing them with water or alcohol in dioxan for one hour. However, these compounds (64) interacted with benzylamine and gave the 6-benzylamino analogue which will be discussed later in this chapter.

The isomeric product (65) from the reaction of one mol. of alcohol with the 7-chloro-2-mercapto compound (13) showed a light absorption maximum at the shorter wavelength of 310 nm. (with a shoulder at 375), which is typical of simple α-pyrones.

In the infrared (Table XLVII), compound (65) showed different absorption from the isomeric products (64). This was consistent with the proposed structure (65).
TABLE XLVII

I.\textsubscript{R}. spectra of compound (65) (Nujol)

<table>
<thead>
<tr>
<th>Compounds (65)</th>
<th>( \nu_{\text{max}} \text{ cm}^{-1} )</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>3290 m</td>
<td>NH</td>
</tr>
<tr>
<td></td>
<td>3090 w</td>
<td>CH</td>
</tr>
<tr>
<td></td>
<td>1740 s</td>
<td>5\text{-} C=O</td>
</tr>
<tr>
<td></td>
<td>1660 s</td>
<td>( \downarrow ) C=O</td>
</tr>
<tr>
<td></td>
<td>1612 m)</td>
<td>C=C</td>
</tr>
<tr>
<td></td>
<td>1515 s)</td>
<td></td>
</tr>
<tr>
<td>b</td>
<td>3220 w</td>
<td>NH</td>
</tr>
<tr>
<td></td>
<td>1740 s</td>
<td>5\text{-} C=O</td>
</tr>
<tr>
<td></td>
<td>1640 s</td>
<td>( \downarrow ) C=O</td>
</tr>
<tr>
<td></td>
<td>1610 w)</td>
<td>C=C</td>
</tr>
<tr>
<td></td>
<td>1515 s)</td>
<td></td>
</tr>
</tbody>
</table>

The \( ^1\text{H} \) n.m.r. data (Table LXVII) were also consistent with structure (65) for the compound.
<table>
<thead>
<tr>
<th>Compound</th>
<th>Line Position</th>
<th>Intensity</th>
<th>Multiplicity</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>-0.69 br</td>
<td>1</td>
<td>s</td>
<td>NH</td>
</tr>
<tr>
<td>3.96</td>
<td></td>
<td>1</td>
<td>s</td>
<td>8-H</td>
</tr>
<tr>
<td>5.74</td>
<td>2</td>
<td>q, J 7Hz</td>
<td>C\text{H}_2 of C\text{H}_2\text{O}^-</td>
<td></td>
</tr>
<tr>
<td>6.08</td>
<td>3</td>
<td>q, J 7Hz</td>
<td>C\text{H}_2 of C\text{H}_5\text{S}</td>
<td></td>
</tr>
<tr>
<td>8.68</td>
<td>6</td>
<td>t, J 7Hz</td>
<td>2 x C\text{H}_3</td>
<td></td>
</tr>
<tr>
<td>b</td>
<td>-0.90 br</td>
<td>1</td>
<td>s</td>
<td>NH</td>
</tr>
<tr>
<td>3.93</td>
<td></td>
<td>1</td>
<td>s</td>
<td>8-H</td>
</tr>
<tr>
<td>6.19</td>
<td>3</td>
<td>s</td>
<td>C\text{H}_3</td>
<td></td>
</tr>
<tr>
<td>6.98</td>
<td>2</td>
<td>q, J 7Hz</td>
<td>C\text{H}_2 of C\text{H}_5\text{S}^-</td>
<td></td>
</tr>
<tr>
<td>8.68</td>
<td>3</td>
<td>t, J 7Hz</td>
<td>C\text{H}_3</td>
<td></td>
</tr>
</tbody>
</table>

It was found that compounds (65) were reactive towards water or alcohol. In dioxan under reflux for two and a half hours with water, the 6-chloro-2,6-dihydroxypyridine (31) was obtained having the same m.p. as the previous sample, 218° (decomp.) and showing no depression in the mixed m.p. The i.r. was identical.

The reaction with ethyl alcohol carried out in the same way, gave 4-chloro-3-ethoxycarbonyl-2,6-dihydroxypyridine (44), identical with the previous sample.
The formation of products (31) and (44a) from compound (65) presumably occur in a manner similar to their formation from the 7-chloro-2-mercapto compounds (13).

Reactions of compound (64) with benzylamine

The reaction was done in dry dioxan with two molecular proportions of benzylamine under reflux for half an hour. A chlorine-free product (66) was obtained.

It was noticed that the thio-group in compounds (64) was more stable towards benzylamine than the chlorine atom, and indeed when compound (66) was boiled with another mol. of benzylamine no reaction took place. Under more vigorous reaction conditions, when the compound (66) was refluxed with benzylamine, malonyldiamide (24) and NN-dibenzyl urea (26) were obtained.
The 6-benzylamino-pyrano derivatives (66) showed maximum light absorption (Table XLIX) at 320 nm. This is at a slightly shorter wavelength than the 6-aminopyranodioxins which absorb in the 335 nm region, but rather similar to the 4,6-diamino-pyrano derivatives (21) which absorbs at 327 nm.
<table>
<thead>
<tr>
<th>Compounds (66)</th>
<th>$\lambda_{\text{max}} , \text{nm}$</th>
<th>$\varepsilon \times 10^{-3}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>326</td>
<td>13.1</td>
</tr>
<tr>
<td></td>
<td>287.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>245</td>
<td></td>
</tr>
<tr>
<td>b</td>
<td>326</td>
<td>12.4</td>
</tr>
<tr>
<td></td>
<td>287.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>245</td>
<td></td>
</tr>
</tbody>
</table>

The infrared spectra also supported the structure (Table L).

**TABLE L**

Infrared spectra of compound (66) (Nujol)

<table>
<thead>
<tr>
<th>Compound (66)</th>
<th>$\nu , \text{cm}^{-1}$</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>3150 w</td>
<td>NH</td>
</tr>
<tr>
<td></td>
<td>1745 s</td>
<td>2- C=O hydrogen bonded</td>
</tr>
<tr>
<td></td>
<td>1670 s</td>
<td>C=O of $\text{NH}_2$-SC$_2$H$_5$</td>
</tr>
<tr>
<td></td>
<td>1640 m</td>
<td>3- C=O</td>
</tr>
<tr>
<td></td>
<td>1577 sh)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1760 s )</td>
<td>C=C</td>
</tr>
</tbody>
</table>
Further structural support came from the \( ^1H \) n.m.r. spectra of compounds (66), recorded in Table LI. The replace of the 6-chlorine atom by the benzylamino group moved the 5-H signal up-field (in \( d_6 \) DMSO) by about 0.6 p.p.m.

**TABLE LI**

\( ^1H \) n.m.r. spectra of compounds (66) in \( d_6 \) DMSO

<table>
<thead>
<tr>
<th>Compounds (66)</th>
<th>Line Position</th>
<th>Intensity</th>
<th>Multiplicity</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>-1.03 br</td>
<td>1</td>
<td>s</td>
<td>3-CO₂NH</td>
</tr>
<tr>
<td></td>
<td>-0.82 br</td>
<td>1</td>
<td>t, J 6Hz</td>
<td>6-NH</td>
</tr>
<tr>
<td></td>
<td>2.66</td>
<td>5</td>
<td>s</td>
<td>Ph</td>
</tr>
<tr>
<td></td>
<td>3.50</td>
<td>1</td>
<td>s</td>
<td>5-H</td>
</tr>
<tr>
<td></td>
<td>5.45</td>
<td>2</td>
<td>d, J 6Hz</td>
<td>( CH_2 ) of PhCH₂</td>
</tr>
<tr>
<td></td>
<td>5.85</td>
<td>2</td>
<td>q, J 7Hz</td>
<td>( CH_2 ) of C₂H₅O</td>
</tr>
<tr>
<td></td>
<td>7.41</td>
<td>2</td>
<td>q, J 7Hz</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8.80 and 8.84</td>
<td>6</td>
<td>t, J 7Hz</td>
<td>2 x CH₃</td>
</tr>
<tr>
<td>b</td>
<td>-0.80 br</td>
<td>1</td>
<td>t, J 6Hz</td>
<td>6-NH</td>
</tr>
<tr>
<td></td>
<td>-0.20 br</td>
<td>1</td>
<td>s</td>
<td>3-CO₂NH</td>
</tr>
<tr>
<td></td>
<td>2.65</td>
<td>5</td>
<td>s</td>
<td>Ph</td>
</tr>
<tr>
<td></td>
<td>3.48</td>
<td>1</td>
<td>s</td>
<td>5-H</td>
</tr>
<tr>
<td></td>
<td>5.44</td>
<td>2</td>
<td>d, J 6Hz</td>
<td>( CH_2 ) of PhCH₂</td>
</tr>
<tr>
<td></td>
<td>6.31</td>
<td>3</td>
<td>s</td>
<td>( CH_3 ) O-</td>
</tr>
<tr>
<td></td>
<td>7.25</td>
<td>2</td>
<td>q, J 7Hz</td>
<td>( CH_2 ) of C₃H₅S</td>
</tr>
<tr>
<td></td>
<td>8.83</td>
<td>3</td>
<td>t, J 7Hz</td>
<td>CH₃</td>
</tr>
</tbody>
</table>
The reaction of the 7-chloro-2-mercapto compound (13) with 2 mols.

of ethyl alcohol

The reaction of the 7-chloro-2-ethyl mercapto compound (13, R = C₂H₅) with 2 mols. of ethyl alcohol in dry dioxan was done under reflux for two and a half hours. After the solvent had been removed under reduced pressure, a mixture of the 6-chloro-4-hydroxy-pyrone derivative (67), the 6-chloro-4-ethoxy-pyrone derivative (64a), and 4-chloro-3-ethoxycarbonyl-2,6-dihydroxypyridine (44a) were obtained. The product (67) was removed by washing the above residue with carbon tetrachloride (100 ml). The action of warming the remaining mixture with carbon tetrachloride dissolved the compound (64a).

It was found that, when the 7-chloro-2-mercapto compounds (13) treated with 3 mols. or more of ethyl alcohol, 4-chloro-3-ethoxycarbonyl-2,6-dihydroxypyridine (44a) was formed, mixed with the 6-chloro-4-ethoxy-pyrone derivative (64a).

The product (67) gave a molecular ion with m/e 289 and an isotopic p + 2 peak, which indicated the presence of one chlorine atom and an odd
number of nitrogen atoms. The infrared spectrum of compound (67) (Table LII) confirmed the pyrone structure by showing absorption at 1786 cm\(^{-1}\) from the 2-carbonyl and at 1690 cm\(^{-1}\) from the 3-carbonyl which was evidently hydrogen-bonded to the 4-hydroxyl group.

![Chemical structure](attachment:image.png)

(67)

**TABLE LII**

**I.R. spectrum of compound (67) Nujol**

<table>
<thead>
<tr>
<th>(\gamma_{\text{max}}) cm(^{-1})</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>3400-2600 br</td>
<td>OH</td>
</tr>
<tr>
<td>3090 v</td>
<td>CH</td>
</tr>
<tr>
<td>1786 s</td>
<td>2-C=O</td>
</tr>
<tr>
<td>1690 s</td>
<td>3-C=O hydrogen-bonded</td>
</tr>
<tr>
<td>1630 m)</td>
<td></td>
</tr>
<tr>
<td>1590 m)</td>
<td></td>
</tr>
<tr>
<td>1520 s)</td>
<td>C=N and C=C</td>
</tr>
</tbody>
</table>

The compound (67) had light absorption maxima (in CH\(_3\)CN) at 337.5 and 269 nm. The \(^1\)H n.m.r. spectrum (Table LIII) showed a good agreement with the structure.
TABLE LIII

\(^1\text{H NMR}\) spectrum of compound (67) in \(\text{CDCl}_3\)

<table>
<thead>
<tr>
<th>Line Position (\delta)</th>
<th>Intensity</th>
<th>Multiplicity</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>-5.00</td>
<td>1</td>
<td>br</td>
<td>4-OH</td>
</tr>
<tr>
<td>3.83</td>
<td>1</td>
<td>s</td>
<td>5-H</td>
</tr>
<tr>
<td>5.48 and 5.58</td>
<td>2 x 2</td>
<td>q, (J = 7) Hz</td>
<td>2 x (\text{CH}_2) of (\text{C}_2\text{H}_5\text{O})-</td>
</tr>
<tr>
<td>8.58</td>
<td>6</td>
<td>t, (J = 7) Hz</td>
<td>2 x (\text{CH}_3)</td>
</tr>
</tbody>
</table>
CHAPTER XIII

$^{13}$C nuclear SPECTRA FOR THE

4-CHLORO-PYRIDINE DERIVATIVES

(31) and (44a)

AND 4-CHLORO-2-PYRONE DERIVATIVES

(35a), (48a) and (51a)
The natural abundance carbon-13 spectrum of compound (31) with wide-band $^1$H-decoupling in d$_6$DMSO as solvent and TMS as internal reference was measured. It was noticed that the 2- and 6- carbons were equivalent and so were the 3- and 5- carbons (Table LIV). This observation confirmed the fast exchange between the two forms b $\rightarrow$ c (see Chapter 7) previously invoked to explain the equivalence of the 3- and 5- protons.

![Chemical Structure of (31)](image)

Table LIV

$^{13}$C n.m.r. Spectrum of compound (31) in d$_6$DMSO

<table>
<thead>
<tr>
<th>Line Position $\delta$</th>
<th>Multiplicity $^1$H Decoupling</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>158.83</td>
<td>s</td>
<td>2- and 6-C</td>
</tr>
<tr>
<td>145.77</td>
<td>s</td>
<td>4-C</td>
</tr>
<tr>
<td>96.76</td>
<td>d, $^1$CH$_2$ 170.6Hz</td>
<td>3,5-C</td>
</tr>
</tbody>
</table>

$^{13}$C n.m.r. Spectrum of 4-Chloro-3-ethoxycarbonyl-2,6-dihydroxy pyridine (44a)

The assignment of the $^{13}$C n.m.r. spectrum of compound (44a) was achieved with the aid of wide-band $^1$H-decoupling and a gated decoupling experiment (Table LV), as well as by comparison with the $^{13}$C n.m.r. spectrum of compound (31).
Table LV

$^{13}$C n.m.r. spectrum of compound (44a) in d$_6$DMSO

<table>
<thead>
<tr>
<th>Line Position $\delta$</th>
<th>Multiplicity</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>163.19</td>
<td>s</td>
<td>1'-C</td>
</tr>
<tr>
<td>158.30</td>
<td>s</td>
<td>2,6-C</td>
</tr>
<tr>
<td>157.73</td>
<td>s</td>
<td>4'-C</td>
</tr>
<tr>
<td>143.49</td>
<td>s</td>
<td>3'-C</td>
</tr>
<tr>
<td>105.41</td>
<td>s</td>
<td>3-C</td>
</tr>
<tr>
<td>94.10</td>
<td>d, $\frac{1}{2}$J$_{CH}$ 170.6 Hz</td>
<td>5-C</td>
</tr>
<tr>
<td>60.24</td>
<td>t, $\frac{1}{2}$J$_{CH}$ 150 Hz</td>
<td>3'-C</td>
</tr>
<tr>
<td>13.77</td>
<td>q, $\frac{1}{2}$J$_{CH}$ 124 Hz</td>
<td>4'-C</td>
</tr>
</tbody>
</table>

$^{13}$C n.m.r. spectrum of 4-Chloro-6-N (ethylthiocarbonyl) amido-2-pyrone (48a)

To assign the $^{13}$C n.m.r. spectrum of compound (48a), wideband $^1$H-decoupling and a gated decoupling experiment were done. The spectrum of the compound enriched with carbon-13 at the carbonyl
of the 6-NH₂COSC₂H₅ group was also obtained (Table LVI).

\[
\begin{align*}
\text{Table LVI} \\
1^{13}C \text{ n.m.r. data for compound (48a) in } d_6\text{DMSO}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Line Position</th>
<th>Multiplicity</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>164.29</td>
<td>s</td>
<td>2'-C</td>
</tr>
<tr>
<td>155.78</td>
<td>s</td>
<td>2-C</td>
</tr>
<tr>
<td>151.68</td>
<td>s</td>
<td>6- and 4-C</td>
</tr>
<tr>
<td>103.85</td>
<td>d, 1^J_{CH} 177.9Hz</td>
<td>3- and 5-C</td>
</tr>
<tr>
<td>90.53</td>
<td></td>
<td></td>
</tr>
<tr>
<td>23.39</td>
<td>t, 1^J_{CH} 147 Hz</td>
<td>4'-C</td>
</tr>
<tr>
<td>14.81</td>
<td>q, 1^J_{CH} 135</td>
<td>5'-C</td>
</tr>
</tbody>
</table>

It appeared (see Table LVI) that the 6- and 4- carbons were accidentally equivalent. That this was indeed so was demonstrated by preparing the N-methyl derivative (51a) and observing that the 6- and 4- carbon chemical shifts then became slightly different (Table LVII).
Table LVII

$^{13}$C NMR results for compound (51a) in $d_6$DMSO

<table>
<thead>
<tr>
<th>Line Position $\delta$</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>166.30</td>
<td>2'-C</td>
</tr>
<tr>
<td>156.23</td>
<td>2-C</td>
</tr>
<tr>
<td>151.75</td>
<td>4-C</td>
</tr>
<tr>
<td>150.32</td>
<td>6-C</td>
</tr>
<tr>
<td>107.75</td>
<td>3- and 5-C</td>
</tr>
<tr>
<td>99.93</td>
<td>3- and 5-C</td>
</tr>
<tr>
<td>33.79</td>
<td>2''-C</td>
</tr>
<tr>
<td>24.50</td>
<td>4'-C</td>
</tr>
<tr>
<td>14.42</td>
<td>5'-C</td>
</tr>
</tbody>
</table>

$^{13}$C NMR spectrum of 6-amino-4-chloro-5-ethylthiocarbonyl-2-pyrene (35a)

To assign the $^{13}$C NMR spectrum of compound (35a) wideband $^1$H-decoupling and a gated decoupling experiment were done.
In addition, comparison was made with the $^{13}$C n.m.r. results from compounds (48a) and (51a) (Tables LVI and LVII).

![Chemical Structure](image)

(35a)

**Table LVIII**

$^{13}$C n.m.r. data for compounds (35a) in $d_{6}$DMSO

<table>
<thead>
<tr>
<th>Line Position $\delta$</th>
<th>Multiplicity</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>184.96</td>
<td>s</td>
<td>1'-C</td>
</tr>
<tr>
<td>161.95</td>
<td>s</td>
<td>6-C</td>
</tr>
<tr>
<td>158.64</td>
<td>s</td>
<td>2-C</td>
</tr>
<tr>
<td>153.70</td>
<td>s</td>
<td>5-C</td>
</tr>
<tr>
<td>148.83</td>
<td>s</td>
<td>4'-C</td>
</tr>
<tr>
<td>97.55</td>
<td>d, $^{1}J_{CH}=179.5$Hz</td>
<td>3-C</td>
</tr>
<tr>
<td>23.72</td>
<td>t, $^{1}J_{CH}=155.0$Hz</td>
<td>3'-C</td>
</tr>
<tr>
<td>14.03</td>
<td>q, $^{1}J_{CH}=130.0$Hz</td>
<td>4'-C</td>
</tr>
</tbody>
</table>
PART III

MASS SPECTROMETRY
INTRODUCTION

Basic Theory

The key reaction in the mass spectrometer takes place in the ion chamber. An electron, which has considerable kinetic energy, hits a molecule in the vapour phase or passes within about 2Å of one of the atoms. One of three reactions can occur: the electron can pass or bounce off without effect; it can be absorbed to form a negative ion; or it can strip an electron from the molecule. Only the last of these is very likely with organic fragments.

Since only about 10 ev. are required to ionise an organic molecule and the electrons are accelerated with an energy of 70 ev. a considerable amount of energy remains in the system, much of which is absorbed by the molecule under consideration. This extra energy causes fragmentation of the molecule and the fragmentation pattern can be studied to yield data on high-energy chemistry, or alternatively, in the case of an unknown compound, to assist in determining the structure of the compound. From the ion chamber the positively charged ion is accelerated through an electric and magnetic field. By this means the beam of ions is separated according to the mass. By varying either the electric or the magnetic field the ions of different mass are focussed in turn on a detector. This records the data as a trace on photographic paper.

A molecule of the sample compound, on being stripped of one electron, is known as the molecular ion and the peak corresponding to this in the mass spectrum is the parent peak of the compound. If the compound shows no parent peak, the excess energy stored as vibrational and rotational energy causes the molecular ion to break up quickly (less than 10^{-5} sec.).
In such cases lower-energy electrons (e.g. 14 ev.) normally produce a parent peak.

Despite the short life of such fragments, enough time elapses before breakdown for electronic rearrangement and energy distribution takes place. Thus the bond which breaks is independent of the position of the initial ionisation.

High resolution may be achieved using a double-focussing instrument. Compounds with the same numerical molecular weight, but different empirical formulae can be resolved and an unambiguous analysis of the fragment is possible by calculation.

In the hypothetical molecule, the following processes may be found to occur:

\[
\begin{align*}
\text{ABCD} + e & \rightarrow \text{ABCD}^+ + 2e \quad \text{(Ionization)} \\
\text{ABCD}^+ & \rightarrow \text{AB}^+ + \text{CD} \\
& \rightarrow \text{CD}^+ + \text{AB}, \text{etc.} \quad \text{(Simple fragmentation)} \\
\text{AB}^+ & \rightarrow \text{A}^+ + \text{B} \\
& \rightarrow \text{B}^+ + \text{A} \\
\text{ABCD} & \rightarrow \text{AD}^+ + \text{BC} \quad \text{(Fragmentation involving rearrangement)}
\end{align*}
\]
CHAPTER XIV

MASS SPECTRA OF THE 7-CHLORO-2-SUBSTITUTED

-PYRONE-OXAZINES (13), (14) AND (62)
The mass spectra of the 7-chloro-2-mercapto-pyrano-oxazines(13)

It was found from the spectra of the 7-chloro-2-mercapto compounds (13) that these compounds were not very stable under the mass spectrometry conditions in that they gave a molecular ion peak of only 21-68% intensity, whereas the first breakdown peak with m/e 198, had 100% intensity. This meant that the loss of RS was energetically very favourable. In the ordinary chemistry, displacement of the RS group was a predominant reaction of the 7-chloro-2-mercapto compounds.

The relative abundance of the parent peak in these compounds increased in the following order with change of RS group: 21% for C₂H₅S to 34% for PhCH₂S and 68% for PhS. This also indicated the order of stability of the compounds.

It was found that these compounds had similar breakdown patterns (see Scheme 1). This scheme was confirmed by labelling the compound (13, R = C₂H₅) with carbon - 13 at the position 2 - and also by finding the corresponding metastable ions.

The fragmentation of 7-chloro-2-ethyl-mercapto compound

(13, R = C₂H₅)

This showed a molecular ion at m/e 259 (21%) with a p + 2 peak. It lost C₂H₅S \[\text{M-61}\] and gave a peak with m/e 198 (100%) together with an isotopic p + 2 peak, which was confirmed by a metastable ion with m/e 151.2. The molecular ion also lost C₂H₅SCN \[\text{M-87}\] and gave m/e 172 (2.4%).

The fragment ion 198 showed three different break-down patterns:

(1) Loss of CO₂ to give m/e 154 (67.7%). This should occur through rearrangement involving oxygen migration.
The above rearrangement showed a large metastable ion with \( m/e \) at 119.8 which confirmed the rearrangement. Other evidence for the loss of \( \text{CO}_2 \) from 2-position came from the spectrum of the C-13 labelled compound which showed the loss of the enriched carbon.

The loss of carbon dioxide through oxygen migration was suggested by Johnstone and Millard\(^4\) for the loss of \( \text{CO}_2 \) from certain cyclic imides.

\[ \text{NCH}_3 - \text{CO} \]

\[ \text{C} = \text{NCH}_3 \]

(2) The ion with \( m/e \) 198 either lost \( \text{CO}_2 \) and gave a peak at \( m/e \) 114 (8.7%) which still contained the carbon-13 label, or lost \( \text{C}_2\text{O}_2 \) and gave an ion with \( m/e \) 130 (21%) which also still contained the carbon-13 label.
(3) The m/e 198 fragment could also lose HCl and give the peak with m/e 162 (5%).

The m/e 154 peak has breakdown by loss of CN giving m/e 128 (4%) which then loses Cl and gives a stable carbonium ion, m/e 93 (100%).
Scheme 1.

- CL - O
  m/e 172

- CL - O
  m/e 198

- CO2
  m/e 154

- CL - O
  m/e 114

C5H10O3
  m/e 128

- C1
  m/e 93

- C5H5O2
  m/e 72

- C2O3
  m/e 130

- C2HCl
  m/e 60

- C2HCl
  m/e 70

RSCN

RS
It was found from the mass spectrum of the 7-chloro-2-ethyl-mercapto compound (13, $R = C_2H_5$), which was carbon-13 enriched at the 2-position, that the following ions contained the label:

$m/e$ 259, 198, 162, 130, 114, 70, 44 and 42.

The spectrum of the 7-chloro-2-mercapto compound ($13, R = C_2H_5$) is recorded in Fig. 16.
The mass spectrum of the 2-amino-7-chloro-pyrano-oxazine (14)

It was noticed that the 2-amino-compound (14) had a more intense molecular ion than its 2-mercapto analogues, which indicated a greater stability of the 2-amino compound (14) under the conditions in the mass spectrometer. The 2-amino compounds (14) showed similar breakdown patterns to the 2-mercapto analogue (13), for which the loss of $R_1R_2N$ to give an ion with m/e 198 or the loss of $R_1R_2N$-CN to give an ion with m/e 172 was observed. The further breakdown of these ions occurred as in Scheme 1.

Scheme 2 shows the fragmentation behaviour of compound (14a).

This showed a parent peak at m/e 214 (32%) with accompanying p + 2 isotopic peak. Then there was loss of $\text{NH}_2$ to give an ion with m/e 198 (3%) or loss of $\text{NH}_2\text{C} = \text{N}$ to give an ion with m/e 172 (16%), but the main fragmentation route of the ion with m/e 214 was by the loss of CO (20) to give an ion with m/e 186 (68%) and this then lost CHNO to give an ion with m/e 143 (58%).

The ion with m/e 143 could break down in three different ways:

1. By loss of CO to give an ion with m/e 115 (14%).
2. By loss of C$_2$H$_4$O with hydrogen migration to give an ion with m/e 102 (21%).
(3) By loss of C₂O₂ giving an ion with m/e 87 (11%).

The fragmentation behaviour of compound (14a) was confirmed by metastable peak measurements and by preparing the compound with carbon-13 enrichment at position 2: this showed that the following ions carried the carbon-13 label: m/e 214, 198 and 186.

Fig. 17 recorded the mass spectrum of compound (14a).
Scheme 2. Fragmentation of Compound (1\textsubscript{4a}).

\begin{align*}
\text{m/e 198 (3\%)} & \quad \text{m/e 172 (16\%)} \\
\text{Cl} & \quad + \quad \text{NH}_2
\end{align*}

\begin{align*}
\text{Cl} \quad & \quad \text{O} \\
\text{m/e 216 (30\%)} & \quad \text{m/e 186 (68\%)} \quad \text{m/e 161.7} \\
\text{O} & \quad \text{m/e 143 (57\%)} \quad \text{m/e 110.0} \\
\text{H} & \quad \text{H} \\
\text{m/e 115 (11\%)} & \quad \text{m/e 102 (21\%)} \\
\text{Cl} & \quad \text{m/e 87 (11\%)}
\end{align*}
The mass spectra of 7-chloro-2-ethyl-2-butyl-, and 2-isopropylamino compounds (14b), (14c), and (14j).

In the spectra of these compounds an ion with m/e 214 was observed which corresponded to the molecular ion of compound (14a). Evidently, therefore, the compounds (14b, c and j) fragmented with hydrogen migration, through a pseudo six-membered ring transition state:

\[
\begin{align*}
\text{Cl} - \text{CHR} \rightarrow \text{NH} + \text{RCH}=\text{CHR}^1
\end{align*}
\]

\[
\begin{align*}
14b, R = R^1 = \text{CH}_3 \\
14c, R = H, R^1 = \text{CH}_2\text{CH}_3 \\
14j, R = \text{CH}_3, R^1 = H
\end{align*}
\]

The above rearrangement was confirmed by a metastable peak at m/e for b = 178.9, c = 169.6 and j = 189.3. The resultant ion, m/e 214, showed further breakdown similar to the compound (14a). The fragmentation of compound (14b) is shown in scheme (3) and the mass spectrum is recorded in Figure 18.
Scheme 4.

Fragmentation of the 7-chloro-2-isopropyl-amino Compound (14j)

\[
\begin{align*}
\text{m/e 256 (40\%)} & \\
\text{m/e 214 (23\%)} & \rightarrow \text{m/e 189.3} & \text{m/e 228 (16\%)} & \rightarrow \text{m/e 203.0} \\
\text{m/e 198 (32\%)} & \rightarrow \text{m/e 172 (15\%)} & \text{m/e 186 (38.2\%)}
\end{align*}
\]
Scheme 5.
Fragmentation of 2-butylamino-7-chloro-pyrano-oxazine (14c)

The breakdown pattern shown in Scheme 5 was confirmed by the various metastable ions at m/e 216.9 and 169.6.
Scheme 6.
Fragmentation of the 2-anilino-7-chloro-
pyrano-oxazine (14e)

The mass spectrum of the 2-anilino-7-chloro compound (14e) which had been enriched with carbon-13 at the 2-position showed the following ions containing carbon-13: - m/e 290, 262, 219 and 119.
The absence of the added enriched carbon-13 label from the ion with m/e 247, which comes from the parent ion of m/e 290 by loss of HNCO, suggested that migration occurred of the phenyl group to the nitrogen atom at position 3. This rearrangement was confirmed by the metastable ion at m/z 210.4.

**Scheme 7.**

Fragmentation of 7-chloro-2-pyrrolidinopyrano-oxazine (14g)
(See Ref 43 for the fragmentation patterns of pyrrolidine and its derivatives). Corresponding to each of the fragmentations in Scheme 7 there were metastable ions.

**Scheme 8.**

Fragmentation of the 7-chloro-2-ethoxy-
-pyrano-oxazine (62)

\[
\begin{aligned}
\text{Cl} & \quad \text{O} \\
\text{C}_2\text{H}_5 \quad \text{O} \\
\text{m/e} 198 \ (6\%) & \quad \text{C}_2\text{H}_5 \quad + \text{C}_2\text{H}_5\text{OCl} \\
\text{m/e} 172 \ (26\%) & \quad \text{m/e} 71
\end{aligned}
\]
Fig. 19 Mass spectrum of compound (62)
CHAPTER XV

MASS SPECTRA OF 4-CHLORO-2-PYRONE DERIVATIVES
Fragmentation of the 6-amino-4-chloro-3-ethyl and benzyl-mercapto-carbonyl-2-pyrone (35a) and (35b).

It was noticed from the mass spectra of compounds (35) that the first fragmentation was either loss of RS giving an ion with m/e 172 or loss of HSH giving an ion with m/e 171. Then the ion with m/e 172 lost HCNO with migration of the hydrogen atom from the NH₂ group to give an ion with m/e 129. In a similar way, the ion with m/e 171 lost CNO and gave an ion with m/e 129. The ion with m/e 129 either lost CO₂ and gave an ion with m/e 73 or lost H⁺ and Cl⁺ and gave an ion with m/e 93. These fragmentations were accompanied by metastable peaks.

Fig. 20 Mass spectrum of compound (35a)
Scheme 9.

$\text{C}_2\text{H}_5\text{S} - \text{C}_\text{N}\text{H}_2\text{O}_2\text{C}_\text{O}\text{C}_\text{O} \rightarrow \text{m/e 233 (51%)}$

\[ \text{m/e 233 (51%)} \]

$\text{H}_2\text{N} - \text{C}_\text{O}_2\text{N} - \text{C}_\text{H}_2\text{O}_2\text{C}_\text{O}\text{C}_\text{O} \rightarrow \text{m/e 172 (100%)}$

\[ \text{m/e 172 (100%)} \]

\[ \text{m/e 127.0} \]

$\text{Cl} \rightarrow \text{m/e 61}$

\[ \text{m/e 61} \]

$\text{m/e 93 (41%)}$

\[ \text{m/e 93 (41%)} \]

\[ \text{m/e 57.1} \]

$\text{m/e 73 (45.8%)}$

\[ \text{m/e 73 (45.8%)} \]

\[ \text{m/e 41.4} \]
Scheme 10.

Showing the fragmentation of compound (35b)

PhCH₂S - C
H₂N

m/e 297 (6%)

Cl

m/e 123 (3%)

/ m/e 172 (56)

m/e 100.2

m/e 98.6

m/e 171 (13%) m/e 91 (100%)
m/z/e 66, 67.5

m/e 124 (17%)

+ PhCH₂SH

m/e 123 (3%)

PhCH₂S

m/e 172 (56)

m/z/e 100.2

m/e 96.8

m/e 129 (20%)

m/z/e 96.8
The mass spectra of the 4-chloro-6-N-(ethylthioxy and benzylthioxy-carbonyl)amidopyran-2-one (48a) and (48b) and the 4-Bromo-N-(ethylthioxy-carbonyl)amidopyran-2-one (49)

It was found that these compounds broke-down either by loss of CO to give an ion with m/e (M-28) or by loss of RSH to give an ion with m/e (N-RSH) in which behaviour they resemble the fragmentation of thiocarbamates. For example, in the case of phenylthiocarbamate there are two weak rearrangement peaks at m/e 139 (M-CO, 1%, and m/e 124 (M - HNCO, 1%).

\[ \begin{align*}
\left[ C_6H_5NHSC\right]^+ & \rightarrow CO \\
C_6H_5NHCOSH & \rightarrow CH_3SH \\
C_6H_5NCO &
\end{align*} \]

m/e 139

\[ \begin{align*}
\left[ C_6H_5NHSC\right]^+ & \rightarrow CH_3SH \\
C_6H_5NCO & \rightarrow HNCO \\
C_6H_5SCH_3 &
\end{align*} \]

m/e 119

m/e 124
Scheme 11, showing the fragmentation of compound (48a)

\[
\text{C}_2\text{H}_5\text{S-C-N-O}^+ \rightarrow \text{m/e 62 (44\%)}
\]

\[
\text{m/e 143 (100\%)} \rightarrow \text{m/e 129 (38.5\%)} \rightarrow \text{m/e 97.3}
\]

\[
\text{m/e 233 (3\%)} \rightarrow \text{m/e 205 (3\%)} \rightarrow \text{m/e 171 (38.3\%)} \rightarrow \text{m/e 119.7}
\]

\[
\text{m/e 115 (6\%)} \rightarrow \text{m/e 92.5}
\]

\[
\text{C}_2\text{H}_5\text{SN}^+ \rightarrow \text{C}_2\text{H}_5\text{SH}
\]

\[
\text{m/e 70 (29\%)} \rightarrow \text{m/e 73 (55\%)} \rightarrow \text{m/e 41.4}
\]
The mass spectrum of the compound (48a) enriched with carbon-13 of the carbonyl group of the 6-NHC-SC\textsubscript{2}H\textsubscript{5} substituent was also examined. This confirmed the fragmentation shown in Scheme 11. The ions which contained the carbon-13 label were as follows: m/e 233, 171, 143 and 70.

**Fragmentation of compound (48b)**

It was found that this compound had a similar fragmentation pattern to that of the compound (48b) except that the parent peak was not observed; the first peak had m/e 171 (M-PhCH\textsubscript{2}SH).
Scheme 12.

Fragmentation of the 4-bromo-6-N-(ethylthioxy carbonyl) amidopyran-2-one (49)

\[ \text{Br} \quad \text{m/e 277} \]
\[ \rightarrow \quad \text{Br} \quad \text{m/e 249} \]
\[ 0 = C = + \]
\[ \text{m/e 215} \]
\[ \rightarrow \quad \text{m/e 187} \]
\[ \rightarrow \quad \text{m/e 173} \]
\[ \rightarrow \quad [\text{C}_2\text{NO}_2]^+ \quad \text{m/e 159} \]
\[ \rightarrow \quad \text{m/e 159} \]
\[ \rightarrow \quad \text{m/e 117} \]
\[ \rightarrow \quad \text{m/e 173} \]

\[ \text{H} \quad \text{Cl} \]
\[ \text{H} \quad \text{m/e 187} \]
\[ \text{H} \quad \text{m/e 159} \]
Fragmentation of the 4-chloro-6-N-methyl-N-(ethylthioxy- and benzylthioxy-carbonyl)asidopyran-2-one (51a) and (51b)

In the mass spectra of the above products there was loss of COS, similarly to the loss of CO$_2$ from carbamates. Also noticed was the loss of CO$_{N-28}$ from the 6-N$_6$-S R chain (as established by carbon-13 labelling). The breakdown pattern of the above compounds were confirmed by the metastable peaks.

Fig. 22 Mass spectrum of compound (51a)
In the mass spectrum of compound (5la), which had carbon-13 labelling at the carbon of the carbonyl group in the 6-<sup>3</sup>H<sub>5</sub>-SC<sub>2</sub>H<sub>5</sub> substituent, only the parent peak showed the presence of the label.
Scheme 14, Fragmentation of compound (51b)

PhCH$_2$S - CO - N$_3$CH$_3$

m/e 309 (28%)

- CO

PhCH$_2$S - N$_3$CH$_3$

m/e 291 (0.5%)

- COS

PhCH$_2$ - N$_3$CH$_3$

m/e 249 (65.5%)

m$^+$/e 200.7

- CO

PhCH$_2$ - N$_3$CH$_3$

m/e 221 (22.2%)

m$^+$/e 196.2
CHAPTER XVI

MASS SPECTRA OF 4-CHLORO AND -BROMO-2,6-DIHYDROXY PYRIDINE AND ITS DERIVATIVES
Fragmentation of the 4-chloro- and -bromo-2,6-dihydroxopyridine

The fragmentations of these compounds, shown in Scheme 15 and 16, were confirmed by the metastable peaks.

Scheme 15.

- HCNO
- CO
- Cl
- H₂CNO

m/e 145 (64%)
m/e 102 (91%)
m/e 71.8
m/e 67 (100%)
m/e 44.0
m/e 117 (8%)
m/e 94.4
m/e 73 (17%)
m/e 36.75
Fig. 23  Mass spectrum of compound (31)
Fragmentation of the 4-chloro-pyridyl-5-ethylthiocarbonate (54) and ethoxycarbonate (59)

It was found that the fragmentation behaviour of compounds (54) and (59) was similar to that of the thiocarbonates and carbonates.

\[
\text{O} = \text{C} \quad \begin{array}{c}
\downarrow \\
\text{S-CH}_3
\end{array} \quad \begin{array}{c}
\downarrow \\
\text{O-C}_6\text{H}_5
\end{array} 
\quad \xrightarrow{-\text{COS}} 
\begin{array}{c}
\text{C}_6\text{H}_5\text{OCH}_3 \\
\text{M - COS (m/e 108)}
\end{array}
\]

The loss of carbonylsulfide (COS) from the molecular ion of 5-methyl phenyl thiocarbonate gave an ion with m/e 108. This was not a single step process because meta stable peaks were found corresponding to the sequential loss of carbon monoxide and sulphur, and none corresponding to the direct production of an M-COS ion. However, in the case of compound (54) there was direct loss of carbonyl sulfide from the molecular ion to give the ion M-COS as shown by a metastable peak, corresponding to this fragmentation, with m/e 128.5.

\[
\text{Cl} \quad \begin{array}{c}
\text{HO} \\
\text{N} \\
\text{OCC}_2\text{H}_5
\end{array} \quad \xrightarrow{-\text{COS}} 
\begin{array}{c}
\text{Cl} \\
\text{HO} \\
\text{N} \\
\text{OC}_2\text{H}_5
\end{array} 
\quad \text{m/e 173 (22%)}
\]

m/e 233 (14%)

It was also found that the loss of ethylene (CH\textsubscript{2} = CH\textsubscript{2}) and COS, and ethylene and CO\textsubscript{2}, from the molecular ion of compounds (54) and (59) respectively, gave an ion with m/e 145 (corresponding to compound 31) which fragmented similarly to ethyl phenyl carbonate.
Scheme 17. Fragmentation of compound (54)

- C₂H₅S
- CO
- COS
- S
- CH₂=CH₂
- CH₃
Scheme 18. Fragmentation of compound (59)

- C<sub>2</sub>H<sub>5</sub>O
- CO<sub>2</sub>

m/e 172 (0.9%)

m/e 217 (3%)

m/e 173 (3%)

m/e 145 (75%)

m/e 144.4

m/e 158 (8%)

m/e 96.9, 121.6

m/e 138.0
Fragmentation patterns of the 4-chloro-3-ethoxy and methoxy carbonyl-2,6-dihydroxy pyridine (44a) and (44b)

These compounds, in the same manner as the salicylates, showed a base peak corresponding to the loss of the alcohol fragment. A six-membered cyclic transition state has been postulated to rationalize this elimination.

The salicylates, as do all alkyl benzoates, lose an alkoxy radical, and this is followed by ejection of carbon monoxide as illustrated below for methyl salicylate:-
In the higher salicylates, there is loss of the alkyl group with rearrangement of one hydrogen atom which gives the salicylic acid positive ion. The last then decomposes further by loss of water through the usual six-membered transition state.

Analogous behaviour was also observed in the spectrum of compound (44a) which is effectively an O-hydroxyaryl ester. It was also noticed that compound (44a) lost CO$_2$ together with $\text{CH}_2=\text{CH}_2$ and gave the ion m/e 145. This whole process giving rise to a metastable peak at m/e 97.0.
It was also noticed that the ion with m/e 145 fragmented similarly to 4-chloro-2,6-dihydroxypyridine (31), but that there was an increase in the relative intensity of the ion at m/e 117 to 100% from only 8% in the spectrum of compound (31). There was also a decrease in the relative intensity of the ion with m/e 102 from 91% for compound (31) to 19%. This indicated that the ion with m/e 145 in the spectrum of compound (54) and (59) preferred to lose CO (28) rather than HCNO (43).

Fig. 24 Mass spectrum of compound (54)
Scheme 19. Fragmentation of compound (44a)

The above fragmentation routes are confirmed by metastable peaks.
Fig. 25 Mass spectrum of compound (44a)
EXPERIMENTAL

PART I
1) Melting points were determined using a Gallenkamp melting point apparatus and they are uncorrected.

2) Microanalyses were performed either by Dr Alfred Bernhardt, Microanalytisches Laboratorium, W. Germany, or by the Microanalytical Service, Chemistry Department, University of Surrey, Guildford.

3) Mass spectra were obtained using an Associated Electrical Industries MS 12 spectrometer (ionization energy 170 ev).

4) Ultra violet data were obtained using a unicam SP 800 B spectro-photometer. The following abbreviations are used after the absorption values: infl, inflection; sh, shoulder.

5) Infrared absorption spectra were obtained using a unicam SP 200 spectrophotometer. The following abbreviations are used after the absorption values: s, strong; br, broad; v, weak; sh, shoulder.

6) The proton magnetic resonance results were obtained using either a Perkin-Elmer R10 60 MHz N.M.R. spectrometer operating at a sample temperature of 34° or a Bruker WH 90 FT N.M.R. spectrometer (25°) operating at 90 MHz. Tetramethyilsilane (T.M.S.) was used as internal standard with all solvents.

7) Carbon-13 Nuclear Magnetic Resonance results were obtained using a Bruker WH 90 FT N.M.R. spectrometer operating at 22.63 MHz. Tetramethyilsilane (T.M.S.) was used as internal standard.
CHAPTER I

2-ARYL-(OR ALKYL)-7-CHLORO-4,5-DIOXO-
PYRANO[3,4-\text{e}] 7-1,3-OXAZINE (13)
Preparation of malonyl chloride

Finely powdered malonic acid (52 g) was mixed with thionyl chloride (120 ml) and heated with stirring on an oil bath at 45°-50° for three days. Then the temperature was raised to 60° for about six hours. Finally, the pale yellow malonyl chloride was distilled at reduced pressure (40 g, 65%), b.p. 51°/21 mm.

7-Chloro-2-phenylmercapto-4,5-dioxopyran-3,4-entropy 7-1,3-oxazine (13, R = Ph)

(a) Malonyl chloride (14.1 g, 2 mols) and phenylthiocyanate (6.7 g, 1 mol) were warmed together on the steam-bath, under anhydrous conditions, until the mixture solidified completely and the evolution of hydrogen chloride gas ceased. The reaction mixture was left overnight at room temperature. A dark solid product was obtained, by repeated crystallization from carbon tetrachloride (charcoal), as fine yellowish needles of 7-chloro-2-phenylmercapto-4,5-dioxopyran-3,4-entropy 7-1,3-oxazine (13, R = Ph) were obtained (9.2 g, 60%), m.p. 191° (decomp). Found: C, 50.7; H, 2.28; Cl, 11.5; N, 4.7; S, 10.4; C<sub>13</sub>H<sub>10</sub>CINO<sub>5</sub>S requires C, 50.7; H, 2.0; Cl, 11.5; N, 4.6; S, 10.5. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 2.42 (b, Ph of the 2-PhS-); 3.65 (s, 3-H); δ<sub>max</sub> (Nujol) 3080 cm<sup>-1</sup>, 1775 sh, 1750 s, 1590 s, 1510 b cm<sup>-1</sup>, λ<sub>max</sub> (CHCl<sub>3</sub>) 279.5, 347 nm (ε 10.7, 1.68 x 10<sup>-3</sup>); m/e 307 M<sup>+</sup>, 309 M + 2 <sup>+</sup>.

(b) 3-Carboxy-6-chloro-4-hydroxy-2-oxopyran (5) (0.25 g) was treated with thionyl chloride (0.6 g) and the mixture was warmed until the solution was clear.
Excess of the thionyl chloride was removed under reduced pressure.

To the residue, phenylthiocyanate (0.22 g) was added and the mixture was heated on the steam-bath, under anhydrous conditions, until the mixture had solidified completely. The reaction mixture was left at room temperature overnight. Repeated crystallization from carbon tetrachloride (charcoal) gave fine yellowish needles of 7-chloro-2-phenylmercapto compound (13, R = Ph) (about 60%), m.p. 191 (decomp.), undepressed by the sample prepared as above.

2-Benzylmercapto-7-chloro-4,5-dioxopyrano-/3,4-c 7-1,3-oxazine

(13, R = PhCH₂)

Malonyl chloride (14.1 g, 2 mols.) and benzyl thiocyanate 20 (7.5 g, 1 mol.) was treated as above. By repeated crystallization from carbon tetrachloride (charcoal), yellowish needles of 2-benzylmercapto-7-chloro-4,5-dioxopyrano-/3,4-c 7-1,3-oxazine (13, R = PhCH₂) were obtained (10.4 g, 65%); m.p. 138°-140°; Found: C, 52.2; H, 2.6; Cl, 10.95; N, 4.32; S, 9.6; C₁₈H₁₄ClNO₅S requires: C, 52.3; H, 2.5; Cl, 11.05; N, 4.35; S, 9.95%. ν(CDC₃) 2,34 (s, Ph of the 2-Ph₂); 3,65 (s, 8CH₂); 5,58 (s, CH₂ of the 2-Ph₂); νmax (Nujol) 3070 cm⁻¹, 1780 cm⁻¹, 1755 cm⁻¹, 1590 cm⁻¹, 1555 cm⁻¹, 1538 cm⁻¹. λmax (CHCl₃) 280, 346 nm (ε 9.8, 13.9 x 10⁻³); m/e 321 M⁺, 323M⁺+2⁺.

7-Chloro-2-p-chlorobenzylmercapto-4,5-dioxopyrano-/3,4-c 7-1,3-oxazine

(13, R = p-Cl-C₆H₄CH₂).

Malonyl chloride (14.1 g, 2 mols.) and p-chloro-benzyl thiocyanate 21 (9.2 g, 1 mol.) was treated as above.
By repeated crystallization from acetonitrile, pale-yellow needles of the 7-chloro-2-p-chlorobenzylmercapto-4,5-dioxopyran-3,4-\(\gamma\)-1,3-oxazine (13, \(R = \text{p-CI-C}_6\text{H}_4\text{CH}_2\)) were obtained (11.0 g, 62%); m.p. 163°;

\[ \text{Found: C, 47.16; H, 1.96; N, 1.96; N, 3.97; C}_{14}\text{H}_9\text{Cl}_2\text{NO}_2\text{S requires: C, 47.19; H, 1.96; N, 3.94%.} \]

7-Chloro-2-ethylmercapto-4,5-dioxopyran-3,4-\(\gamma\)-1,3-oxazine

(I3, \(R = \text{C}_2\text{H}_5\text{S}^-\))

Ice-cooled malonylchloride (14.1 g, 2 mol.) was mixed with ethylthiocyanate (4.4 g, 1 mol.). The mixture was allowed to reach room temperature, then heated on the steam-bath, under anhydrous conditions, until the mixture solidified completely and the evolution of hydrogen chloride gas ceased. The reaction mixture was left overnight at room temperature.

A dark solid product was obtained, by repeated crystallization from carbon tetrachloride (charcoal), fine pale-yellow needles of 7-chloro-2-ethylmercapto-4,5-dioxopyran-3,4-\(\gamma\)-1,3-oxazine (13, \(R = \text{C}_2\text{H}_5\text{S}^-\)) were obtained (9.2 g, 72%);

\[ \text{Found: C, 41.6; H, 2.3; N, 5.4; C}_{9}\text{H}_6\text{ClNO}_2\text{S requires: C, 41.6; H, 2.3; N, 5.4%.} \]

\(\nu\) (Nujol) 3080 w, 1785 m, 1750 s, 1590 m, 1555 m, 1515 s, 1407 m cm\(^{-1}\); \(\lambda_{\text{max}}\) (CHCI\(_3\)) 278 s, 341 \(\pi\) nm; (\(\xi 15.0, 1.70 \times 10^{-3}\)) m/e 356 M\(^+\), 358 \(\sum M + 2\gamma^+\); \(p + 4, p + 6\).
CHAPTER II

2-AMINO-7-CHLORO-4,5-DIOXOPYRANO[3,4-b]-1,3-OXAZINES (14)
7-Chloro-2-pyrrolidino-4,5-dioxopyrano/3,4-e/7-1,3-oxazine (14 g)

2-Benzylmercapto-7-chloro-4,5-dioxopyrano/3,4-e/7-1,3-oxazine (13, R = PhCH₂) (3.21 g, 1 mol.) was dissolved in dry chloroform (35 ml) and pyrrolidine (0.92 ml, 1 mol.), in dry chloroform (10 ml), was added dropwise, while the mixture was stirred. The reaction mixture was refluxed for one hour.

After evaporation the reaction mixture was reduced to dryness under pressure, the solid was washed with water. 7-Chloro-2-pyrrolidino-4,5-dioxopyrano/3,4-e/7-1,3-oxazine (14 g) (2.38 g, 84%) crystallized from dichloromethane to give yellow plates had m.p. 267° (decomp). Found: C, 49.0; H, 3.4; N, 10.45. C₁₁H₉CN₂O₄ requires: C, 49.2; H, 3.35; N, 10.5.

7-Chloro-2-morpholino-4,5-dioxopyrano/3,4-e/7-1,3-oxazine (14 h)

2-Benzylmercapto-7-chloro-4,5-dioxopyrano/3,4-e/7-1,3-oxaziné (3.21 g, 1 mol.) was dissolved in dry chloroform (35 ml) and morpholine (0.9 g, 1 mol.), in dry chloroform (10 ml) was added dropwise, while the mixture was stirred. The reaction mixture was refluxed for one hour.

The reaction mixture was treated as above. 7-Chloro-2-morpholino-4,5-dioxopyrano/3,4-e/7-1,3-oxazine, crystallized from acetic acid to give colourless needles (2.37 g, 80%) had m.p. 249°. Found: C, 46.3; H, 3.3; N, 9.78. C₁₁H₉CN₂O₅ requires: C, 46.4; H, 3.12; N, 9.8. (CDCl₃) 3.95 (s, 8-H), 6.12 (b, 4 x CH₂ of the 2-morpholino).
(b) 7-Chloro-2-ethylmercapto-4,5-dioxopyrano[3,4-e]1,3-oxazine
(13, R = C₂H₅⁻) (2.59 g, 1 mol.) was dissolved in dry chloroform (35 ml.) and morpholine (0.9 g, 1 mol.) in dry chloroform (10 ml.), was added dropwise, while the mixture was stirred. The reaction mixture was refluxed for one hour.

After evaporation the reaction mixture to dryness under reduced pressure, the solid was washed with water. The residue was crystallized from acetic acid to give colourless needles (2.5 g, 85%) had m.p. 249° undepressed by the sample prepared as above.

2-Anilino-7-chloro-4,5-dioxopyrano[3,4-e]1,3-oxazine (14a)

2-Benzylmercapto-7-chloro-4,5-dioxopyrano[3,4-e]1,3-oxazine
(13, R = PhCH₂) (3.21 g, 0.01 mol.) was dissolved in dry chloroform (35 ml.) and aniline (0.83 g, 0.01 mol.), in dry chloroform (10 ml.), was added dropwise, while the mixture was stirred. The reaction mixture was refluxed for one hour.

After the reaction mixture was treated as above, crystallization from acetic acid gave a pale-yellow plate 2-anilino-7-chloro-4,5-dioxopyrano[3,4-e]1,3-oxazine product (2.7 g, 95%) had m.p. 184°; λ_{max} (CH₃CN) 297.5, 340 nm (ε 12.5, 20.3 x 10⁻³); m/e 290 M⁺, 292 \( \sum \text{M} + 2\).
7-Chloro-2-octylamino-4,5-dioxopyran-3,4-endo-1,3-oxazine (14d)

The 7-chloro-2-ethylmercapto compound (13, \( R = \text{C}_2\text{H}_5 \)) (2.5 g, 0.01 mol.) was treated with dry octylamine (1.29 g, 0.01 mol.). The reaction was carried out as above. The product was crystallized from carbon tetrachloride to give a colourless crystalline compound of 7-chloro-2-octylamino-4,5-dioxopyran-3,4-endo-1,3-oxazine (2.2 g, 80%), had m.p. 199° (Found: C, 55.3; H, 5.7; N, 8.4. \( \text{C}_{15}\text{H}_{19}\text{ClN}_2\text{O}_4 \) requires: C, 55.1; H, 5.8; N, 8.6) (CDCl\(_3\)) 2.12, 3.35 (by total intensity one proton NH); 3.90, 3.94 (s, s, total intensity one proton 8-H); 6.53 (q, CH\(_2\)), 8.1 - 9.1 (c, 6 x CH\(_2\)), 9.13 (ca. t, Me J 5.1 Hz); \( \gamma \) max (Nujol) 3330m, 3270w, 1766m, 1716s, 1652s, 1580s, 1507v, 1490w cm\(^{-1}\); \( \lambda \) max (CH\(_2\)CN) 294.5, 338 nm (\( \varepsilon 1.4 \times 10^{-3}\)).

2-Amino-7-chloro-4,5-dioxopyran-3,4-endo-1,3-oxazine (14a)

The 7-chloro-2-ethylmercapto-compound (2, \( R = \text{C}_2\text{H}_5 \)) (2.6 g, 0.01 mol.) was dissolved in dry chloroform (50 ml) in a conical flask (100 ml.) fitted with a carbon dioxide cooled condenser. The solution was cooled in solid carbon dioxide-acetone, and liquid ammonia (0.4 ml) was added, while the reaction mixture was stirred. The reaction mixture was allowed to stand at room temperature for half an hour, then refluxed for half an hour. After evaporating the reaction mixture to dryness under reduced pressure, the residue was washed with acetone and crystallized from acetic acid-dimethylsulphoxide to give pale-yellow crystals of 2-amino-7-chloro-4,5-dioxopyran-3,4-endo-1,3-oxazine (1.4 g, 65%); had m.p. 300 (decomp.) (Found: C, 39.0; H, 1.45; N, 12.9. \( \text{C}_{15}\text{H}_{19}\text{ClN}_2\text{O}_4 \) requires: C, 39.2; H, 1.4; N, 13.0) (d\(_6\) DMSO) 0.85 br and 1.0 br (NH\(_2\)), 3.84 (s, 8-H); \( \gamma \) max (Nujol) 3360m, 3330w, 2330v, 3170w, 3070w, 1750m, 1654s, 1578m, 1550s, 1500m cm\(^{-1}\); \( \lambda \) max (CH\(_2\)CN) 291, 333.5 nm (\( \varepsilon 1.6 \times 10^{-3}\)); m/c 214 M\(^{+}\), 216 \( \Sigma \text{M} + 2 \Sigma \text{H} \).
2-Benzylamino-7-chloro-4,5-dioxopyrano[3,4-e]7-1,3-oxazine (14f)

7-Chloro-2-ethylmercapto-4,5-dioxopyrano[3,4-e]7-1,3-oxazine

(2.59 g, 1 mol.) was dissolved in dry chloroform (35 ml) and benzylamine (1.07 g, 1 mol.) in dry chloroform (10 ml), was added dropwise, while the mixture was stirred. The reaction mixture was refluxed for one hour. After evaporating the reaction mixture to dryness under reduced pressure, the solid was washed with water. 2-Benzylamino-7-chloro-4,5-dioxopyrano[3,4-e]7-1,3-oxazine (2.73 g, 90%) crystallized from acetic acid to give pale-yellow needles had m.p. 186°; Found: C, 54.8; H, 3.0; N, 9.3.

C_{14}H_{19}CIN_{2}O_{4} requires: C, 55.2; H, 2.95; N, 9.2%. 

7-Chloro-2-ethylamino-4,5-dioxopyrano[3,4-e]7-1,3-oxazine (14b)

7-Chloro-2-ethylmercapto-4,5-dioxopyrano[3,4-e]7-1,3-oxazine (2.59 g, 1 mol.) was dissolved in dry chloroform (35 ml) and ethylamine (0.45 g, 1 mol.) in dry chloroform (10 ml), was added dropwise, while the mixture was stirred. The reaction mixture was refluxed for one hour. After evaporating the reaction mixture to dryness under reduced pressure, the residue was washed with water and crystallized from ethanol (96%) to give colourless needles of 7-chloro-2-ethylamino-4,5-dioxopyrano[3,4-e]7-1,3-oxazine (2.0 g, 85%) had m.p. 180°; Found: C, 44.7; H, 2.8; N, 11.6.

C_{14}H_{19}CIN_{2}O_{4} requires: C, 44.5; H, 2.9; N, 11.5%. 

7-Chloro-2-ethylamino-4,5-dioxopyrano[3,4-e]7-1,3-oxazine (14d)

7-Chloro-2-ethylmercapto-4,5-dioxopyrano[3,4-e]7-1,3-oxazine (2.59 g, 1 mol.) was dissolved in dry chloroform (35 ml) and benzylamine (1.07 g, 1 mol.) in dry chloroform (10 ml), was added dropwise, while the mixture was stirred. The reaction mixture was refluxed for one hour. After evaporating the reaction mixture to dryness under reduced pressure, the solid was washed with water. 7-Chloro-2-ethylamino-4,5-dioxopyrano[3,4-e]7-1,3-oxazine (2.73 g, 90%) crystallized from acetic acid to give pale-yellow needles had m.p. 186°; Found: C, 54.8; H, 3.0; N, 9.3.

C_{14}H_{19}CIN_{2}O_{4} requires: C, 55.2; H, 2.95; N, 9.2%. 

7-Chloro-2-ethylamino-4,5-dioxopyrano[3,4-e]7-1,3-oxazine (14d)

7-Chloro-2-ethylmercapto-4,5-dioxopyrano[3,4-e]7-1,3-oxazine (2.59 g, 1 mol.) was dissolved in dry chloroform (35 ml) and ethylamine (0.45 g, 1 mol.) in dry chloroform (10 ml), was added dropwise, while the mixture was stirred. The reaction mixture was refluxed for one hour. After evaporating the reaction mixture to dryness under reduced pressure, the residue was washed with water and crystallized from ethanol (96%) to give colourless needles of 7-chloro-2-ethylamino-4,5-dioxopyrano[3,4-e]7-1,3-oxazine (2.0 g, 85%) had m.p. 180°; Found: C, 44.7; H, 2.8; N, 11.6.

C_{14}H_{19}CIN_{2}O_{4} requires: C, 44.5; H, 2.9; N, 11.5%. 

7-Chloro-2-ethylamino-4,5-dioxopyrano[3,4-e]7-1,3-oxazine (14d)

7-Chloro-2-ethylmercapto-4,5-dioxopyrano[3,4-e]7-1,3-oxazine (2.59 g, 1 mol.) was dissolved in dry chloroform (35 ml) and benzylamine (1.07 g, 1 mol.) in dry chloroform (10 ml), was added dropwise, while the mixture was stirred. The reaction mixture was refluxed for one hour. After evaporating the reaction mixture to dryness under reduced pressure, the solid was washed with water. 7-Chloro-2-ethylamino-4,5-dioxopyrano[3,4-e]7-1,3-oxazine (2.73 g, 90%) crystallized from acetic acid to give pale-yellow needles had m.p. 186°; Found: C, 54.8; H, 3.0; N, 9.3.

C_{14}H_{19}CIN_{2}O_{4} requires: C, 55.2; H, 2.95; N, 9.2%. 

7-Chloro-2-ethylamino-4,5-dioxopyrano[3,4-e]7-1,3-oxazine (14d)

7-Chloro-2-ethylmercapto-4,5-dioxopyrano[3,4-e]7-1,3-oxazine (2.59 g, 1 mol.) was dissolved in dry chloroform (35 ml) and ethylamine (0.45 g, 1 mol.) in dry chloroform (10 ml), was added dropwise, while the mixture was stirred. The reaction mixture was refluxed for one hour. After evaporating the reaction mixture to dryness under reduced pressure, the residue was washed with water and crystallized from ethanol (96%) to give colourless needles of 7-chloro-2-ethylamino-4,5-dioxopyrano[3,4-e]7-1,3-oxazine (2.0 g, 85%) had m.p. 180°; Found: C, 44.7; H, 2.8; N, 11.6.

C_{14}H_{19}CIN_{2}O_{4} requires: C, 44.5; H, 2.9; N, 11.5%. 

7-Chloro-2-ethylamino-4,5-dioxopyrano[3,4-e]7-1,3-oxazine (14d)

7-Chloro-2-ethylmercapto-4,5-dioxopyrano[3,4-e]7-1,3-oxazine (2.59 g, 1 mol.) was dissolved in dry chloroform (35 ml) and benzylamine (1.07 g, 1 mol.) in dry chloroform (10 ml), was added dropwise, while the mixture was stirred. The reaction mixture was refluxed for one hour. After evaporating the reaction mixture to dryness under reduced pressure, the solid was washed with water. 7-Chloro-2-ethylamino-4,5-dioxopyrano[3,4-e]7-1,3-oxazine (2.73 g, 90%) crystallized from acetic acid to give pale-yellow needles had m.p. 186°; Found: C, 54.8; H, 3.0; N, 9.3.

C_{14}H_{19}CIN_{2}O_{4} requires: C, 55.2; H, 2.95; N, 9.2%. 

7-Chloro-2-ethylamino-4,5-dioxopyrano[3,4-e]7-1,3-oxazine (14d)
7-Chloro-2-iso-propylamino-4,5-dioxopyran-3,4-endo-1,3-oxazine (14j)

The 7-chloro-2-ethylmercapto compound (13, R = C₂H₅) (2.59 g, 1 mol.), was treated with iso-propylamine (0.59 g, 1 mol.). The reaction was carried out as above.

The product was crystallized from ethyl alcohol to give colourless needles of 7-chloro-2-iso-propylamino-4,5-dioxopyran-3,4-endo-1,3-oxazine (1.9 g, 74%) had m.p. 200°C; Found: C, 46.75; H, 3.55; N, 11.0.

C₁₀H₉ClN₂O₄ requires: C, 46.8; H, 3.5; N, 10.9%. δ (Dioxane) 2.35 (b 9 NH), 3.85 and 3.88 (s, s, 8-H); 8.78 (d, 2 x CH₃ of the 2-(CH₃)₂CHNH₂, J 7 Hz); νmax (Nujol) 3245m, 3080w, 1743s, 1640s, 1580m, 1517s cm⁻¹; m/e 256 M⁺, 258 [M - 2J⁺.

2-Butylamino-7-chloro-4,5-dioxopyran-3,4-endo-1,3-oxazine (14c)

The 7-chloro-2-ethylmercapto compound (13, R = C₂H₅) (2.6 g, 1 mol.) was treated with dry butylamine (0.74 g, 1 mol.). The reaction was carried out as above.

The product was crystallized from carbon tetrachloride to give a colourless crystalline compound of 2-butylamino-7-chloro-4,5-dioxopyran-3,4-endo-1,3-oxazine (2.2 g, 81%), had m.p. 142°C; Found: C, 48.9; H, 4.0; N, 10.4.

C₁₁H₁₁ClN₂O₄ requires: C, 48.9; H, 4.1; N, 10.5%. δ (CDCl₃) 1.98, 3.34 (b, total intensity 1 proton NH); 3.91, 3.93 (s, total intensity one proton 8-H); 6.38 (q, CH₂ at the 2-CH₃(CH₂)₂CH₂NH₂, J 6.3 Hz); 8.1 - 8.8 (b - β, γ - CH₂ at 2-CH₃(CH₂)₂CH₂NH₂; 9.04 (ca. t CH₃ of the butylamino); νmax (Nujol) 3245m, 3150w, 3080v, 1770(s), 1735s, 1626s, 1580m, 1530s, 1450v cm⁻¹; λmax (CH₂CN) 294, 336.5 μm (ε 13.3, 16.9 x 10⁻³); m/e 270 M⁺, 272 [M - 2J⁺.
2-7-Dimorpholino-4,5-dioxopyrano[3,4-\(\gamma\)-1,3-oxazine (15a)

(a) 7-Chloro-2-morpholino-4,5-dioxopyrano[3,4-\(\gamma\)-1,3-oxazine (14h)

(2.9 g, 1 mol.) was dissolved in dry chloroform (35 ml.) and morpholine
(1.8 g, 2 mols.) in dry chloroform (10 ml.) was added dropwise, while the
mixture was stirred.

The reaction mixture was refluxed for one hour. After the reaction
mixture had been evaporated to dryness under reduced pressure, the residue
was washed with water, and crystallised from ethylacetate to give colourless
needles of 2,7-dimorpholino-4,5-dioxopyrano[3,4-\(\gamma\)-1,3-oxazine (1 g, 30%),
had m.p. 215°. Found: C, 53.7; H, 5.0; N, 12.6. 
\(\text{C}_{15}\text{H}_{17}\text{N}_{3}O_{6}\) requires:
C, 53.7; H, 5.1; N, 12.5%. \(\delta\) (\(\text{CDCl}_3\)) 4.82 (s, 3-H); 6.15 (\(\text{C}1\text{HCH}_2\) of
\(\alpha\), \(\beta\) of 2-morpholino and \(\alpha\) of 7-morpholino); 6.82 (C 2 x \(\text{CH}_2\) of
\(\beta\) of the 7-morpholino); \(\nu_{\max} (\text{Nujol})\) 3060w, 1764m, 1714s, 1621m, 1580m,
1514m cm\(^{-1}\); \(\lambda_{\max}\) (CH\(_3\)CN) 289.5, 325 nm (\(\varepsilon 15.5, 7.7 \times 10^{-3}\)) m/e 335 M\(^{+}\).

(b) 7-Chloro-2-ethylmercapto-4,5-dioxopyrano[3,4-\(\gamma\)-1,3-oxazine (13,
R = \(\text{C}_2\text{H}_5\)) (2.6 g, 1 mol.) was dissolved in dry chloroform (35 ml.)
and morpholine (2.7 g, 3 mols.) in dry chloroform (15 ml.), was added
dropwise, while the mixture was stirred.

The reaction mixture was refluxed for 1 hour. After evaporation
of the reaction mixture to dryness under reduced pressure, the residue was
washed with water and crystallised from ethylacetate to give colourless
needles of the 2,7-dimorpholino-4,5-dioxopyrano[3,4-\(\gamma\)-1,3-oxazine (1 g, 30%) had m.p. 215° undepressed by the sample prepared as above (method (a)).
2-Butylamino-7-morpholino-4,5-dioxopyran-3,4-e,7-1,3-oxazine (15b)

(2.7 g, 1 mol.) was dissolved in dry chloroform (35 ml) and morpholine (1.8 g, 2 mol.) in dry chloroform (10 ml), was added dropwise, while the mixture was stirred. The reaction mixture was refluxed for one and a half hours. After evaporation of the reaction mixture to dryness under reduced pressure, the residue was washed with water, and triturated with methyl alcohol to give colourless 2-butylamino-7-morpholino-4,5-dioxopyran-3,4-e,7-1,3-oxazine (15b) (1.7 g, 50%), recrystallized from ethyl acetate m.p. 182°. Found: C, 56.1; H, 5.9; N, 13.1. C_{19}H_{19}N_{3}O_{5} requires: C, 56.0; H, 6.0; N, 13.4%. 1H (CDCl_{3}) 1.9 and 3.8 (b, total one proton, NH); 4.78 and 4.85 (s, total of one proton 8-H), 6.15 (ca. t, 2 x CH_{2} of the 7-morpholino); 6.55 (q, 2 - CH_{2} at the 2-butylamino) 6.85 (b, 2 x CH_{2} of the 7-morpholino); 8.1 - 8.8 (b, 2 x CH_{2} of BuN); 9.05 (t, Me, J 6.8 Hz); ν_{max.} (Nujol) 3180m, 3060w, 1767 s, 1690s, 1636s, 1576, 1545w, 1510s (b) cm^{-1}; λ_{max.} (CHCl_{3}) 287, 323 nm (ε 7.9, 20.9 x 10^{-3}); m/e 321 M^{+}.

2,7-Dibenzyl amino-4,5-dioxopyran-3,4-e,7-1,3-oxazine (15c)

7-Chloro-2-ethylmercapto-4,5-dioxopyran-3,4-e,7-1,3-oxazine (13, R = C_{2}H_{5}) (2.6 g, 1 mol.) was dissolved in dry chloroform (35 ml) and dry benzylamine (3.2 g, 3 mol.) in dry chloroform (10 ml) was added dropwise, while the mixture was stirred. The reaction mixture was refluxed for one hour. After the solvent was removed under reduced pressure, the residue was washed with warmed ethyl alcohol (50 ml) to remove the 4,6-dibenzyl amino-3(benzyl amido carbonyl-amido carbonyl)-2-oxopyrano (18b) (1 g, 20%) m.p. 200° (decomp.) (The physical properties will
be discussed later).

The solid remained after the washing with warmed ethyl alcohol was recrystallized from acetonitrile to give a colourless crystalline product of 2,7-dibenzyl amino-4,5-dioxopyran-3,4-e-1,3-oxazine (15c)
(0.5 g, 13.5%) m.p. 218° (decomp.) \( \int \) Found: N, 11.4%. \( \text{C}_{21} \text{H}_{17} \text{N}_3 \text{O}_4 \) requires: N, 11.2%. m/e 375 M+; \( \text{C} \left( \text{d}_6 \text{ DMSO} \right) \) -1.19 (s, ring NH of tautomer), and -0.85 br (2 NH), 1.21 br (t, 7-NH), 2.70 (2 x Ph), 4.26 (s, 8-H); 5.57 br (2 x CH₂); \( \gamma_{\text{max}} \) (Nujol) 3190, 1712, 1664, 1600, 1570, 1542, 1500 cm⁻¹

3-Ethoxy 2-ethoxy carbonyl-4-morpholine amido, but-2-enoic acid N-butyrate (16)

On recrystallizing the 2-butylamino-7-morpholino-4,5-dioxopyran-3,4-e-1,3-oxazine (15b) from ethyl alcohol only a partial recovery of the compound (14c) (1.4 g) was achieved. Evaporation of the filtrate gave a colourless residue of 3-ethoxy-2-ethoxy carbonyl-4-morpholine carbonyl but-2-enoic acid N-butyrate (16) (0.2 g), m.p. 112° \( \int \) from petroleum ether (b.p. 80-100°). \( \int \) Found: C, 55.4; H, 7.3; N, 10.0. \( \text{C}_{19} \text{H}_{31} \text{N}_3 \text{O}_7 \) requires: C, 55.5; H, 7.3; N, 10.2%. \( \text{C} \left( \text{C}_{6} \text{DCl}_3 \right) \) -0.35 br (s, CO.NH.CO) 1.35 br (t, NH of NHBu N 5.6 Hz); 5.78 and 5.83 (q, q, 2 x CH₂ of etho groups); 6.15 (c, CH₂ N of BuN and CH₂ O.CH₂), 6.3 (s, 4-CH₂), 6.77 (ca.t, CH₂ N.CH₂), 3.3 – 3.9 (2 x CH₂ of Bu), 8.69 (t, Me of EtOCO N 6.8 Hz), 8.75 (t, Me of 3 EtO N 6.8 Hz), 9.09 (ca.t, Me of Bu); \( \gamma_{\text{max}} \) (Nujol) 3320, 1740, 1698, 1670, 1630, 1540 cm⁻¹

4-Morpholino carbonyl-3-morpholino but-2-enoic acid morpholide (17)

(a) The 7-chloro-2-ethylmercapto-compound (13, R = C₂H₅) 2.6 g) was dissolved in dry chloroform (35 ml) and treated with an excess of morpholine
The reaction mixture was refluxed for one hour, cooled and washed with water. The solution was dried over sodium sulphate, and the solvent was removed under reduced pressure.

The residue was treated with ethyl alcohol. The solid was separated and crystallized from ethyl alcohol to give colourless needles of 4-morpholido carbonyl-3-morpholino but-2-enolic acid morpholide (17) (1.7 g, 50%) m.p. 207° (decomp.). Found: C, 57.4; H, 7.7; N, 11.85. C_{17}H_{27}N_{3}O_{5} requires: C, 57.7; H, 7.6; N, 11.9%. \nu (CDCl_3) \ 4.88 (s, 2-H); 5.88 (s, 2-CH_2), 6.37 (c, 10 x CH_2); 6.97 (c, 2 x CH_2); \nu_{\text{max}} (Nujol) 1655 s, 1620 s, 1570 cm\(^{-1}\) \lambda_{\text{max}} (CHCl_3) 286 nm (\varepsilon 151 x 10\(^{-3}\)); m/e 353 M\(^+\).

(b) The 7-chloro-2-morpholino-compound (14h) (2.9 g) was dissolved in dry chloroform (40 ml) and treated with excess of morpholine (5 ml). The reaction mixture was treated as above from ethyl alcohol colourless needles of 4-morpholido carbonyl-3-morpholino but-2-enolic acid morpholide (17) (18 g, 51%) were obtained, m.p. 207° (decomp.), undepressed by the sample prepared as above.

(c) The 2,7-dimorpholino compound (15a) (0.34 g) was treated with an excess of morpholine (3 ml) as above from ethyl alcohol, crystalline 4-morpholido carbonyl-3-morpholino but-2-enolic acid morpholide (17) (0.2 g, 55%) was obtained, m.p. 207° (decomp.), undepressed by the sample prepared as above.
CHAPTER IV

4,6-DIAMINO-PYRON-DERIVATIVE

(18) AND (19)
4,6-Dibenzylamino-3( benzylamidocarbonyl-amidocarbonyl)-2-oxo pyran (18b)

(a) The 2-benzylamino-7-chloro-4,5-dioxo-pyran-3,4-e,7-1,3-oxazine (14f) (1.5 g, 1 mol) was suspended in dry dioxan (35 ml) and dry benzylamine (1.1 g, 2 mols) in dry dioxan (10 ml), was added dropwise, while the mixture was stirred.

The reaction mixture was refluxed for two and a half hours. After evaporation of the reaction mixture to dryness under reduced pressure, the residue was washed with water and crystallized from ethyl alcohol to give colourless crystalline of 4,6-dibenzylamino-3(benzylamidocarbonylamidocarbonyl)-2-oxo pyran (18b) (0.5 g, 20%) had m.p. 200° (decomp); \( \text{Found: C, 69.6; H, 5.45; N, 11.6%} \)
\( \text{requires: C, 69.7; H, 5.4; N, 11.6%} \)
\( \text{ Ż (CDCl}_3) -1.19 \text{ br (s, CONHCO, bonded);} \)
\( -0.58 \text{ br (t, 4-NH, bonded), 1.15 br (t, N H remote at 3), 3.24 br (t, 6-NH); 2.53 - 3 (C, 3 x Ph); 5.28 (s, 5-H); 5.52, 5.72, 5.75 (d, 3 x CH}_2 \text{ of the benzylamino groups, } J = 6 \text{ Hz); \text{ vmax (Nujol) 3250 m, 1690cover, 1675 s, 1620 s, 1600(s), 1580m, 1550m cm}^{-1} \text{; } \lambda_{max} (\text{CHCl}_3) 252, 312 \text{ nm (ε 1299, 16.4 x 10}^{-3} \text{); } \text{m/e M^+} \)

(b) The 7-chloro-2-ethylmercapto-4,5-dioxopyran-3,4-e,7-1,3-oxazine (13, R = C}_2H_5(-) (2.6 g, 1 mol) was dissolved in dry dioxan (35 ml) and dry benzylamine (3.1 g, 3 mols), in dry dioxan (10 ml), was added dropwise, while the mixture was stirred. The reaction mixture was refluxed for two and a half hours. After evaporation of the reaction mixture to dryness under reduced pressure, the residue was washed with water, and crystallized from ethyl alcohol to give colourless crystalline of 4,6-dibenzylamino-3(benzylamidocarbonylamidocarbonyl)-2-oxo pyran (18b) (1 g, 20%), m.p. 200° (decomp.), undepressed by the sample prepared as above.
4,6-Dibenzylamino-3(morpholidocarbonylamidocarbonyl), 2-oxopyrane (18c)

7-Chloro-2-morpholo-4,5-dioxopyran-3,4-c-1,3-oxazine (14h)

(2.9 g, 1 mol) was suspended in dry chloroform (35 ml) and benzylamine (2.2 g, 0.2 mol%) in dry chloroform (10 ml), was added dropwise, while the mixture was stirred. The reaction mixture was refluxed for two and a half hours. After evaporation of the reaction mixture to dryness under reduced pressure, the residue was washed with water, and crystallized from ethyl alcohol to give colourless crystalline of 4,6-dibenzylamino-3-(morpholino-carbonylamidocarbonyl)-2-oxopyrane (18c) (1.8 g, 40%), m.p. 216° (decomp); Found: C, 64.7; H, 5.6; N, 12.1. \( C_{25}H_{26}N_4O_5 \) requires C, 64.9; H, 5.6; N, 12.1. \( \tau (CDCl_3) \) -1.50 br (3-NH, bonded), -1.05 br (4-NH, bonded), 3.8 br (6-NH), 2.76 (c, 2 x Ph); 5.21 (s, 5-H), 5.75 (d, 2 x CH₂, J 6 Hz), 6.47 (c, 4 x CH₂ of the morpholino-); \( \lambda_{\text{max}} \) (nujol) 3250m, 3090w, 1710m, 1660s, 1610m, 1575s, 1535 cm\(^{-1}\); \( \lambda_{\text{max}} \) (CH₃CN) 249, 311s nm (E 10.7, 1.5 x 10\(^{-3}\)); m/e 376 \( \Sigma \text{M-86}^+ \) (86 for morpholino group).

3-(Aminocarbonylamidocarbonyl)-4,6-dibenzylamino-2-oxopyran (18d)

2-Amino-7-chloro-4,5-dioxopyran-3,4-c-1,3-oxazine (14a) (2.1 g, 0.01 mol) was dissolved in dry DMSO (30 ml) and dry benzylamine (2.2 g, 0.02 mol) in dry DMSO (10 ml) was added dropwise, while the mixture was stirred. The reaction mixture was then refluxed for one and a half hours. After the reaction mixture had been evaporated to dryness under reduced pressure, the residue was washed with water and crystallized from ethyl alcohol to give colourless needles of 3-(aminocarbonylamidocarbonyl)-4,6-dibenzylamino-2-oxopyrane (18d) (1.9 g, 30%), m.p. 244° (decomp); Found: C, 64.5; H, 5.1; N, 14.5. \( C_{21}H_{20}N_4O_4 \) requires C, 64.3; H, 5.1; N, 14.3.
(d$_6$ DMSO) -0.88 (s, CO$_2$NH\cdot CO, bonded), -0.4 br (4-NH, bonded), 1.30 br 
(6-NH), 2.50 br (NH$_2$), 2.73 (s, 2 x Ph), 4.9 (s, 5-H). 5.61 (c, 2 x CH$_2$
overlapped); $\nu_{\text{max}}$ (Nujol) 3400m, 3230b, 3080sh, 1690sh, 1650s, 1646sh,
1618w, 1590w, 1555b, 1540sh cm$^{-1}$; $\lambda_{\text{max}}$ (CH$_3$CN) 247.5, 311 nm ($\varepsilon$ 12.2,
170 x 10$^{-3}$); m/e 392 M$^+$. 

4,6-Dianilino-3-(ethylmercaptocarbonyl amidocarbonyl)-2-oxopyrane (20b)

7-Chloro-2-ethylmercapto-4,5-dioxopyrano$\gamma$-3,4-e$\gamma$-1,3-oxazine 
(13, R = C$_2$H$_5$) (1.3 g) was dissolved in dry dioxan (30 ml), and mixed with 
aniline hydrochloride (3 g).

The reaction mixture was refluxed for two and a half hours. After 
the reaction mixture had been evaporated to dryness under reduced pressure, the 
residue was washed with water, and crystallized from acetic acid (charcoal) 
to give greenish crystalline product of 4,6-dianilino-3-(ethylmercaptocarbonyl 
amidocarbonyl)-2-oxopyrane (20b) (1.0 g; 50%), m.p. 203° (decomp); 
$\frac{m}{e}$ 392 M$^+$. 

4,6-Dianilino-3(benzylmercaptocarbonyl amidocarbonyl)-2-oxopyrane (20a)

2-Benzylmercapto-7-chloro-7, 5-dioxopyrano$\gamma$-3,4-e$\gamma$-1,3-oxazine 
(13, R = PhCH$_2$) (1.5 g) was dissolved in dry dioxan (30 ml), and mixed 
with aniline hydrochloride (3 g). The reaction mixture was refluxed for 
two and a half hours.
After the reaction mixture had been evaporated to dryness under reduced pressure, the residue was washed with water and crystallized from acetic acid (charcoal) to give colourless plates of 4,6-dianilino-3-(benzylmercaptocarbonyl amidocarbonyl)-2-oxopyrane (20a) (1.3 g; 50%); m.p. 213° (decomp.), \[C_{26}H_{21}N_{3}O_{4}S \] requires: C, 66.1; H, 4.65; N, 8.9%; \[\text{Found: C, 66.1; H, 4.65; N, 8.8%} \] \[\text{CDCl}_3\] -2.15, -1.30, -0.57 (b, 3 x NH), 2.75 (c, 3 x Ph), 4.09 (s, 5-H), 5.83 (s, 1 x CH$_2$ at the PhCH$_2$S-); \[\text{max}_\text{max}(\text{Nujol}) 3230\text{w}, 1705\text{m}, 1690\text{s}, 1618\text{s}, 1598\text{s}, 1550\text{m cm}^{-1}; \text{max} (\text{CH$_3$CN}) 251\text{y} 327.5\text{nm (Ɛ 21.2, 24.5 x 10}^{-3}); \text{m/e 471 M}^+ \]
CHAPTERS V AND VI
Reaction of 7-chloro-2-ethylmercapto-4,5-dioxopyran-3,4-oxazine with four moles of benzylamine

R = C_2H_5

The 7-chloro-2-ethylmercapto compound (13, R = C_2H_5) (2.6 g, 0.01 mol) was dissolved in dry dioxan (35 ml) and dry benzylamine (4.5 g, 0.04 mol) in dry dioxan (10 ml), was added dropwise, while the reaction mixture was stirred.

The mixture was refluxed for 2 hours. After the reaction mixture had been evaporated to dryness, under reduced pressure the residue was washed with water and then extracted with boiling ethyl alcohol to dissolved the 2,4-di(benzylamidocarbonyl)-3-benzylaminobut-2-enoc acid-N-benzylureide (23b) which was obtained (1.5 g) on cooling of the extract.

The residue remaining after the extraction with boiling ethyl alcohol was crystallized from acetonitrile. Repeated crystallization from acetonitrile gave colourless needles of 2-benzylamino-5-benzylamidocarbonyl-2-oxo-1,3-oxazineyl-acetobenzylamide (22) (0.3 g), m.p. 199° (decomp.); Found: C, 69.9; H, 5.5; N, 11.5; C_{38}H_{36}N_{10}O_{4} requires: C, 69.7; H, 5.4; N, 11.6%

T (d_6 DMSO) 0.26, 0.83, 1.45 (b, 3 x NH); 2.7 (c, 3 x C_6H_5); 5.47 - 5.85 (e, 3 x CH_2 of the PhCH_2 NH), 6.06 (s, CH_2); Y_{max} (Nujol) 3350m, 3270sh, 3070sh, 1708s, 1675s, 1652s, 1630w, 1601b, 1545s, 1505w cm^{-1}; \lambda_{max} (96% C_2H_5OH) 222 nm ( E 11.6 x 10^{-3}).

2,4-Di(benzylamidocarbonyl)-3-benzylaminobut-2-enoc acid-N-benzylureide (23b)

(a) This compound from the above reaction was repeatedly crystallized from ethylalcohol; it then formed colourless needles, m.p. 165°; Found: C, 71.4; H, 6.1; N, 12.0; C_{33}H_{35}N_{5}O_{4} requires: C, 71.3; H, 5.9; N, 11.9%
(CDCl₃) -0.70 br (NH, bonded), -0.22 br (s, CO,NH,CO), 1.23 br and 1.67 br and 2.33 br (3 x NH), 2.82 (4 x Ph), 5.73 (4 x CH₂ of the benzyl groups), 6.57 (s, 3-Hz); ν<sub>max</sub> (Nujol) 3250m, 3080w, 1674s, 1650s, 1634s, 1597s, 1550s, 1500s cm<sup>-1</sup>, λ<sub>max</sub> (CH₃CN) 280 nm (ε 10.9 x 10<sup>-3</sup>).

(b) The 7-chloro-2-ethylmercapto compound (13, R = C₆H₅) (2.6 g, 0.01 mol) was dissolved in dry chloroform (40 ml.) and benzylamine (5.5 g, 0.05 ml.) in dry chloroform (10 ml.) was added dropwise while the mixture was stirred. The reaction mixture was refluxed for two and a half hours. The solvent was removed under reduced pressure. The residue was washed with water and crystallized from ethyl alcohol to give colourless needles of 2,4-di(benzylamidocarbonyl)-3-benzyaminobut-2-enoic acid-N-benzylureide (23b) (3 g, 52%) m.p. 165°, undepressed by the above sample.

(c) The 2-benzylamino-7-chloro compound (14f) (3 g, 0.01 mol) was dissolved in warmed dry dioxan (35 ml.) and benzylamine (4.5 g, 0.05 mol) in dry dioxan was added dropwise, while the reaction mixture was stirred. The reaction mixture was refluxed for two and a half hours.

The solvent was removed under reduced pressure, and the residue was washed with water and crystallized from ethyl alcohol to give colourless crystals of 2,4-di(benzylamidocarbonyl)-3-benzyaminobut-2-enoic acid-N-benzylureide (23b) (2.9 g, 50%) m.p. 165°, undepressed by the above sample.

(d) The 4,6-dibenzylamino-3-(benzylamidocarbonylamidocarbonyl),2-oxopyrane (18b) (0.5 g, 0.01 mol) was dissolved in dry dioxan (10 ml.) and mixed with dry benzylamine (0.1 g, 0.01 mol).
The reaction mixture was refluxed for one and a half hours. The solvent was removed under reduced pressure. The residue was crystallized from ethyl alcohol to give colourless needles of 2,4-(benzylamidocarbonyl)-3-benzylaminobut-2-enoic acid-N-benzylureide (23b) (0.4 g., 70%), m.p. 165°, undepressed by the above sample.

(e) The 2-benzylamino-5-benzylamidocarbonyl-4-oxo-1,3-oxazin-6-yl-acetobenzylamide (22) (0.2 g.) was dissolved in dry dioxan (10 ml.) and treated as above with one mol. of benzylamine (0.04 g.). The solvent was removed under reduced pressure. The residue was crystallized from ethyl alcohol to give colourless needles of 2,4-di(benzylamidocarboxyl)-3-benzylamino-but-2-enoic acid-N-benzylureide (0.14 g., 60%), m.p. 165°, undepressed by the above sample.

2,4-Di(morpholidocarbonyl)-3-morpholinobut-2-enoic acid-N-butylureide (23a)

(a) The 2-butylamino-7-morpholino compound (15b) (0.32 g., 0.01 mol.) was dissolved in dry chloroform (5 ml.) and mixed with dry morpholine (0.19 ml.; 0.02 mol.). The mixture was refluxed for one and a half hours.

After the solvent was removed under reduced pressure, the residue was crystallized from acetonitrile to give colourless crystalline of 2,4-di(morpholidocarbonyl)-3-morpholinobut-2-enoic acid-N-butylureide (0.4 g., 96%; m.p. 160° (decomp.), Found: C, 55.4; H, 7.6. C23H37N5O7 requires: C, 55.8; H, 7.5%; $\frac{1}{2}$ (CDCl3) 0.77 br (CO.NH.CO) 1.63 br (ca. t, NH of NHBu), 6.55 (s, 12 x CH2), 6.7 (c, CH2.N.CH2 at 3), 8.2 - 8.9 (CH2.CH2 of Bu), 9.08 (ca. t, Ne); $\gamma_{max}$ (Nujol) 3310b, 1700s, 1640m, 1595m, 1530b cm$^{-1}$, n/e 495 M$^+$. 
(b) The 2-butylamino-7-chloro-compound (14c) (1.4 g, 0.05 mol) was dissolved in dry chloroform (20 ml) and dry morpholine (1.74 g, 0.02 mol) in dry chloroform (10 ml) was added dropwise, while the mixture was stirred. The reaction mixture was refluxed for two hours. After the solvent was removed under reduced pressure, the residue was washed with water and then crystallized from acetonitrile to give colourless crystalline of 2,4-di(morpholidocarbonyl)-3-morpholinobut-2-enoic acid-N-butylureide (23a) (1.8 g, 70%) m.p. 160° (decomp.), undepressed by the sample prepared as above.

**Reaction of 2,4-di(benzylamidocarbonyl)-3-benzylaminobut-2-enoic acid-N-benzylureide (23b)** with benzyamine

(a) The 2,4-di(benzylamidocarbonyl)-3-benzylaminobut-2-enoic acid-N-benzylureide (23b) (1 g) was dissolved in dry dioxan (15 ml) and mixed with benzyamine (1.5 ml). The mixture was refluxed for one and a half hours. After the reaction mixture was evaporated to dryness under reduced pressure, the residue was washed with ethyl alcohol (50 ml).

The remaining residue was crystallized from ethyl alcohol to give colourless needles of N-benzyl-N-benzylamidoacetylurea (25) (0.52 g, 80%) m.p. 182° (decomp.), \( \text{Found: } C, 66.8; H, 5.8; N, 12.9; \text{requires: } C, 66.5; H, 5.8; N, 12.9\% \); \( \text{C(}^6\text{DMSO) 0.41 br (s, CO}_{\text{NH}}\text{CO)}, 1.36 \text{br and } 1.45 \text{br (t, t, 2 x NH of NHCH}_{2}\text{H)}, 2.70 (s, 2 x Ph), 5.62 \text{and } 5.72 (d, d, 2 x CH}_{2}, 6.69 (s, CO}_{\text{CH}}\text{CO); } \text{TFA) 1.02, 1.76 (b, 2 x NH of the PhCH}_{2}\text{NH, 2.66 (s, 2 x Ph), 5.41 (d, 2 x CH}_{2}\text{, J } 5.1 \text{Hz}, 6.16 (s, 1 x CH}_{2} \text{); } \nu_{\text{max}} \text{ (Nujol) 3300s, 1680s, 1640s, 1560s, 1522w, 1500m cm}^{-1}; \text{ m/e 325 M}^\text{+}. \)
The ethyl a cohol from washing the above reaction mixture was evaporated to dryness under reduced pressure. The residue was crystallized from ethylacetate to give malonodibenzylamide (24) (0.2 g, 40% (m.p. 140°, undepressed by authentic sample) \( \text{^1} \) \((\text{CDCl}_3) 2.50 (5, 2 \times \text{NH}), 2.77 (s, 2 \times \text{Ph})

5.65 (d, 2 \times \text{CH}_2, J 5.5 \text{Hz}), 6.83 (s, \text{CH}_2); \text{^1} \nu_{\text{max}} \text{(Nujol}) 3300 \text{s}, 3080 \text{w}, 1640 \text{s}, 1610 \text{m}, 1550 \text{s}, 1500 \text{w} \text{ cm}^{-1}\).

(b) The 2,4-di(benzylamidocarbonyl)-3-benzylaminobut-2-enoic acid-N-benzylureide (23b) (1 g.) was dissolved in benzylamine (15 ml.). The reaction mixture was refluxed for one and a half hours. The excess of the benzylamine was removed under reduced pressure. The residue was washed with ethyl alcohol (50 ml.).

The remaining solid was crystallized from ethyl alcohol to give colourless needles of N,N-dibenzylurea (25) (0.15 g., 30%) m.p. 169° (L.t. m.p. 168°) (L.t. dictionary of organic compound, p.907) \((\text{CDCl}_3) 2.75 (s, 2 \times \text{Ph}), 5.0 (b, 2 \times \text{NH}), 5.75 (d, 2 \times \text{CH}_2, J 6 \text{Hz}); \text{^1} \nu_{\text{max}} \text{(Nujol)} 3350 \text{s}, 1625 \text{s}, 1590 \text{m}, 1578 \text{m}, 1537 \text{w}, 1500 \text{w} \text{ cm}^{-1}; \text{m/e 240 H}^+\).

The ethyl alcohol from washing the above reaction mixture was evaporated to dryness under reduced pressure. The residue was crystallized from ethylacetate to give colourless needles of malonodibenzylamide (24), (m.p. and mixed m.p. 140°), \( \text{^1} \) (0.7 g., 70%).

**Reaction of the N-benzyl-N-benzylamidoacetylurea (25) with benzyl amine**

The N-benzyl-N-benzylamidoacetylurea (25) (0.4 g.) was dissolved in benzylamine (10 ml.) and refluxed for one and a half hours. The excess benzylamine was removed under reduced pressure.

The residue was washed with ethyl alcohol (20 ml.). The remaining
solid was crystallized from ethyl alcohol to give colourless needles of 
N N-dibenzylurea (26) (0.09 g), m.p. 169° undepressed by the above sample.

The ethyl alcohol from washing the above reaction mixture was evaporated to dryness under reduced pressure.

The residue was crystallized from ethyl acetate to give colourless needles of malonodibenzylamide (24) (0.19 g, 70%) (m.p. and mixed m.p. 140°).

**Preparation of Specifically Labelled $^{13}$C- Compounds**

Potassium $^{13}$C-cyanide (1.5 g) (Prochem, 66% enriched in $^{13}$C) was heated in ethanol with sulphur to afford labelled potassium thiocyanate (100%) which was diluted with an equal weight of ordinary potassium thiocyanate. This was converted into ethyl thio($^{13}$C)cyanate (33% enriched) and thence with malonyl chloride into the compound ($^{13}$; R = Et) (72% yield).
4-Chloro-2,6-dihydroxy pyridine (31)

(a) The 7-chloro-2-ethylmercapto-4,5-dioxopyran-3,4-e-1,3-oxazine (13, R = C₂H₅) (2.6 g.) was dissolved in dry dioxan (30 mL) and mixed with water (0.5 g.). The mixture was refluxed for two hours.

After the solvent had been removed under reduced pressure, the residue was washed with chloroform and ether, and then crystallized from acetic acid (charcoal) to give colourless plates of 4-chloro-2,6-dihydroxy pyridine (31) (0.5 g., 35%), m.p. 224° (decomp.). Found: C, 41.4; H, 2.75; N, 9.6; C₅H₄ClNO₂ requires C, 41.2; H, 2.7; N, 9.6. (DMSO) ν max (OH) 3200 b, 1695 s, 1615 s (b), 1540 s, vmax (CH₃OH) 235, 316 nm (ε 5.2, 9.2 x 10³), m/e 145 M+ 147 J ν + 2 J ν.

(b) The 2-benzylmercapto-7-chloro-4,5-dioxopyran-3,4-e-1,3-oxazine (13, PhCH₂) (3.21 g.) was dissolved in dry dioxan (30 mL) and mixed with water (0.5 g.). The mixture was refluxed for two hours.

After the solvent had been removed under reduced pressure, the residue was washed with chloroform and diethyl ether and recrystallized from acetic acid (charcoal). Colourless plates of 4-chloro-2,6-dihydroxy pyridine (31) (0.33 g., 30%) were obtained, m.p. 224° (decomp.), undepressed by the sample prepared by the method (a).

(c) The 4-chloro-2,6-dihydroxy pyridine was also obtained from the 7-chloro-2-phenylmercapto-4,5-dioxopyran-3,4-e-1,3-oxazine (13, R = Ph) (3.0 g.) by treatment with water (0.5 g.) in dry dioxan (30 mL) as in method (a). The product (0.33 g., 30%) had m.p. 224° (decomp.), undepressed by the sample prepared as in method (a).
The 6-amino-4-chloro-5-ethylmercaptocarbonyl-2-pyrene (35a) (1 g.) was suspended in dry dioxan (25 ml.) and mixed with water (0.18 g.). The mixture was refluxed for three hours. After the solvent had been evaporated to dryness under reduced pressure, the residue was crystallized from acetic acid (charcoal) to give colourless plates of 4-chloro-2,6-dihydroxy pyridine (31) (0.5 g., 70%), m.p. 224° (decomp.), undepressed by the sample prepared by method (a), m/z 145 M⁺, 147 [M + 2]⁺.

(e) The 6-amino-4-chloro-5-p-chlorobenzylmercaptocarbonyl-2-pyrene (35c) (1.6 g.) was suspended in dry dioxan (25 ml.) and mixed with water (0.18 g.). The mixture was refluxed for two hours, then the solvent was removed under reduced pressure. 4-chloro-2,6-dihydroxy- pyridine (0.53 g., 75%) was obtained, m.p. 224° (decomp.), undepressed by a sample prepared as in method (a).

(f) The 4-chloro-3-ethoxycarbonyl-2,6-dihydroxy pyridine (44a) (0.5 g.) was suspended in dry dioxan (20 ml.) and concentrated hydrochloric acid (1 ml.) added. The mixture was refluxed for one hour. Evolution of carbondioxide was indicated. The reaction mixture was evaporated to dryness under reduced pressure and the residue extracted with acetone (50 ml.). Evaporation of the extract gave 4-chloro-2,6-dihydroxy pyridine (0.2 g.), m.p. 224° (decomp.), undepressed by the sample prepared as in method (a), m/z 145 M⁺, 147 [M + 2]⁺. The remaining residue (0.2 g.) was the unreacted compound (mixed m.p.).

(g) The 4-chloro-2,6-dihydroxy pyridine was also obtained from the hydrolysis of the 4-chloro-3-methoxycarbonyl-2,6-dihydroxy pyridine (44b) with hydrochloric acid.
Reaction of 7-chloro-2-ethylmercapto-4,5-dioxopyrano[3,4-3,7-1,3-oxazine with hydrobromic acid

The 7-chloro-2-ethylmercapto compound (13, \( R = \text{C}_2 \text{H}_5 \) (2.6 g.) was dissolved in dry dioxan (30 ml.) and mixed with hydrobromic acid (1.5 ml., 64%). The mixture was refluxed for two hours. After the reaction mixture had been evaporated to dryness under reduced pressure, the residue was washed with chloroform and diethyl ether and then crystallized from acetic acid (charcoal) to give colourless plates (0.9 g.), m.p. 222° (decomp.).

Undepressed by 4-chloro-2,6-dihydroxy pyridine (3a). Mass spectrometry results, m/e 189, 191, 161, 145, 147, 117, indicated the presence of both 4-bromo-2,6-dihydroxy pyridine and 4-chloro-2,6-dihydroxy pyridine m/e 145, 147, 117.

Hydrogenolysis of the 4-chloro-2,6-dihydroxy pyridine (3a)

Hydrogenation of the 4-chloro-2,6-dihydroxy pyridine (3a) (1 g.) in ethanol (85%, 100 ml.) over 10% palladium charcoal catalyst (0.05 g.) at atmospheric pressure and room temperature affected the theoretical uptake (2 moles) in 100 min. Filtration, evaporation to dryness under reduced pressure and crystallization from benzene to give pale-yellow crystals of glutarimide (33) (0.7 g., 90%) m.p. 154° (L. t. 25 m.p. 154 - 155°); m/e 113 M⁺; \( ^1H \text{NMR} (\text{CDCl}_3) 1.18 \text{ (b, NH)}, 7.18 - 7.70 \text{ (c, 3,5 - CH}_2\text{)}, 7.98 \text{ (c, 4 - CH}_2\text{)}; \nu_{\text{max}} \text{(Nujol)} 3200 \text{v, 3100w, 1817w, 1702s (b), 1665s cm}^{-1}
Reaction of the 4-chloro-2,6-dihydroxy pyridine with phosphorus oxychloride

The 4-chloro-2,6-dihydroxy pyridine (1 g.) was heated with phosphorus oxychloride (15 ml.) in a sealed tube at 180° for twenty-four hours. By steam distillation a colourless needles crystal of 2,4,6-trichloro pyridine (32) were obtained (0.5 g.) m.p. 31 - 32 (L.o.t. 24 m.p. 33°); m/e 181 M+, P + 2, P + 4, P + 6; G(CDC13) 2.73 (s, 3,5 - H); T max. (Nujol) 3080w, 1555s, 1543s cm⁻¹

Preparation of diazomethane

Potassium hydroxide (5 g.) in water (8 ml.) and 95% ethyl alcohol (25 ml.) were placed in a 100-ml. distillation flask which was fitted with a dropping funnel and a double surface condenser. The receiving flask, placed in a freezing mixture (solid carbon dioxide-acetone), contained ether (20 ml.) and the end of the receiving adaptor dipped below the surface of the ether. The distillation flask was heated to 65° on a water bath.

A solution of N-methyl-N-nitroso-η-toluene sulfonamide (21.5 g.) in ether (200 ml.) was added through the dropping funnel at a rate equal to the rate of distillation. After the addition, more ether (40 ml.) was added slowly, and distillation was continued until the distillate was colourless.

Reaction of the 4-chloro-2,6-dihydroxy pyridine (31) with diazomethane

The 4-chloro-2,6-dihydroxy pyridine (0.4 g.) was suspended in diethyl ether (5 ml.). Excess of ethereal diazomethane was added dropwise. The reaction mixture was kept for ten minutes at room temperature, then the ether
was evaporated on a steam bath. The residue was washed with petroleum ether (b.p. 40 - 60°) (50 ml.), and the solid remaining was crystallized from petroleum ether (b.p. 60 - 80°) to give colourless crystals of 4-chloro-6-methoxy- methy]pyrid-2(1H)-one (34a) (0.23 g.), which finally was sublimed (74°/16 mm), m.p. 104°. Found: C, 48.1; H, 4.6; N, 8.0. C7H8ClNO2 requires C, 48.4; H, 4.6; N, 8.1%. m/e 173 M+, 175 (M + 2)+; 7(CDCl3) 3.76, 4.05 (d, d, 3,5-CH, 2 Hz), 6.10 (s, CH3)-), 6.60 (s, N-CH3); 7max (Nujol) 3060w, 1658s, 1582m, 1542s cm⁻¹; λmax (96% CH2OH) 233, 308 nm (ε 4.18, 8.06 × 10⁻³).

After the petroleum ether (b.p. 40 - 60°) which was used for washing the residue above had been evaporated to dryness, the residue was crystallized from ethyl alcohol water, and finally sublimed (58°/16 mm) to give colourless needles of 4-chloro-2,6-dimethoxy pyridine (34) (0.23 g.), m.p. 64°. Found: C, 48.25; H, 4.6; N, 8.0. C7H8ClNO2 requires C, 48.4; H, 4.6; N, 8.1%. m/e 173 M⁺, 175 (M + 2)+; 7(CCl4) 3.73 (s, 3, 5-H), 6.13 (s, 2 x CH3 of 2,6-methoxy); 7max (Nujol) 3090w, 1592s, 1585s cm⁻¹; λmax (96% CH2OH) 230, 278 nm (ε 8.34, 11.21 x 10⁻³)
CHAPTER VIII
**6-Amino-4-chloro-5-ethylmercaptocarbonyl-2-pyrene (35a)**

The 7-chloro-2-ethylmercapto-4,5-dioxopyranor3,4-en 1,3-oxazine (13, R = C₂H₅) (2.6 g, 0.01 mol) was dissolved in dry dioxan (30 ml), mixed with water (0.18 g, C₁₀H₁₀O), and heated on an oil bath at (80 – 85°C) for one and a half hours.

After the reaction mixture had been evaporated to dryness under reduced pressure, the residue was washed with, and crystallized from, chloroform (charcoal) to give pale yellow plates of 6-amino-4-chloro-5-ethylmercaptocarbonyl-2-pyrene (35a) (0.83 g, 40%) m.p. 170°C (decomp).

Found: C, 41.5; H, 3.6; N, 6.1. C₈H₈ClNO₂S requires: C, 41.2; H, 3.4; N, 6.0.

The solvent was removed under reduced pressure. The residue was washed and crystallized from chloroform (charcoal) to give pale yellow plates of 6-amino-4-chloro-5-ethylmercaptocarbonyl-2-pyrene (35a) (0.83 g, 40%) m.p. 170°C (decomp).

**6-Amino-5-benzylmercaptocarbonyl-4-chloro-2-pyrene (35b)**

The 2-benzylmercapto 7-chloro-4,5-dioxopyranor3,4-en 1,3-oxazine (13, R = PhCH₂) (3.21 g, 0.01 mol) was dissolved in dry dioxan (35 ml), and mixed with water (0.18 g, 0.01 mol). The reaction mixture was heated on an oil bath at (80 – 85°C) for one and a half hours.

The solvent was removed under reduced pressure. The residue was washed and crystallized from chloroform (charcoal) to give colourless crystalline 6-amino-5-benzylmercaptocarbonyl-4-chloro-2-pyrene (35b) (1.3 g, 45%), m.p. 186 (decomp).

Found: C, 52.6; H, 3.3; N, 4.7.

C₁₃H₁₀ClNO₂S requires: C, 52.8; H, 3.4; N, 4.7.

The solvent was removed under reduced pressure. The residue was washed and crystallized from chloroform (charcoal) to give colourless crystalline 6-amino-5-benzylmercaptocarbonyl-4-chloro-2-pyrene (35b) (1.3 g, 45%), m.p. 186 (decomp).
1733s, 1618m, 1600m, 1550s cm$^{-1}$; $\lambda_{max}$(CH$_2$CN) 302.5, 343 n m($\varepsilon$13.8, 17.6 x 10$^{-3}$), m/e 295 M$^+$, 297 $\sqrt{M+2}$.  

6-Amino-4-chloro-5-p-chlorobenzylmercaptocarbonyl-2-pyrone (35c) 

The 7-chloro-2-β-chlorobenzylmercapto-4,5-dioxopyran-$\beta$-1,3-oxazine (13, R = p-Cl-C$_6$H$_4$-CH$_2$-) (3.6 g, 0.01 mol) was dissolved in dry dioxan (35 ml) and mixed with water (0.18 g, 0.01 mol). The reaction mixture was heated on an oil bath at (80 - 85$^o$) for one and a half hours.

The solvent was removed under reduced pressure. The residue was washed and crystallized from chloroform (charcoal) to give colourless crystals of 6-amino-4-chloro-5-p-chlorobenzylmercaptocarbonyl-2-pyrone (35a) (1.4 g, 42%) m.p. 200 (decomp); $\sum$ Found, C, 47.7; H, 2.65; N, 4.0; C$_{13}$H$_2$Cl$_4$NO$_3$ requires: C, 47.3; H, 2.7; N, 4.0.

$\nu_{max}$ (d$_2$DMSO) 0.63 (b, NH$_2$), 2.61 (C, C$_6$H$_4$-); 4.25, 4.31 (s, total of two protons CH$_2$) $\nu_{max}$ (Nujol) 3315w, 3150w, 1720s, 1668s, 1610s, 1560s, 1500w cm$^{-1}$; $\lambda_{max}$ (CHCl$_3$) 308sh, 331 nm ($\varepsilon$ 20 x 10$^{-3}$) m/e 329 M$^+$, p + 2, p + 4.

Reaction of the 2-benzylmercapto-7-chloro-4,5-dioxopyran-$\beta$-1,3-oxazine (13, R = PhCH$_2$-, 3.21 g, 0.01 mol) was dissolved in dry dioxan (35 ml) and mixed with water (0.18 g, 0.01 mol), then with p-chlorobenzylmercaptane (4.0 g). The reaction mixture was heated on an oil bath at (80 - 85$^o$) for one and a half hours.

The 2-benzylmercapto-7-chloro-compound (13, R = PhCH$_2$-) (3.21 g, 0.01 mol) was dissolved in dry dioxan (35 ml) and mixed with water (0.18 g, 0.01 mol), then with p-chlorobenzylmercaptane (4.0 g). The reaction mixture was heated on an oil bath at (80 - 85$^o$) for one and a half hours.
After the reaction mixture had been evaporated of under reduced pressure, the residue was washed and crystallized from chloroform (charcoal) to give colourless crystalline mixture (1.6 g.) m.p. 169° (decomp.) of 6-amino-4-chloro-5-p-chlorobenzylmercapto-carbonyl-2-pyrene (35c) (70% from the N.M.R. spectra) and 6-amino-4-chloro-5-benzylmercapto-carbonyl-2-pyrene (35b).

The mass spectrum at 180° showed m/e 295 M⁺, 297 M⁺ + 2 and at 200° showed m/e 321 M⁺, p + 2, p + 4.

4-Chloro-3-ethoxycarbonyl-2,6-dihydroxypyridine (44a)

(a) The 7-chloro-2-ethylmercapto-4,5-dioxopyran(13, R - OH) (2.6 g., 0.01 mol) was dissolved in dry dioxan (35 ml) and mixed with absolute ethyl alcohol (1.5 ml, 0.03 mol). The reaction mixture was refluxed for two hours with the exclusion of moisture.

After the reaction mixture had been evaporated to dryness under reduced pressure, the residue was washed with carbon tetrachloride (50 ml). The residue was crystallized from acetonitrile to give colourless crystals (chamoing to yellow at 184° and decomposing at 222°) of 4-chloro-3-ethoxycarbonyl-2,6-dihydroxypyridine (44a) (1.1 g., 50%) Found: C, 44.1; H, 3.9; N, 6.6; C₈H₈ClNO₄ requires: C, 44.0; H, 3.9; N, 6.7; C₈H₄ClNO₄ requires: C, 44.1; H, 3.9; N, 6.6; ¹ (d6 DMSO) 1.75 (b, NH/ OH, OH); 4.25 (S, 5-H), 5.78 (q, CH₂, J 6.8 Hz), 8.76 (t, CH₃, J 6.8 Hz), ¹ (Nujol) 3080w, 2900 - 2600b, 1662 - 1650s (b), 1583m, 1408s cm⁻¹; ¹(CH₃CN) 272.5, 292.5 (inff), 315 (sh) nm (11.8, 10.28 x 10⁻³); m/e 217 M⁺, 219 M⁺ + 2, which gave a purple colour with alcoholic ferric chloride.
(b) The 2-benzylmercapto-7-chloro-compound (13, R = PhCH₂) (3.21 g, 0.01 mol) was treated with absolute ethyl alcohol (1.65 ml, 0.03 mol) as above to give crystalline 4-chloro-3-ethoxy carbonyl-2,6-dihydroxypyridine (44a) (0.9 g, 41%) (decomp.) at 222° after changing to yellow at 184° undepressed by the sample prepared as above.

(c) The 7-chloro-2-phenylmercapto-compound (13, R = Ph) (3.0 g, 0.01 mol) was treated with absolute ethyl alcohol (1.65 ml, 0.03 mol) as in method (a). 4-Chloro-3-ethoxy carbonyl-2,6-dihydroxypyridine (44a) (0.82 g, 40%) was obtained, decomp. point 222° undepressed by the sample prepared by the method (a).

(d) The 6-amino-4-chloro-5-ethylmercapto carboxylic acid (35a) (1 g) was suspended in dry dioxan (15 ml) and mixed with absolute ethyl alcohol (0.5 ml). The reaction mixture was refluxed for two and a half hours. After the solvent was removed under reduced pressure, the residue was crystallized from acetic acid (charcoal) to give colourless plates changed to yellow at 184° and decomposed at 222°, undepressed by the sample prepared by the method (a), of the 4-chloro-3-ethoxy carbonyl-2,6-dihydroxypyridine (44a) (0.8 g, 80%), gave a purple colour with alcoholic ferric chloride, m/e 217 M⁺, 219 [M + 2]⁺.

(e) The 6-amino-5-benzylmercaptocarboxylic acid (35b) (1.5 g) was suspended in dry dioxan (15 ml) and mixed with absolute ethyl alcohol (0.7 ml). The reaction mixture was refluxed for two and a half hours. The solvent was evaporated off under reduced pressure. The residue was crystallized from acetic acid (charcoal) to give
colourless plates of 4-chloro-3-ethoxy carbonyl-2,6-dihydroxypyrrole (44a) (0.3 g, 80%) decomposed at 222°, undepressed by the sample prepared by the method (a).

4-Chloro-3-methoxy carbonyl-2,6-dihydroxypyrrole (44b)

(a) The 7-chloro-phenylmercapto-4,5-dioxopyran-3,4-e-1,3-oxazine (13, R = Ph) (3.0 g, 0.01 mol) was dissolved in dry dioxan (35 ml) and mixed with absolute methyl alcohol (1.2 ml, 0.03 mol).

The reaction mixture was refluxed for two and a half hours with the exclusion of moisture. After the reaction mixture had been evaporated to dryness under reduced pressure, the residue was washed with carbon tetrachloride (50 ml). 4-Chloro-3-methoxy carbonyl-2,6-dihydroxypyrrole (44b) (1.1 g, 55%) was obtained, and recrystallized from acetonitrile (charcoal) to give the colourless crystalline compound, m.p. 300° (decomp.), which gave a purple colour with alcoholic ferric chloride. Found: C, 41.3; H, 2.9; N, 6.9. C₇H₆ClNO₂ requires: C, 41.2; H, 2.0; N, 6.7%. T(d₅ DMSO) 1.2 (b, NH/CH, OH), 4.2 (s, 5-H); 6.25 (s, CH₃); γ max. (Nujol) 3100 – 230 (b), 1650s (b), 1588s, cm⁻¹; λ max. (CHCN) 275, 292.5 (infl.), 317 (sh) nm (ε, 12.76, 11.56 x 10⁻³); m/e 203 M⁺, 205 M + 2⁺.

(b) The 2-benzylmercapto-7-chloro-4,5-dioxopyran-3,4-e-1,3-oxazine (13, R = PhCH₂) (3.21 g, 0.01 mol) was dissolved in dry dioxan (35 ml) and mixed with absolute methyl alcohol (1.1 ml, 0.03 mol).

The reaction was carried out as in method (a) to give colourless crystalline 4-chloro-3-methoxy carbonyl-2,6-dihydroxy pyridine (1 g, 50%), m.p. 300° (decomp.), undepressed by the sample prepared as in method (a).
(c) The 7-chloro-2-ethylmercapto-compound (13, \( R = \text{C}_2 \text{H}_5 \)) (2.6 g, 0.01 mol) was dissolved in dry dioxan (35 ml) and mixed with absolute methyl alcohol (1.1 ml, 0.03 ml).

The reaction was carried out as in method (a) to give the 7-chloro-3-methoxy carbonyl-2,6-dihydroxypyridine (44b) (1.1 g, 55%), m.p. 300° (decomp.), undepressed by the sample prepared in the method (a).

(d) The 6-amino-4-chloro-5-ethylmercaptocarbonyl-2-pyrone (35a) (1 g) was suspended in dry dioxan (15 ml) and mixed with absolute methyl alcohol (0.4 ml). The reaction mixture was refluxed for two and a half hours. After the solvent was removed under reduced pressure, the residue was crystallized from acetonitrile (charcoal) to give colourless needles of 4-chloro-3-methoxy carbonyl-2,6-dihydroxypyridine (44b) (0.7 g, 80%), m.p. 300° (decomp.) undepressed by the sample from the method (a).

Ethyl 4-benzylcarbamoyl-3-benzylamino-2-carbamoylbut-2-enthiolate (40)

The 6-amino-4-chloro-ethylmercaptocarbonyl-2-pyrone (35a) (1.1 g) was suspended in dry dioxan (25 ml), and mixed with dry benzylamine (2 ml). After ten minutes water was added and the solid collected. The residue was washed with water and with (petroleum ether b.p. 40-60°) and recrystallized from nitromethane to give colourless needles of ethyl 4-benzylamido-3-benzylamino-2-carbamoylbut-2-enthiolate (40) (1.2 g, 55%), m.p. 190° (decomp.) \[ \text{Found: } C, 64.2\%; H, 6.2\%; N, 10.2\% \text{ requires: } C, 64.6\%; H, 6.1\%; N, 10.2\% \]

m/e 411 M⁺; \( ^{13}C \) (CDCl₃) -1.01 (b, 4-NH), 1.53 (b, 3-NH), 4.05 (b, NH₂), 2.74 (S, 2 x Ph), 5.25, 5.60 (d, d, 2 x CH₂, J 6 Hz), 6.61 (S, 4-CH₂), 7.12 (q, CH₂, J 6.3 Hz), 8.74 (t, CH₂, J 6.8 Hz); \( \gamma_{\text{max}} \) (Nujol) 3420m, 3320m, 3200w, 1642sh, 1637s, 1592s, 1580m, 1547m, 1500w cm⁻¹.
The 4-chloro-3-ethoxycarbonyl-2,6-dihydroxypyridine (44) (0.4 g, 0.02 mol) was suspended in dry dioxan (10 ml), and dry benzylamine (0.4 ml, 3 mol%) was added. The mixture was refluxed for 1.5 hours, then the reaction mixture was removed under reduced pressure, and the residue washed with water and crystallized from acetonitrile to give 4-benzylamino-3-ethoxycarbonyl-2,6-dihydroxypyridine (47) (0.32 g, 50%), m.p. 159° (decomp.) (Found: C, 55.1; H, 5.3; N, 8.55.

C_{15}H_{16}N_{2}O_{4} requires C, 55.5; H, 5.1; N, 8.6%); \nu_{\max} (Nujol) 3650 br, 3110 w, 3180 - 2600, 1660 br s, 1640 br s, 1600 m, 1555 m cm^{-1}; \nu (d_{6}DMSO) 1.80 br (NH/OH), 2.6 (s, \delta \chi \chi \text{ of Ph}), 4.99 (s, 5 - H), 5.95 (q, J 7Hz, CH_{2} \text{ of } C_{2}H_{5}-CO), 5.99 (s, \text{ CH of PhCH}_{2}-), 8.82 (t, J 7Hz, \text{ CH}_{3} \text{ of } C_{2}H_{5}-CO).
CHAPTER (IX)

FORMATION OF THE

6-N-ACYL-HALO-2-PYRONE (48) and (49)

AND SOME OF ITS REACTIONS
4-Chloro-6-$\text{II}$-(ethylthioxycarbonyl) amido pyran-2-one (48a)

The 7-chloro-2-ethylmercapto-4,5-dioxopyrano$\tilde{3},4$-$\text{II}$,1,3-oxazine (13, R = $\text{C}_2\text{H}_5$) (2.59 g, 0.01 mol) was dissolved in dry dioxan (30 ml.) in a two necked, round-bottomed flask (100 ml.), fitted with a water condenser, calcium chloride tube and gas bubbler. Water (0.4 g, 0.02 mol) was added to the reaction mixture and dry hydrogen chloride was bubbled through with heating on an oil-bath ($74^\circ$) for 1½ hours.

The reaction mixture was evaporated to dryness under reduced pressure. The residue was washed with carbon tetrachloride and crystallized from nitromethane (charcoal) to give colourless needles of 4-chloro-6-$\text{II}$-(ethylthioxycarbonyl) amido pyran-2-one (48a) (0.72 g; 30%) m.p. 202° (decomp) Found: C, 41.1; H, 3.6; N, 6.0.

$\text{C}_9\text{H}_8\text{ClNO}_3$S requires C, 41.1; H, 3.4; N, 6.0°; $m/e$ 235 M$^+$, $\nu^p_{\text{M}+2}$ (Nujol) 3180 w, 3120 w, 1713 s, 1691 s, 1617 m, 1550 b cm$^{-1}$; $\lambda_{\text{max}}$ (96% C$_2$H$_7$OH) 242.5, 341, 389 nm ($\varepsilon$ 9.24, 14.79, 4.8 x $10^{-3}$); $\tau$(d$_6$ DMSO) 1.97 b (S, NH), 3.33, 3.83 (d, d, 3,5-H, J 1.53Hz); 7.11 (q, CH$_2$, J 7Hz), 8.78 (t, CH$_3$, J 7Hz).

6-$\text{II}$-(5-Benzylthiocarbonyl) amido-4-chloro-pyruro-2-one (48b)

The 2-benzylmercapto-7-chloro-4,5-dioxopyrano$\tilde{3},4$-$\text{II}$-1,3-oxazine (13, R = PhCH$_2$) (3.05 g, 0.1 mol) was dissolved in dry dioxan (30 ml.) and mixed with water (0.4 g, 0.2 mol). Dry hydrogen chloride was bubbled through whilst the solution was kept at $74^\circ$ for 1½ hours. (The reaction was carried out as above). The reaction mixture was evaporated to dryness under reduced pressure. The residue was washed with carbon tetrachloride and crystallized from nitromethane (charcoal) to give colourless needles of 6-$\text{II}$-
(benzylthioxycarbonyl) amido-4-chloropyran-2-one (48b) (0.97 g., 30%), m.p. 197° (decomp.) Found: C, 52.8; H, 3.3; N, 4.9.

C_{13}H_{16}ClNO_{3}S requires C, 52.8; H, 3.4; N, 4.7%. m/e 171 (M-PhCH_{2}SH), \nu_{max} (Nujol) 3180 w, 3135 w, 1713 s, 1690 s, 1622 m, 1617 m, 1555 s, 1542 s cm^{-1}; \lambda_{max} (96% H_{2}O) 241, 341, 378 nm (\varepsilon 9.02, 15.26, 2.46 x 10^{-3}); \tau (\ddot{DMSO}) -2.02 b (s, NH), 2.68 (s, Ph), 3.33, 3.82 (d, d, 3,5-H, J 1.7Hz), 5.83 (s, CH_{2} at the PhCH_{2}S-).

4-Bromo-6-N-(ethylthioxycarbonyl) amido pyran-2-one (49a)

The 7-chloro-2-ethylmercapto-4,5-dioxopyrone \( \xrightarrow{3,4-\theta} \), 1,3-oxazine (13, \( \chi = \text{C}_{2}H_{5} \)) (2.59 g, 0.01 mol) was dissolved in dry dioxan (30 ml) in a two necked, round-bottomed flask (100 ml) fitted with a water-condenser, calcium chloride tube, and gas bubbler. Water (0.4 g, 0.02 mol) was added to the reaction mixture and dry hydrogen bromide was bubbled through, with heating on an oil-bath at 74° for 1 1/2 hours. The reaction mixture was evaporated to dryness under reduced pressure, and then the residue was washed with carbon tetrachloride and crystallized from nitromethane (charcoal) to give colourless needles of 4-bromo-6-N-(ethylthioxycarbonyl) amido pyran-2-one (49a) (0.72 g, 30%) (and from the N\(_{2}\)Me\(_{2}\), 4-chloro-6-N-(S-ethylthiocarbonyl) amido pyran-2-one, (3%) was found present) m.p. 210 (decomp.) Found: C, 35.0; H, 3.1; N, 5.05. C\(_{6}H_{8}BrNO_{3}S\) requires C, 34.55; H, 2.9; N, 5.0%. m/e 277 M\(^{+}\), 279 \( \sqrt{\text{M} + 2\text{J}} \); \nu_{max} (Nujol) 3180 w, 3120 w, 1713 s, 1691 s, 1617 m, 1550 b cm^{-1}; \tau (\ddot{DMSO}) -1.92 b (s, NH); 3.19, 3.64 (d, d, 3,5-CH, J 1.2Hz), 7.13 (q, CH_{2} J 7Hz), 8.76C\(^{+}\), CH\(_{3}\) of C\(_{2}H_{5}S-\) J 7Hz).

4-Chloro-6-(N-methyl-N-ethylthiocarbonyl) amido pyran-2-one (51a)

The 4-chloro-6-N-(ethylthiocarbonyl) amido pyran-2-one (48a)
was suspended in diethylether (5 ml). An excess of diazomethane was added dropwise. The reaction mixture was left at room temperature for 10 min. and then evaporated to dryness. The residue was triturated with petroleum ether (b.p. 40-60°). Yellow solid was obtained, which on recrystallization from petroleum ether (60-80°) (charcoal) gave colourless needles of 4-chloro-6-(N-methyl-N-ethylthioxycarbonyl) amido pyron-2-one (51a) (0.2 g, 96%), m.p. 102°. Found: C, 43.7; H, 4.2; N, 5.6. C_{10}H_{10}ClNO_S requires C, 43.6; H, 4.0; N, 5.65%. m/e 247 M+, 249 M+2. \nu_{\text{max}} (Nujol) 3080 w, 1750 s, 1674 s, 1606 m, 1590 m, 1535 s, 1523 s cm^{-1}; \lambda_{\text{max}} (96\% C_{2}H_{5}OH) 223, 336 nm (\lambda \times 10^{-3}); \nu (CCl_{4}) 2828, 4.03 (d, d, 3.5-H, J 1.6Hz), 6.62 (s, N-CH), 7.08 (q, CH, J 7Hz), 8.67 (t, CH of the C_{2}H_{5} J 7Hz).

6-N-(Benzythioxycarbonyl-N-methyl) amido-4-chloro-pyron-2-one (51b) (48b) (0.2 g) was suspended in diethylether (5 ml). An excess of diazomethane was added dropwise. The reaction mixture was left at room temperature for 10 min. and then evaporated to dryness. The residue was triturated with petroleum ether (40-60°). The yellow solid obtained was recrystallised from petroleum ether (60-80°) (charcoal) to give colourless needles of 6-(N-benzythioxycarbonyl-N-methyl)amido-4-chloro-pyron-2-one (51b) (0.2 g, 96%) m.p. 74°. Found: C, 54.1; H, 3.8; N, 4.5. C_{14}H_{12}ClNO_S requires C, 54.3; H, 3.9; N, 4.5%. m/e 309 M+, 311 M+2. \nu_{\text{max}} (Nujol) 3050 sh, 1736 s, 1678 s, 1640 w, 1610 sh, 1598 m, 1537 s, 1530 sh, 1503 w cm^{-1}; \lambda_{\text{max}} (96\% C_{2}H_{5}OH) 337 nm (\lambda \times 10^{-3}); \nu (CCl_{4}) 2872 (s, Ph), 3.27, 3.99 (d, d, 3.5-H, J 1.6Hz), 5.86 (s, CH, of PhCH), 6.61 (s, N-CH).
4-Carboxy-3-chloro-N-(ethylmercaptocarbonyl)but-2-enoamide (55a)

a) The 7-Chloro-2-ethylmercapto-4,5-dioxopyrano[3,4-e]1,3-oxazine (13, R = C₂H₅) (2.6 g) was dissolved in acetone (30 ml), and mixed with water (10 g). The mixture was kept at room temperature for four three days. After the reaction mixture had been evaporated to dryness under reduced pressure, the residue was washed with chloroform, and then crystallized from nitromethane (charcoal) to give colourless needles of 4-carboxy-3-chloro-N(ethylmercaptocarbonyl)but-2-enoamide (55a) (1 g, 40%), m.p. 140° (Found: C, 38.5; H, 4.0; N, 5.7; C₈H₁₀ClNO₂S requires C, 38.2; H, 4.0; N, 5.6%); m/e 251 M⁺ and 253 [M+2]⁺; νmax (Nujol) 3180 w, 3080 w, 1735 m, 1635 s, 1317 w cm⁻¹, ν̃(d₆DMSO) 1142 br (S, OH), 18 br (NH), 3.71 (S, 2-H), 5.84 (s, 4-CH₂), 7.19 (q, J 7Hz, CH₂ of C₂H₅S), 8.79 (t, J 7Hz, CH₃), (The product was soluble in 5% sodium bicarbonate solution, and decolourised KMN₃O₄ solution).

b) The 4-chloro-6-(N-ethylmercaptocarbonyl)aminopyran-2-one (48a) (0.23 g) was dissolved in acetic acid (10 ml) and mixed with 3N hydrochloric acid (1.5 ml). The mixture was refluxed for 20 min., then cooled and filtered and diluted with water. Colourless crystals of 4-carboxy-3-chloro-N-(ethylmercaptocarbonyl)but-2-enoamide (55a) (0.15 g, 60%) were obtained, m.p. 140°, under-pressed by the sample prepared as in method (a).

N-(Benzylmercaptocarbonyl)-4-carboxy-3-chlorobut-2-enoamide (55b)

a) The 2-benzylmercapto-7-chloro-4,5-dioxopyrano[3,4-e]1,3-oxazine (13, R = PhCH₂) (3.2 g) was dissolved in acetone (30 ml), and mixed with water (10 g). The mixture was kept at room temp-
ture for three days. After the reaction mixture had been evaporated to dryness under reduced pressure, the residue was washed with chloroform and crystallized from nitromethane (charcoal) to give colourless needles of N-(benzylmercaptocarbonyl)-4-carboxy-3-chloro-but-2-enamide (55b) (1.2 g, 40%), m.p. 166° (found: C, 50.0; H, 3.9; N, 4.5%; C_{13}H_{11}ClNO_{x}S requires C, 49.8; H, 3.8; N, 4.5%); m/e 313 (M^+ and 315 [M+2]^+); \nu_{max} (Nujol) 3170 w, 3060 w, 2220 br, 1730 m, 1627 s, 1505 w, 1500 m cm^{-1}; \tau (d_{6}DMSO) -1.95 br (s, CH), 2.7 br (NH), 2.72 (s, Ph), 3.73 (s, 2-H), 5.87 (s, 4-CH_{2}), 5.93 (s, CH_{2} of PhCH_{2}S). 

b) The pyrone (48b) (0.3 g) was dissolved in acetic acid (10 ml) and mixed with 3N-hydrochloric acid (1.5 ml). The mixture was refluxed for 20 min., then cooled, filtered and diluted with water. Colourless crystals of N-(benzylmercaptocarbonyl)-4-carboxy-3-chloro-but-2-enamide (55b) (0.18 g, 58%) were obtained, m.p. 166°, under-pressed, by the sample prepared as in method (a) (The produce was soluble in 5% sodium bicarbonate solution and decolourised KMnO_{4} solution).

3-Chloro-N-(ethylmercaptocarbonyl)-4-methoxycarbonylbut-2-enamide (56a)

The 4-carboxy-3-chloro-N-(ethylmercaptocarbonyl)but-2-enamide (55a) (0.2 g) was suspended in diethyl ether (10 ml). An excess of diazomethane was added dropwise. The mixture was left at room temperature for 10 min., then evaporated. The residue was crystallized from petroleum ether (b.p. 80-100°) (charcoal) to give colourless needles of 3-chloro-N-(ethylthiocarbonyl)-4-methoxycarbonyl but-2-enamide (56a) (0.2 g, 96%), m.p. 112° (Found: C, 40.7; H, 4.5; N, 5.3%; C_{11}H_{11}ClNO_{4}S requires C, 40.7; H, 4.5; N, 5.3%).
N-(Benzylmercaptocarbonyl)-3-chloro-4-methoxycarbonylbut-2-enoamide (56b)

The N-(benzylmercaptocarbonyl)-4-carboxy-3-chloro-but-2-enoamide (55b) (0.2 g) was suspended in diethylether (10 ml). An excess of diazomethane was added dropwise. The mixture was kept at room temperature for 10 min., then evaporated. The residue was crystallized from petroleum ether (b.p. 80-100°) (charcoal) to give colourless needles of the product (56b) (0.2 g, 96%), m.p. 140° (Found: C, 51.3; H, 4.3; N, 4.1. C_{14}H_{13}ClNO_{4}S requires C, 51.3; H, 4.3; N, 4.3%). m/e 327 M^+ and 329 [M+2]^+; \nu max. (Nujol) 3265 m, 3175 w, 3050 w, 1710 s, 1672 m, 1635 m, 1525 s m\(^{-1}\); \lambda max. (96% \text{C}_2\text{H}_5\text{OH}) 229 nm (\varepsilon 2.0 \times 10^{-3}); \tau (\text{CDCl}_3) 1.00 \text{br(s, NH)}, 3.68 (s, 2-H), 5.9 (s, 4-CH\(_2\)), 6.24 (s, 0-CH\(_3\)), 7.08 (q, J 7Hz, CH\(_2\)), 8.70 (t, J 7Hz, CH\(_2\) of \text{C}_2\text{H}_5).
CHAPTER (X)

FORMATION OF COMPOUNDS

(54) and (59)
Reaction of 4-chloro-2,6-dihydroxypyridine (31) with ethylthiochloroformate

The 4-chloro-2,6-dihydroxypyridine (0.5 g.) was suspended in dry dioxan (10 ml.) and mixed with ethylthiochloroformate (3 ml.). The mixture was heated on an oil-bath at (140°) for four hours. The reaction mixture was evaporated to dryness under reduced pressure. The residue was washed with carbon tetrachloride (50 ml.). The remaining solid was unreacted 4-chloro-2,6-dihydroxypyridine (0.2 g.). After the carbon tetrachloride had been removed under reduced pressure, the residue was crystallized from petroleum ether (b.p. 60-80°) (charcoal) to give colourless needles of 4-chloro-2-S-ethylthiocarbonate-6-hydroxypyridine (54) (0.28 g., 60%), m.p. 106°, Found: C, 41.2; H, 3.4; N, 6.0. C₈H₈ClNO₅S requires C, 41.1; H, 3.4; N, 6.0%. m/e 233 M⁺, 235 M⁺+2; Ψmax (Nujol) 3300 - 2700 (b), 1730 s, 1647 (sh), 1600 s (b), 1575 sh cm⁻¹; λ max. (CH₃OH) 273.5 nm (ε 9.4 x 10⁻³).

Reaction of the 4-chloro-2,6-dihydroxypyridine (31) with ethylchloroformate.

The 4-chloro-2,6-dihydroxy pyridine (1.5 g.) was suspended in dry dioxane (20 ml.) and mixed with ethylchloroformate (3 ml.). The mixture was heated on an oil-bath at 140° for six hours. The reaction mixture was evaporated to dryness under reduced pressure. The residue was triturated with petroleum ether (40-60°) and crystallized from petroleum ether (80-100°) (charcoal) to give light-brown needles of 4-chloro-2-ethylcarbonate-6-hydroxypyridine (59) (1.1 g., 50%), m.p. 112°, Found: C, 43.7; H, 3.6; N, 6.2. C₈H₈ClNO₄ requires, C, 43.1; H, 3.8; N, 6.4%. m/e 217 M⁺, 219 M⁺+2; Ψmax (Nujol) 3300 - 2600, 1753 s, 1710 sh, 1645 sh, 1625 s, 1575 s cm⁻¹, λ max. (CH₃CN) 273.5 nm (ε 6.7 x 10⁻³).
CHAPTER XI

REACTIONS OF THE
7-CHLORO-2-ETHYL Mercapto-
COMPOND (13, $R = C_2H_5$)
WITH EXCESS OF ETHYL
ALCOHOL AT
ROOM TEMPERATURE
Reaction of the 6-chloro-2-ethylmercapto-4,5-dioxopyrono
3,4-1,3-oxazine (13, R = C₂H₅) with an excess of ethyl
alcohol at room temperature

The 7-chloro-2-ethylmercapto compound (13, R = C₂H₅) (2.6 g.)
was dissolved in dry chloroform (20 ml.) and mixed with absolute
ethyl alcohol (25 ml.). The mixture was kept at room temperature,
with exclusion of moisture, for four days. After the reaction
mixture had been evaporated to dryness under reduced pressure,
the residue was triturated with petroleum ether, and then crystallized
from carbon tetrachloride to give colourless needles of 7-chloro-2-
ethoxy-4,5-dioxopyrano/3,4-1,3-oxazine (62) (1.5 g., 62.3%);
m.p. 130° (Found, C, 44.1; H, 2.5; N, 3.5; C₉H₆ClO₂ requires C,
44.35, H, 2.5; N, 3.7%; m/e 243 M⁺, 245 M⁺+2; ν max. (Nujol)
1780 s, 1750 b, 1595 s, 1545 s, 1520 b cm⁻¹; λ max. (CHC₁₇) 275,
282.5, 322 nm (ε 9.68, 11.939, 11.8 x 10⁵); τ(CDCl₃) 3.72 (s, 8-H),
5.37 (q, J 7Hz, CH₂), 8.51 (t, J 7Hz, CH₃).

The small portion of solid which did not dissolve in the
carbon tetrachloride (throughout the crystallizations in the above
experiment) was crystallized from acetonitrile (charcoal) to give
greenish plates of 6-chloro-3-(amidocarbonyl)-4-hydroxy-2-oxopyran
(63) (0.2 g., 10%) m.p. 200° (decomp.) (Found: C, 37.9; H, 2.0; N,
7.4; C₆H₄ClNO₄ requires C, 38.0; H, 2.1; N, 7.3%; m/e 189 M⁺;
191 M⁺+2; λ max. (Dioxan) 271, 330 nm (ε 11.3 x 10⁻³); ν max.
(Nujol) 3360 m, 3210 m (b), 1720 m, 1700 m, 1675 s, 1656 (sh), 1610 m,
1550 s (b); τ(CHDMSO) 0.99 br(s, NH₂, OH), 4.4 (s, 5-H).
CHAPTER XII

REACTIONS OF THE 7-CHLORO-2-
MERCAPTO-COMPOUNDS (13) WITH
ONE OR TWO MOLS. OF
ALCOHOL
3-(Benzy1mercapto carbonylamido carbonyl)-6-chloro-4-ethoxy-2-oxopyran (64c)

The 2-benzylmercapto-7-chloro-4,5-dioxopyran [3,4-e]-1,3-oxazine (13, R = PhCH$_2$) (3.2 g, 0.01 mol.) was dissolved in dry dioxan (50 ml.) and mixed with absolute ethyl alcohol (0.57 ml, 0.01 mol.). The mixture was refluxed for one hour, with exclusion of moisture. After the reaction mixture had been evaporated to dryness under reduced pressure, the residue was crystallized from ethyl acetate (charcoal) to give colourless small crystals of 3-(benzy1mercapto carbonylamido carbonyl)-6-chloro-4-ethoxy-2-oxopyran, (64c) (1.4 g, 40.5%), m.p. 180° (decomp.) (Found: C, 51.9; H, 3.8; N, 3.6; C$_{16}$H$_{14}$ClNO$_3$S requires C, 52.2; H, 3.8; N, 3.8%);

m/e 367 M$^+$ and 369 [M+2]+; $\lambda_{\text{max}}^\text{Nujol}$ 3150 w, 3095 w, 1745 m, 1705 m, 1618 m, 1600 s, 1550 s, 1500 s cm$^{-1}$; $\lambda$ max. (CH$_3$CN) 372 nm ($\varepsilon$ 17.9 x 10$^{-3}$); $\tau$ (CDCl$_3$) 1.98 br(s, NH); 2.7 (c, Ph), 3.08 (s, 5-H), 5.70 (s, CH$_2$ of PhCH$_2$S), 2.75 (q, J 6.8 Hz, CH$_2$); 8.70 (t, J 6.8 Hz, CH$_3$ of C$_2$H$_5$).

6-Chloro-4-ethoxy-3-(phenylmercapto carbonylamido carbonyl)-2-oxopyran (64b)

The 7-chloro-2-phenylmercapto-4,5-dioxopyran [3,4-e]-1,3-oxazine (13, R = Ph- ) (3.05 g, 0.01 mol.) was dissolved in dry dioxan (35 ml.) and mixed with absolute ethyl alcohol (0.57 ml., 0.01 mol.). The mixture was refluxed for one hour with exclusion of moisture. After the reaction mixture had been evaporated to dryness under reduced pressure, the residue was washed and then crystallized from carbon tetrachloride (charcoal) to give pale yellow needles of 6-chloro-4-ethoxy-3(phenylmercapto carbonylamido carbonyl)-2-oxopyran (64b) (1.3 g, 40%), m.p. 182° (decomp.) (Found: C, 50.6; H, 3.4; N, 3.8; C$_{15}$H$_{12}$ClNO$_3$S requires C, 50.9;
H, 3.4; N, 3.7); \( \nu_{\text{max}} \) (Nujol) 3150 w, 3095 w, 1740 m, 1703 s, 1650 m, 1598 s, 1550 s cm\(^{-1}\); \( \lambda_{\text{max}} \) (CH\(_3\)CN) 556 nm (\( \varepsilon 16.41 \times 10^{-3} \)); \( \Upsilon \) (CDCl\(_3\)) 1.76 br(s, NH), 2.55 (s, Ph), 3.10 (s, 5-H); 5.76 (q, \( J 6.8\text{Hz}, \text{CH}_2 \)); 8.68 (t, \( J 6.8\text{Hz}, \text{CH}_3 \) of C\(_{2}H_5\)).

Reaction of 7-Chloro-2-ethylmercapto-4,5-dioxopyrano/3,4-e/-1,3-oxazine (13, R = C\(_2\)H\(_5\)) with one mole of absolute ethyl alcohol

The 7-chloro-2-ethylmercapto compound (13, R = C\(_2\)H\(_5\)) (2.6 g, 0.01 mol) was dissolved in dry dioxan (35 ml) and mixed with absolute ethyl alcohol (0.57 g, 0.01 mol). The mixture was refluxed for 2 hours with exclusion of moisture. The solvent was removed under reduced pressure. The residue was washed with carbon tetrachloride (50 ml) and the solid obtained was crystallized from carbon tetrachloride (charcoal) to give colourless crystals of 6-chloro-4-ethoxy-3-(ethylmercaptopcarbonylamidocarbonyl)-2-oxopyran (64a) (1.5 g, 50%), m.p. 173\(^\circ\) (decomp) (Found: C, 43.1; H, 3.95; N, 4.6. C\(_{11}H_{12}ClNO_5\) requires C, 43.3; H, 3.9; N, 4.6\%); m/e 305 M\(^+\) and 307 \( \sqrt{M+2} \); \( \nu_{\text{max}} \) (Nujol), 3160 v, 3100 w, 1740 s, 1710 s, 1637 s, 1603 s, 1555 s, 1508 s cm\(^{-1}\); \( \Upsilon \) (CDCl\(_3\)) 1.70 br(s, NH), 3.14 (s, 5-H), 5.73 (q, \( J 7\text{Hz}, \text{CH}_2 \) of C\(_{2}H_5\)) 6.95 (q, \( J 7\text{Hz}, \text{CH}_2 \) of C\(_{2}H_5\)), 8.65 (t, \( J 7\text{Hz}, 2 \times \text{CH}_3 \)).

From the evaporation of the carbon tetrachloride (which was used for washing the first residue) an oil was obtained. This oil was extracted with hot petroleum ether (b.p. 60-80\(^\circ\)). 7-chloro-2-ethoxy-2-ethylmercapto-2,3-dihydro-4,5-dioxopyrano/3,4-e/-1,3-oxazine (65a) (0.3 g, 10%) was obtained and recrystallised from petroleum ether (b.p. 60-80\(^\circ\)) (charcoal) to give pale yellow crystals, m.p. 105\(^\circ\) (Found: C, 43.5; H, 4.0; N, 4.2. C\(_{11}H_{12}ClNO_5\) requires C, 43.3; H, 3.9; N, 4.6\%); m/e 305 M\(^+\) and 307 \( \sqrt{M+2} \); \( \lambda_{\text{max}} \) (CH\(_3\)CN) 312 nm (\( \varepsilon 13.02 \times 10^{-3} \)); \( \nu_{\text{max}} \) (Nujol) 3275 m, 3080 v, 173\(\frac{1}{2}\) s, 1662 s.
Reaction of the 7-Chloro-2-ethylmercapto-4,5-dioxopyrone
\(3,4\)-cyclic-1,3-oxazine (13, R = C\(_2\)H\(_5\)) with one mole of absolute methyl alcohol

The 7-chloro-2-ethylmercapto compound (13, R = C\(_2\)H\(_5\)) (2.6 g, 0.01 mol) was dissolved in dry dioxan (50 ml) and mixed with absolute methyl alcohol (0.42 mol, 0.01 mol). The mixture was refluxed for 2 hours with exclusion of moisture. The solvent was removed under reduced pressure and then the residue was washed with carbon tetrachloride (50 ml). The solid obtained was crystallized from carbon tetrachloride (charcoal) to give colourless needles of 6-chloro-3-(ethylmercapto carbonylamidocarbonyl)-4-methoxy-2-oxopyran (64d) (1.4 g, 50%). m.p. 153° (Found: C, 41.1; H, 3.6; N, 4.8). C\(_{10}\)H\(_{10}\)ClNO\(_5\) requires C, 41.2; H, 3.5; N, 4.5%). m/e 291 M\(^+\) and 293 \(\gamma\)\(^{max}\) (Nujol) 3150 v, 3096 w, 1745 s, 1692 s, 1570 s, 1492 s cm\(^{-1}\); \(\lambda\)\(^{max}\) (CH\(_3\)CN) 3160,5 nm (\(\varepsilon\) 11.6 x 10\(^{-3}\)); \(\tau\) (CDCl\(_3\)) 1.39 br (s, NH), 3.12 (s, 5-H), 3.18 (s, MeO), 6.96 (q, J 7 Hz, \(\text{CH\(_2\)}\) of C\(_2\)H\(_5\)), 8.67 (t, J 7 Hz, \(\text{CH}\) of C\(_2\)H\(_5\)). From the evaporation of the carbon tetrachloride (which was used for washing the first residue) an oil was obtained. This oil was extracted with hot petroleum ether (b.p. 60-80°). 7-chloro-2-methoxy-2-ethylmercapto-2,3-dihydro-5,5-dioxopyrone/3,4-cyclic-1,3-oxazine (65b) (0.3 g, 10%) was obtained and recrystallized from petroleum ether (b.p. 60-80°) (charcoal) as pale yellow needles, m.p. 127° (Found: C, 41.3; H, 5.0; N, 3.5%). C\(_{10}\)H\(_{10}\)ClNO\(_5\) requires C, 41.2; H, 4.8; N, 3.5%). m/e 291 M\(^+\) and 293 \(\gamma\)\(^{max}\) (Nujol) 3175 v, 1740 m, 1640 m, 1610 w, 1535 sh, 1525 s cm\(^{-1}\); \(\lambda\)\(^{max}\) (CH\(_3\)CN)
Reaction of 7-Chloro-2-ethylmercapto-4,5-dioxopyrano[3,4-e]-

1,3-oxazine (13, R = C₂H₅) with 2\(\frac{1}{2}\) moles of ethyl alcohol

The 7-chloro-2-ethylmercapto compound (13, R = C₂H₅) (2.6 g, 0.01 mol) was dissolved in dry dioxan (35 ml) and mixed with absolute ethyl alcohol (1.44 ml, 0.025 mol). Then the mixture was refluxed for 1½ hours. The solvent was removed under reduced pressure, the residue was washed with hot carbon tetrachloride, and the remaining solid was crystallised from acetic acid (charcoal) to give colourless plates of 4-chloro-3-ethoxycarbonyl-2,6-dihydroxy-

pyridine (44a) (0.88 g, 40%), m.p. 224° (decomp.), undepressed by the sample prepared previously.

The carbon tetrachloride was allowed to evaporate slowly. Crystalline 6-chloro-3-(2'-aza-3'-ethoxy-4'-oxa-1'-oxo-hexyl)-4-

hydroxy-2-pyrone (67) (0.5 g, 15%) was obtained and recrystallized from carbon tetrachloride (charcoal) to give pale yellow crystals, m.p. 144° (Found: C, 45.3; H, 4.1; N, 4.6. C₁₁H₁₂ClNO₆ requires C, 45.6; H, 4.1; N, 4.8%); m/e 289 [M⁺] and 291 [M⁺ + 2]. \(\nu\max (\text{Nujol}) 3080 \text{ w}, 1783 \text{ s}, 1688 \text{ s}, 1627 \text{ m}, 1593 \text{ m}, 1518 \text{ s} \text{ cm}^{-1}; \lambda \max (\text{CHCl₃}) 269, 337 \text{ nm} (\varepsilon 12,0, 13.99 \times 10^{-3}); \text{T} (\text{CDCl₃}) 4.93 \text{ br(CH)}; 3.81 (s, 5-H); 5.47, 5.56 (q, q, J 7Hz, 2 x CH₃); 8.57 (t, J 7Hz, 2 x CH₃); (the product gave a purple colour with alcoholic ferric chloride).
Reaction of the 7-Chloro-2-ethoxy-2-ethylmercapto-2,3-dihydro-4,5-dioxopyrrolo[3,4-e]1,3-oxazine (65a) with ethyl alcohol

The 7-chloro-2-ethoxy-2-ethylmercapto compound (65a) (0.3 g.) was dissolved in dry dioxan (10 ml.) and mixed with absolute ethyl alcohol (1 ml.). Then the mixture was refluxed for 2½ hours with exclusion of moisture. The solvent was removed under reduced pressure, and the residue washed with carbon tetrachloride. Crystallization from acetic acid (charcoal) gave colourless plates of 4-chloro-3-ethoxycarbonyl-2,6-dihydroxyypyridine (44a) (0.11 g., 50%), m.p. 224° (decomp.), undepressed by a previously obtained sample.

Reaction of the 7-Chloro-2-ethoxy-2-ethylmercapto-2,3-dihydro-4,5-dioxopyrrolo[3,4-e]1,3-oxazine (65a) with water

The 7-chloro-2-ethoxy-2-ethylmercapto compound (65a) (R = C\textsubscript{2}H\textsubscript{5}) (0.3 g.) was dissolved in dry dioxan (10 ml.) and mixed with water (1 ml.). Then the mixture was refluxed for 1½ hours. The solvent was removed under reduced pressure, and the residue was washed with carbon tetrachloride and crystallized from acetic acid (charcoal) to give colourless plates of 4-chloro-2,6-dihydroxyypyridine (31) (0.05 g., 30%), m.p. 222° (decomp.), undepressed by the sample prepared earlier.

6-Benzylamino-4-ethoxy-3-(ethylmercaptocarbonylamidocarbonyl)-2-oxopyran (66a)

The 6-chloro-4-ethoxy-3-(ethylmercaptocarbonylamidocarbonyl)-2-oxopyran (64a) (0.33 g.) was dissolved in dry chloroform (15 ml.), and dry benzylamine (0.2 ml., 0.02 mol.) was added dropwise over a period of 15 min., while the mixture was stirred, then the mixture
was refluxed for ½ hour. After the solvent had been removed under reduced pressure, the residue was washed with water then crystallized from acetonitrile (charcoal) to give colourless needles of 6-benzylamino-4-ethoxy-3-(ethylmercapto carbonylamidocarbonyl)-2-oxopyran (66a) (0.25 g., 80%), m.p. 226° (decomp.) (Found: C, 57.2; H, 5.4; N, 7.4. C_{18}H_{20}N_{2}O_{5} requires C, 57.4; H, 5.3; N, 7.5%). m/e 375 M⁺; λ max. (Nujol) 3150 v, 1747 s, 1690 s, 1640 m, 1570 s cm⁻¹; 1747 s, 1690 s, 1640 m, 1570 s cm⁻¹; λ max. (CH₃CN), 245, 287.5, 321 nm (ε 13.1 x 10⁻³); τ (d₆-DMSO) 1.02 br(s, CONH-COₗ), -0.82 br(t, J 5.1Hz, NH of PhCH₂NH), 2.66 (s, Ph), 3.59 (s, 5-H), 5.40 (d, J 5.4Hz, CH₂ of PhCH₂NH), 5.85 (q, J 7Hz, CH₂ of C₆H₅); 7.38 (q, J 7Hz, CH₂ of C₆H₅); 8.80, 8.83 (t, t, J 7Hz, 2 x CH₃).

6-Benzylamino-3-(ethylmercapto carbonylamidocarbonyl)-4-methoxy-2-oxopyran (66b)

The 6-chloro-3-(ethylmercapto carbonylamidocarbonyl)-4-methoxy-2-oxopyran (66d) (0.3 g., 0.01 mol.) was dissolved in dry chloroform (10 ml.), and dry benzylamine (0.2 ml., 0.02 mol.) was added dropwise over a period of 15 min., while the mixture was stirred, then the mixture was refluxed for ½ hour. After the solvent had been removed under reduced pressure, the residue was washed with water, then crystallized from acetonitrile (charcoal) to give colourless needles of 6-benzylamino-3-(ethylmercapto carbonylamidocarbonyl)-4-methoxy-2-oxopyran (66b) (0.3 g., 75%), m.p. 213° (decomp.) (Found: C, 56.2; H, 5.1; N, 7.9. C_{18}H_{18}N_{2}O_{5}S requires C, 56.35; H, 5.0; N, 7.7%). m/e 362 M⁺; λ max. (Nujol) 3110 ν, 1738 s, 1690 s, 1618 s, 1554 s (b); λ max. (CH₃CN) 287.5, 320.5 nm (ε 12.4 x 10⁻³); τ (d₆-DMSO) 0.80 br(t, J 5.1Hz, NH of PhCH₂NH), 0.20 br(CONHCO), 2.05 (s, Ph), 3.57 (s, 5-H), 5.43 (d, J 5.3Hz, CH₂ of PhCH₂NH), 6.32 (s, OMe), 7.25 (q, J 7Hz, CH₂ of C₆H₅); 8.83 (t, J 7Hz, CH₃ of C₆H₅S).
Reaction of the 6-chloro-4-ethoxy-3-(ethylmercaptocarbonyl-amidocarbonyl)-2-oxopyran (66a) with an excess of benzylamine

The 6-chloro-4-ethoxy-2-oxopyran (66a) (0.3 g.) was dissolved in dry benzylamine (10 ml.). The mixture was refluxed for 3 hours, then the excess of benzylamine was removed under reduced pressure. The residue was washed with water and then with ethyl alcohol (50 ml.). The residue was crystallized from ethyl alcohol to give colourless crystals of NN'-dibenzylurea (26) (0.16 g., 80%), m.p. 169°, undepressed by the sample prepared earlier.

Evaporation under reduced pressure of the ethyl alcohol (which was used for the washing) gave malonodibenzylamide (24) (0.45 g., 80% for 2 moles), m.p. 140°, undepressed by an authentic sample.

The NN'-dibenzylurea (26) and malonodibenzylamide (24) were also obtained in about the same yields as above by treating the 6-benzylamino-4-ethoxy-3-(ethylmercaptocarbonylamidocarbonyl)-2-oxopyran (66b) with an excess of benzylamine.
3. Ibid., 1962, 3553.
15. Ibid., 1968, 99, 1454.
20. L. Henry, Ber., 1869, 2, 634.
22. F. Walden, Ber., 1907, 40, 3215.
37. O. Dimroth, Ber., 1902, 35, 2882.


