DISCUSSION
DISCUSSION

The reaction of 4-hydroxycoumarin with aldehydes and ketones gives substituted dicoumaroles but literature does not record any work on the reaction of 3-bromo and 3-nitro coumarin with carbonyl compounds. Specially interesting in the context of earlier studies appeared to be the reaction of 3-bromo-4-hydroxycoumarin with aldehydes as the initial product (57) can suffer loss of HBr to give 3-formyl-4-hydroxycoumarin (58). Since existing methods for the synthesis of 3-formyl-4-hydroxycoumarin are cumbersome and give low yields which are not consistently reproducible the new approach could provide a more convenient route to this compound. Alternatively the addition product (57), no longer stabilised by the C-4 OH group, could suffer hydrolysis with opening of the lactone ring and recyclisation to hydroxymethyl coumaranone (59). Both compounds (58) and (59) were of interest at the time in connection with another project and the reaction was, therefore, worth attempting. It should be added that (59) is not available through direct formaldehyde addition to coumaranone as this leads to the disubstituted (60) which cyclises to the spiran (61) with involvement of another formaldehyde molecule.
When formalin was added to a hot ethanolic solution of 3-bromo-4-hydroxycoumarin the solution turned light yellow and showed strong acidic reaction pointing to HBr elimination. Gradually a yellow mass separated out. It was filtered and checked through tlc. Iodine staining showed two compounds which could be separated through crystallization. Their spectral data did not fit any of the expected compounds and was found to be identical with that of compounds (22) and (67) which were isolated and identified unambiguously earlier in the DMSO/AC₂O reaction of 4-hydroxycoumarin. Their formation in almost quantitative conversion suggests that the bromohydrin (57) is extremely unstable and decomposes spontaneously either to the formylcoumarin (58) through HBr loss or to 3-methylene chroman-2,4-dione (62) through HOBr elimination (Scheme-1).
Whatever the structure of the intermediate, addition of unreacted 3-bromo-4-hydroxycoumarin leads to dimers (63) or (65). The further transformation of these to 2,3-dihydro-2(2-hydroxybenzoyl)-4H-furo [3,2-c][1] benzopyran-4-one (22) and its dehydro-derivative (67) must involve cyclisation to spirans (64) or (66) for if hydrolysis were to occur first (68) should be one of the products of the reaction.

![Diagram](68)

Though unexpected the dimerization step is in accord with the chemistry of 4-hydroxycoumarin. The spontaneous extrusion of bromide ion by hydroxylic attack in strongly acidic medium is, however, an unusual feature of the reaction. Further if formyl-coumarin is an intermediate in the reaction (Scheme-3), the assumption that HOBr elimination is spontaneous, as in (scheme-2), is not valid as formation of (69) is not observed. It might be reasoned that this elimination is now avoided by participation of the OH group in Br\(^-\) elimination. This would, however, require polarisation of C-Br bond in such a way that the positive charge resides on a carbon flanked by two carbonyl groups. It is possible therefore that this step involves elimination of Br\(^+\) as the environment of bromine is similar to that in NBS\(^{50}\).
Scheme 2

\[ \text{(22)} \xrightarrow{\text{+Br}^+ - \text{HBr}} \text{(67)} \]

\[ \text{(22)} \xrightarrow{-\text{HBr}} \text{(64)} \]

\[ \text{(64)} \xrightarrow{\text{+H}_2\text{O} - \text{CO}_2} \text{(63)} \]

\[ \text{(63)} \xrightarrow{\text{Br}} \]
Scheme 3

(65) → (66) → (67) via hydrogenolysis

(22)
This made it desirable to check if 3-formyl-4-hydroxycoumarin was indeed an intermediate in the reaction. Attempts to prepare this compound by the published methods met with poor success. Attempted formylation by the Vilsmeir-Haack procedure gave only the trimer (71), while if Cheechi's procedure was employed hydrolysis of the immino intermediate gave a mixture from which only insignificant amounts of the formyl compound could be obtained through chromatography. In the light of these results it seemed likely that the reaction of 4-hydroxycoumarin with ethyl orthoformate under acid catalysis would also lead to the trimer and initial attempts justified the assumption. However, there seemed a possibility that if the reaction was conducted in presence of traces of moisture and ethyl orthoformate was used both as reagent and solvent the intermediate (70) could suffer hydrolysis to the formyl compound which may not be exposed to unreacted 4-hydroxycoumarin at high dilution. The device worked
better than expected and afforded, along with (72), the cyclisation product of the trimer (71), 3-formyl-4-hydroxycoumarin in high yields which were found to be easily reproducible.

**The reaction of 3-formyl-4-hydroxycoumarin with active methylene compound:**

Whereas the reactions of 3-formylchromones have received much attention only two references could be found in literature on 3-formylcoumarin. The first of these concerns its conversion with malonic acid derivatives to pyranopyran (73). The second simply notes that while 3-acetylcoumarin reacts with phenylhydrazine to give pyrazoles e.g. (28) the hydrazone of 3-formyl-4-hydroxycoumarin failed to cyclise under the same conditions. With larger amounts of 3-formylcoumarin easily accessible through the improved synthetic procedure it appeared attractive to explore other such reactions. Since formylcoumarin is labile under strongly acidic or basic conditions only the more reactive nucleophiles, which are sufficiently enolised at pH close to 7 could be considered for the purpose. 2'-hydroxy-2-nitroacetophenone (74) appeared promising from this viewpoint. Its reactivity was checked first with some simple aldehydes. This led to rather
unexpected results for when the nitroketone in 98% ethanol was refluxed for some hours with formalin a reaction occurred but the product was the oxime (76) and not the expected chromone (75). Conversion of the nitroketone (74) to the oxime has been reported but only under pronounced basic conditions. Thus it was obtained by Ellis and Becket in their attempted synthesis of 3-nitrochromone-2-carboxylic acid from the nitroketone and ethyl oxalyl chloride in pyridine, in agreement with the earlier finding of instability of the ketone in pyridine. It was found that the oxime was also produced on heating the ketone with aqueous sodium acetate- but it's solution in ethanol could be refluxed for several hours without any change. Since ethanol from the same bottle- was used oxime formation can not be attributed to presence of traces of basic impurities in it and it must be assumed that formaldehyde plays a key role in the reaction- perhaps by binding the phenolic hydrogen.
The expected chromanone was, however, formed when benzaldehyde was used together with small amounts of the oxime. Chromone formation in the reaction was earlier reported by K.V. Rao who employed NaOAc/AcOH. Salicylaldehyde, o-acetoxybenzaldehyde and o-nitrobenzaldehyde, however, again gave only the oxime. This dichotomy of behaviour is difficult to understand but might be rationalised in terms of stability of the intermediate adduct (77). In the case of benzaldehyde the adduct is stable and undergoes dehydration, while in other cases it is either not formed or does not survive long enough for dehydration to occur. The situation does not change if a base such as pyridines is added to coax the reaction.

When 3-formyl-4-hydroxycoumarin was employed as the aldehyde neither addition nor oxime formation occurred probably due to suppression of reactivity of the aldehydic function by chelation and acidity of the C-4 OH group. Addition of catalytic amounts
of pyridine as before made no difference but when excess pyridine
was added to the ethanol solution of the 3-formyl-4-hydroxycoumarin
and nitroketone and it was refluxed for an hour a compound gradually
crystallised out. It was filtered and the mother liquor worked up after dilution with water. Chromatography then supplied more
of the crystalline material, labelled NC-1, along with another
compound NC-2 and salicylic acid, the sparingly soluble NC-1 being
the major product of the reaction. Tlc examination of the residue
from the mother liquor had indicated presence of yet another com­
pound, NC-3 which was initially overlooked but results of subse­
quent experiments made it necessary to concentrate on its isolation
which was achieved through further careful chromatography of the
eluate from which other products had been separated.

Similar reaction was also carried out with methyl substi­
tuted nitroketone and 3-formyl-4-hydroxycoumarin in order to
simplify the aromatic region of the nmr spectrum and to establish
whether the reaction was intra or intermolecular. This led to
products labelled as NC-1b and NC-3b.

NC-1

\[ M^{+} 277, \text{m.p. 287}^\circ \text{C} \] is a colourless compound which tested
positive for nitrogen and hence was assumed to arise through combi­
nation of the nitroketone with the 3-formyl-4-hydroxycoumarin. On
this basis the bands at 1720 and 1680 cm\(^{-1}\) in the i.r. spectrum
(Fig.1) should belong to the lactone and ketone carbonyls but
structure (78) requires \[ M^{+}\] at m/z 342. The nmr spectrum indicates
a total of 8 aromatic protons and shows at higher field a 2H doublet at 6.20 and 1H triplet at 4.52. These signals cannot be reconciled with structure (78) which has only two protons resonating in the high field region. It is thus apparent that the course of the reaction is radically altered from that in the case of benzaldehyde. Crucial to the structural elucidation of NC-1 is the presence of an XCH-CH\textsubscript{2}Y grouping responsible for the two signals at higher field. Since nitrogen is present X is in all probability NO\textsubscript{2} but because of the multiplicity of the methylene signal the intact ketone moiety cannot be present in the compound. To check this the reaction was carried out with substituted 2'-hydroxy-2-nitroacetophenone (74b). The nmr spectrum of the compound corresponding to NC-1 did not display any methyl singlets. Consequently the 8 proton multiplets in the aromatic region of the nmr spectrum must all arise from two coumarin moieties. Since salicylic acid is a product of the reaction it is apparent that the adduct (79) decomposes with elimination of salicylic acid (81).
This course of the reaction is assumed because both in aqueous basic solution and in pyridine decomposition of the nitroketone is slow and produces mostly the oxime and hence it can not decompose directly to nitromethane prior to the reaction with aldehyde.

![Chemical Structure](image)

Addition of another molecule of coumarin with elimination of the aldehydic group should give the dicoumarol derivative (82) with molecular weight equal to 395. Since M\(^+\) is 18 mass units (Fig.2) lower (82) must have suffered elimination of water to give (83). The ir band at 1680 cm\(^{-1}\) in the spectrum therefore is not that of ketone carbonyl but of the enol ether moiety. The aromatic region of the high resolution nmr spectrum (Fig.3) is composed of a 2H double doublet at 68.12 [J=8.3 and 1.7], a sextet at 67.70 [J=8.5 and 1.6]. The signal at lowest field is reasonably assigned to H\(_a\) and that giving rise to the sextet to H\(_b\) which is meta coupled to H\(_a\) and ortho coupled to H\(_c\) and H\(_b\), the 4H multiplet at 67.47 is reasonably assigned then to H\(_c\) and H\(_x\).
MASS SPECTRUM
04/06/88 8:41:00 + 0:58
SAMPLE: NCI
CONDs.: +/CI-ISOBUT/Q3 MASS SPECTRUM-DEF
GC TEMP: 120 DEG. C

DATA: 8C1'795 #58
CALI: 210CH03 #1
RIC: 275968.

BASE M/Z: 378
The $^{13}$C spectrum of (Fig. 4) NC-1 is in accord with structure (83) showing only 11 of the 20 carbon atoms because of the symmetrical structure. It shows only one C=O supporting the assumption that the IR band at 1680 cm$^{-1}$ arises from a double bond but the other assignments are made on the basis of values reported$^{54,55}$ for (84) and (85).
FIG. 4
Table 1. $^{13}$C N.M.R. spectra (δ Scale; in CDCl$_3$ and DMSO$_d^6$ at 25.2 MHz)

<table>
<thead>
<tr>
<th>Structure</th>
<th>(83)</th>
<th>(84)</th>
<th>(85)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbon No.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td>159.97</td>
<td>160.53s</td>
<td>161.75</td>
</tr>
<tr>
<td>2.</td>
<td>100.99</td>
<td>101.60s</td>
<td>90.98</td>
</tr>
<tr>
<td>3.</td>
<td>152.20</td>
<td>166.10</td>
<td>165.45</td>
</tr>
<tr>
<td>4.</td>
<td>123.28</td>
<td>122.50</td>
<td>123.01</td>
</tr>
<tr>
<td>5.</td>
<td>125.27</td>
<td>123.70</td>
<td>123.62</td>
</tr>
<tr>
<td>6.</td>
<td>133.87</td>
<td>132.00</td>
<td>132.34</td>
</tr>
<tr>
<td>7.</td>
<td>116.83</td>
<td>116.60</td>
<td>116.14</td>
</tr>
<tr>
<td>8.</td>
<td>155.42</td>
<td>154.70</td>
<td>153.38</td>
</tr>
<tr>
<td>9.</td>
<td>112.58</td>
<td>112.50</td>
<td>115.37</td>
</tr>
<tr>
<td>10.</td>
<td>75.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11.</td>
<td>29.54</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Since the nitroketone simply provides the -CH$_2$NO$_2$ group, 3-formyl-4-hydroxycoumarin was treated with nitromethane in pyridine/ethanol. As expected the reaction supplied (83)(Scheme-4) but the reaction time had to be increased and the conversion was not complete. This justifies the suggested mechanism involving attack by the reactive methylene of the nitroketone—rather than its initial decomposition to salicylic acid and nitromethane.
Chemical reaction: 

\[ \text{CH}_3\text{NO}_2 + \text{Ethanol} \xrightarrow{\text{Pyridine}} \text{Product} \]

Diagram: 

- (80)
- (82)
- (83)
NC-2

M⁺ 266, m.p. 214-16°C is sparingly soluble in chloroform though much more so than NC-1. Its IR spectrum (Fig. 5) also has two bands in C=O region—one sharp at 1685 cm⁻¹, the other broadish at 1650 cm⁻¹ and thus points to the presence of a chromone nucleus and o-hydroxybenzoyl group in NC-2. The o-hydroxybenzoyl grouping is evident also from the positive ferric reaction, though this is observed only if the reagent is added to the alcoholic solution in a test tube and not when it is sprayed on the TLC plate—perhaps due to poor solubility of the compound. Assembly of these structural elements leads to (86) or (87). This agrees with the

\[ \text{Scheme-5} \]
mass spectrum (Fig. 6) of the compound which exhibits the typical fragmentation pattern of chromones \(^5\text{6}^\text{6}\) (Scheme-5) with peaks at m/z 64, 92, 118, 120, 121, 145, 146, 173.

The nmr spectrum (Fig. 7) of NC-2 does not allow a choice to be made between (86) and (87)- and moreover raises doubts about purity of the sample. Thus there are two singlets for the OH group of varying intensity, the proton peri to the carbonyl group appears again as two overlapping double doublets also, of different intensities. The multiplet at \(\delta 7.60\) and that between \(\delta 7.20\)-7.50 do not seem to belong to the same compound. Repeated tlc of the sample used for the above spectral measurements did not, however, reveal any impurity and spectra run after further crystallisations did not show any change in relative intensities of the signals. But what is striking is that the mass spectrum too has no indication of an impurity and seems clearly to belong to a compound having the suggested structure. The material used for both spectral measurements was taken from the same tube- and the mass and nmr spectra are, therefore, of the same sample. The mass spectrum (Fig. 3) of the sample prepared later shows some indication of an impurity but the peaks above m/z 266 suggest it is present only in traces. Interestingly multiple peaks are observed in this spectrum for \(M^+\) and ions with m/z 117, 121, 145 are as abundant as the molecular ion. Since the molecule is not rigid the existence of two conformational isomers is not feasible. One explanation of this anomaly could be that there are two isomers having almost the same fragmentation pattern- and on this basis one may suggest that
ZAMAN, 300
DATE 23-5-88

SOLVENT 25°C
SF 300.133
D1 4900.000
SI 16384
SW 3537.122

PW 4.0
AG 2.277
RG 160
NS 16

OX 26.50
CY 0.0
F1 9.250P
F2 7.000P
PPM/CM .100

FIG. 7
the other isomer is (88).

This could have provided an ideal solution but for the fact that the nmr spectrum does not contain any signal at higher field which could be assigned to two protons on saturated carbons for though one of these is doubly deshielded by adjacent oxygen and the other by neighbouring carbonyl groups their signals should not get lost in the aromatic region.

Mechanistically any route to (87) would be too speculative for inclusion here but structure (86) can be rationalised as shown (Scheme-6). It was hoped that the reaction with substituted nitroketone or coumarin would clarify the situation but the product corresponding to NC-2, NC-2b was formed in too small amounts to allow spectral measurements and the major product was NC-3b- which corresponds to NC-3 obtained in this reaction.
NC-3

M^+ 306, m.p. 180-185°C in the ir spectrum (Fig. 9) of the compound the ketone carbonyl of the coumarin moiety appears at 1760 cm⁻¹ accompanied by a band at 1690 cm⁻¹. The compound does not give any colour with ferric chloride and does not contain nitrogen.

To check if 4-hydroxycoumarin was incorporated in the product the reaction was conducted with 5,7-dimethyl-3-formyl-4-hydroxycoumarin. The nmr spectrum of the resulting compound NC-3b, M^+ 334, m.p. 212°C showed two methyl singlets confirming its participation in the reaction.
In the mass spectrum of NC-3b (Fig. 10) the molecular ion peak at m/z 334 forms the base peak. The other major peak is at m/z 214 and is followed by others due to loss of carbon monoxide and methyl (Scheme-7).

\[
\begin{align*}
R' & \quad m/z \ 334 \\
& \downarrow \\
& \quad m/z \ 306 \\
& \downarrow \\
& \quad m/z \ 186 \\
& \downarrow \\
& \quad m/z \ 148 \\
& \downarrow \\
& \quad m/z \ 120 \quad m/z \ 214 \\
& \downarrow \\
& \quad m/z \ 199 \\
\end{align*}
\]

\[
R' = R'' = \text{CH}_3
\]

Scheme-7
MASS SPECTRUM: (15 TO 17)
SAMPLE: NC38/216C
NOTE: 70EV/EI
BASE PEAK: M/E 334.0 INT. 499.3

FIG. 10
The nmr spectrum (Fig. 11) shows a 1H singlet at 67.8 and a double doublet at 68.2. The presence of intact coumarin moiety is evident from the singlet of the OH proton in the offset. Combining the data one arrives at structure (89b) for the compound and its formation can be rationalised as shown (Scheme-8).

\[ \text{Scheme-8} \]

(89) \( R' = R'' = H \)

(89b) \( R' = R'' = \text{CH}_3 \)
The band 1760 cm\(^{-1}\) is at much higher value than in 4-hydroxy-coumarin and its other 3-substituted derivatives so that the compound, in the solid state, at least, must be assumed to exist in the tautomeric form (90) exclusively. It is interesting to note that

this product was expected to be formed in the reaction of 3-formyl-4-hydroxycoumarin with coumaranone, but ring expansion there led to the 2,3-dihydro [2,3-b] benzopyrano-4H-furo[3,2-c][1] benzopyran-12-one (96).
The reaction of 3-formyl-4-hydroxycoumarin with coumaranone

**3.FC-1**

Coumaranones react with aromatic aldehydes to give aurones (91) and by analogy the reaction with 3-formyl-4-hydroxycoumarin should give (89) or if disubstitution occurs (92).
Treatment of coumaranone with 3-formyl-4-hydroxycoumarin in ethanol at room temperature overnight gave a granular crystalline product m.p. 210-12°C, which showed M⁺⁺ at m/z 306 in its mass spectrum as required for (89) but this structure for the compound has to be rejected as it is colourless whereas aurones are deep yellow to orange in colour. The ir spectrum of 3 FC-1 shows bands at 1720 and 1660 cm⁻¹ whereas that of (93), prepared from o-nitrobenzaldehyde and coumaranone, has bands at 1710 and 1660 cm⁻¹ which arise from stretching vibrations of the carbonyl group

![Scheme 9](image)

(93)

and the double bond, the carbonyl absorption being stronger. In the ir spectrum (Fig. 12) of 3 FC-1 the absorption at 1720 cm⁻¹ is however weaker than that at 1660 cm⁻¹, which seems to have contribution from two chromophores. The nmr spectrum (Fig. 13) completely eliminates structure (89) as it contains no singlet of the olefinic proton at δ7.5 and shows, apart from the multipletes of aromatic protons, 1H doublets at δ5.91 and 5.13(J=11.73). These spectral features can be accommodated only if rearrangement of the initially formed (94) to (96) is assumed (Scheme-9). The doublet at δ5.13 can now be reasonably assigned to C-3 of the chromanone.
ring as besides being allylic and \( \alpha \) to the carbonyl group it is enclosed in the cage like structure formed by the chromanone and lactone carbonyls. The band at 1660 cm\(^{-1}\) in the ir spectrum is stronger than that at 1720 cm\(^{-1}\) because it contains the absorption of the chromanone carbonyl as well as that of the enol ether linkage.

![Diagram](image)

Scheme-9
The mass spectrum (Fig. 14) of the compound shows (Scheme-10) all the expected ions on the basis of (96) and thus confirms this novel structure.
NMR SPECTRUM
SAMPLE: FE-1 OR A SHOE.
NOTE: 13/3/78.
F.T. RECOR 0.1 RTG 481.5
GALILE PEAK M/E 120.0 INT. 515.6

FIG. 14
The reaction of 3-formyl-4-hydroxycoumarin with triacetic acid lactone.

3 FP-1

In the context of the reactions of 3-formyl-4-hydroxycoumarin and triacetic acid lactone it was pertinent to study the reactions of the two with each other since o-hydroxybenzaldehyde reacts with the lactone to give the rearranged product (97).

\[
\begin{align*}
\text{CHO} & \quad \text{O} \\
\text{HO} & \quad \text{CH}_3 \\
\end{align*}
\]

3-formyl-4-hydroxycoumarin reacted in exactly analogous manner to give (98) as the exclusive product of the reaction as shown in (Scheme-11). Structure (98) is in complete agreement with spectral features of the compound e.g. $M^+ 298$, C=O 1760, 1730, 1640 (Fig. 15), singlets at 62.40(-C-CH$_3$), 7.1(1H,s), 8.95 (1H,s) (Fig. 16). The mass spectrum (Fig. 17) shows losses of methyl, acetyl and acetoacetyl group from the $M^+$ and is similar to other compounds having this side chain.
Scheme-11
The reaction of 4-hydroxy-6-methyl-2H-pyran-2-one (triacetic acid lactone) with ethyl orthoformate.

The successful conversion of 4-hydroxycoumarins to the 3-formyl derivative in good yields with ethyl orthoformate prompted investigation of the further potential of this reagent. Triacetic acid lactone was selected as it is the aliphatic analogue of 4-hydroxycoumarin but exposure of the lactone to moist ethyl orthoformate/PTS gave exclusively a dimer which was initially identified as (99) the structure given by Hirsch and Hoefgen\textsuperscript{4} to the compound they obtained by treatment of the triacetic acid lactone, triethylammonium/piperidine with ethyl orthoformate. Again the same structure was given by same workers\textsuperscript{5} to the product of the Vilsmeir-Haack reaction of lactone, however, since no detailed information was available from the literature it was decided to characterise it afresh on the basis of its mass spectrum and IR and NMR data. The IR spectrum has bands at 1770, 1725 and 1640 cm\textsuperscript{-1} which can be assigned to carbonyl groups of the enol lactone and γ-pyrone systems. Extended conjugation is also evident from its deep yellow colour. The most deshielded olefinic proton in the compound is $H_b$ and the singlet at 6.87 can be assigned to it. The olefinic

![structure](image-url)
proton adjacent to the methyl group in triacetic acid lactone spectrum resonates at 66.2 and that adjacent to carbonyl at 66.5. The singlets at 66.2 and 6.6 can therefore be assigned to $H_a$ and $H_c$ in the dimer spectrum. Though it comes as a surprise that the methyls resonate at different values the spectral features are generally consistent with the assigned structure but the strong ferric colouration sounded a discordant note.

The erroneous structure (100) was assigned to the product arising from reaction of salicylaldehyde with 4-hydroxycoumarin\textsuperscript{47}. The mistake was corrected after many years by Spanish workers\textsuperscript{57} who formulate it as (101).

![Diagram](100)

![Diagram](101)

Rearrangements of this type are common to products of the reaction of o-hydroxybenzaldehyde with enol lactones. Thus (102) resulting from the reaction of triacetic acid lactone with salicylaldehyde rearranges to (97) during the reaction.

![Diagram](102)

![Diagram](97)
A similar rearrangement is thus possible in the case at hand and the strong ferric colour is an indication that this indeed has happened. Thus the ir spectrum is equally compatible with structure (103) as it contains the enol lactone moiety and the chelated ketone carbonyl can account for the band at 1640 cm\(^{-1}\) (Fig. 18). The singlets at 68.7, 6.7 and 6.2 (Fig. 19) can now be assigned to \(H_b\), \(H_{a/c}\) and \(H_{c/a}\). Thus it is difficult to make a definite choice on the basis of ir and nmr spectra alone but the mass spectrum (Fig. 20) of the compound more or less fixes the structure of the product in terms of (103) as the most prominent ion after \(M^{+}\) is at m/z 262, a loss of 57 mass units corresponding to elimination of \(\text{CH}_3\text{C}-\text{CH}_2\). Smaller peaks at m/z 247, and 220 indicate losses of \(\text{CH}_3\) and \(\text{CH}_2\text{CO}\) group. The mass spectrum of 3-acetoacetylcoumarin studied by Dean et al.\(^{58}\) is also characterised by losses of \(\text{CH}_3\text{CO}\) and \(\text{CH}_3\text{COCH}_2\) groups. Hence a wrong
MASS SPECTRUM

SAMPLE: TM-1, F.R.A. SHOEB
NOTE: 12-12-85
P.T. R: 25.0
R.I.C. 1000.0
BASE PLK: M/E 205.0 INT. 133.4

FIG.20
structure was assigned to this product earlier and it should be revised to (103).

Conclusive chemical evidence in support of (103) is available from the fact that when the yellow product is treated with $\text{Ag}_2\text{O}$ in CHCl$_3$ no reaction occurs and it is recovered unchanged. However if CH$_3$I is added a C-methyl derivative (104) is formed as the nmr spectrum shows a methyl doublet at δ1.35 and methine quartet at δ4.55 (Fig.21).

![structure](image)

The important point as far as the reaction with $\text{Ag}_2\text{O}$ is concerned is that if the initial product is formulated as (99) and it rearranges under basic conditions to (103) then rearrangement should occur even in the absence of CH$_3$I and as this does not happen (103) must be the actual product of the reaction of the triacetic acid lactone with ethyl orthoformate.
Compounds derived from triacetic acid lactone and ethyl orthoformate have served as starting materials for aromatics and nitrogen heterocycles. Such syntheses have little practical utility but are of biogenetic interest as the starting materials can be regarded as masked polyketomethylene. In the light of this work it appeared worthwhile to study the reaction of (103) with ammonia and aminocompounds. The reaction with ammonia gave mixtures from which a compound TLN-3 could be isolated through repeated column chromatography. As against this the reaction with phenylhydrazine and hydroxylamine supplied only one product which crystallised out from the reaction medium. These were given the codes TLN-1 and TLN-2. Both are high melting and soluble with difficulty in all organic solvents.

**TLN-1**

M.P. 225-27°C, M⁺ 334 is a yellow crystalline compound. The immediate point of interest in its mass spectrum (Fig. 22) is the very weak molecular ion peak which is followed by the base peak at m/z 244. This amounts to loss of 90 amu since β-diketones react with phenylhydrazine to give N-phenylpyrazolones the expected products of the reaction were pyrazoles (105) or (106). One would have to assume simultaneous departure of Ph⁺ (77 amu) and CH₃ (14 amu) to accommodate the 90 amu—which is very unlikely specially as the resulting ion forms the base peak. This suggests that the compound has part structure Ph.NH.N-R and suffers a loss of PhNH.
The alternative (107) where PhNH elimination is favoured by presence of the adjacent carbonyl group is not acceptable as the compound does not exhibit β-diketone absorption in its IR spectrum, it's fragmentation on electron impact differs radically from that of the starting material and it is not ferric positive. The acetoacetyl group must, therefore, have participated in the reaction and on this basis the compound was formulated initially as (108).
The ir spectrum agrees with this structure if it is assumed that the broad carbonyl band at 1700 cm\(^{-1}\) has contributions from both the lactone and chromone carbonyls. The \(^{1}\)H nmr (Fig. 23) seems to clinch the issue as it shows three \(^{1}\)H singlets at 66.05, 8.2, 9.8 and a 6H singlet at 62.2. The overlapping of methyl resonances in view of their substantially different environment is unusual. The structure (108) is however completely ruled out by the \(^{13}\)C nmr spectrum which shows only 11 carbon atom whereas (108) has at least 14 non-equivalent atoms as indicated.

\[
\begin{array}{c}
\text{H}_3\text{C}_4 \\
\text{2} \quad \text{3} \quad \text{4} \quad \text{5} \quad \text{6} \quad \text{7} \quad \text{8} \\
\end{array}
\]

Only if the compound is symmetrical as in (109) or (110) would it have just 11 nonidentical carbons. The ir spectrum(Fig. 24) favours(110) but does not completely eliminate (109). The \(^{13}\)C spectrum does not permit a clear cut distinction to be made between these two alternative structures and the \(^{1}\)H nmr is in apparent disagreement with both (109) or (110)- as it has 3 \(^{1}\)H singlets instead of a 2H singlet and a \(^{1}\)H singlet the former due to identical pyrone hydrogens at higher field and the latter due to lone hydrogen of the pyridine ring.
Structure (109) is, however, mechanistically improbable as its formation would involve prior opening of the lactone ring—a reversal of the process that led to formation of (103) from triacetic acid lactone and ethyl orthoformate.
Even if it is assumed that such a thermodynamically unfavourable reaction occurs before the Ph NHNH₂ group attacks any of the reactive sites of the molecule the product should be the unsymmetrical compound (108) formed through attack by the reagent on the intermediate (99).
No such difficulty is presented by the conversion of (103) to (110).

The reaction is similar to the acyl lactone rearrangement except that the rotation of (111) to (112) involves conversion to a geometrical isomer. However, this is not improbable under the mild acidic reaction conditions. A direct analogy is afforded by conversion of dehydroacetic acid (113) to (114).
In a separate investigation with primary amines the intermediate (115) leading to (116) was isolated under mild reaction conditions.
This leaves the problem of non-equivalence of the two hydrogens adjacent to the methyl groups and one possible explanation is restricted rotation of the NPh group due to partial double bond character of the N-N bond which effectively leads to non-equivalence of the two hydrogens because of proximity of $H_a$ to the benzene ring.

The $^{13}$C spectrum (Fig. 25) as stated shows 11 carbons. The assignments shown in (110) are made on the basis of values computed from those of N-methyl pyridinium iodide (117)$^{62}$, pyranopyran (118)$^{63}$ and aniline (119)$^{64}$. 
Table 2. $^{13}$C N.M.R. spectra (δ Scale; in CDCl₃ and DMSO-d$_6$ at 25.2 MHz)

<table>
<thead>
<tr>
<th>Structure</th>
<th>(110)</th>
<th>(117)</th>
<th>(118)</th>
<th>(119)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbon No.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C(1)</td>
<td>171.60</td>
<td></td>
<td>165.90</td>
<td></td>
</tr>
<tr>
<td>C(3)</td>
<td>163.56</td>
<td></td>
<td>154.60</td>
<td></td>
</tr>
<tr>
<td>C(4)</td>
<td>95.90</td>
<td></td>
<td>101.80</td>
<td></td>
</tr>
<tr>
<td>C(4a)</td>
<td>162.48</td>
<td>145.8</td>
<td>136.10</td>
<td></td>
</tr>
<tr>
<td>C(8a)</td>
<td></td>
<td>103.30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C(10)</td>
<td>142.16</td>
<td>145.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C(10a)</td>
<td>102.03</td>
<td>128.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C(3)-Me</td>
<td>19.58</td>
<td></td>
<td></td>
<td>19.40</td>
</tr>
<tr>
<td>C(1')</td>
<td>144.46</td>
<td></td>
<td></td>
<td>147.70</td>
</tr>
<tr>
<td>C(2')</td>
<td>111.92</td>
<td></td>
<td></td>
<td>116.10</td>
</tr>
<tr>
<td>C(3')</td>
<td>129.46</td>
<td></td>
<td></td>
<td>129.80</td>
</tr>
<tr>
<td>C(4')</td>
<td>119.91</td>
<td></td>
<td></td>
<td>119.00</td>
</tr>
</tbody>
</table>
Replacement of phenylhydrazine by hydroxylamine in the above reaction gave a yellow crystalline product m.p. 258-60°C, $M^+$ 259, which was formulated, by analogy with TLN-1 as (110).

![Chemical Structure](image)

The mass spectrum (Fig. 26) of TLN-2 also shows losses of methyl and carbon monoxide but the main difference between it and the mass spectrum of TLN-1 is that $M^+$ now forms the base peak. This created doubts about the validity of structure (120) for the compound as amine oxides show an abundant M-16 peak which is some times the base peak. The M-15 peak, assigned to loss of the methyl group is too weak to qualify for an M-16 one. However other discrepancies in the mass spectrum and lack of any response by the compound to $\text{PCl}_3$- rules out the aminoxide structure (120). The alternative structure (121) is therefore assigned to this compound on the basis of spectral evidence.
**** E I MASS MAT.112.S ****

ANALYSIS NAME: TLNZ.DAT     SPEC# 15     NORM: B /SCALE :11056
DATE: MAY 20 87  09:06:38   U03.6
     FIG.26
The ir spectrum (Fig. 27) of TLN-2 is similar to that of TLN-1 but the carbonyl band is at higher frequencies and broader suggesting merger of two bands, one at 1760 cm\(^{-1}\) the other at 1730 cm\(^{-1}\). The mass spectrum shows a strong peak at m/z 82 of about equal intensity as the base peak and M\(^{+} - 82\) at m/z 177/176 is also strong. These can be accommodated only on the basis of loss of the isoxazole moiety. The nmr spectrum (Fig. 28) shows three 1H singlets at \(\delta\) 6.6, 7.2 and 8.7 – the one at lowest field, being sharp, may be safely assigned to the C-8 hydrogen, the other two showing allylic coupling with the methyl group cannot be unambiguously assigned but their position agrees with values expected for C-4 and isoxazole hydrogens. The 6H singlet at \(\delta\) 2.5 is an indication that the environment of the two methyls is identical and this, while not conclusively eliminating the alternative structure (122) favours (121).
M.P. 185-90°C, M* 245, was obtained as a yellow crystalline compound on extensive chromatography of the mixture resulting from treatment of (103) with methanolic ammonia. By analogy with TLN-1 it was assigned structure (123). This is supported by its nmr spectrum (Fig. 29) which shows the allylic hydrogens as a 2H singlet at δ 3.3 and the olefinic hydrogens as a 2H singlet at δ 5.63. The 6H singlet of the methyls is at δ 0.12. The mass spectrum (Fig. 30) has M* at m/z 245, M* -Me at m/z 230 followed by loss of carbon monoxide and again of methyl to give rise to peaks at m/z 202 and 187.
The alternative structure (124) for the compound is ruled out by the position of the carbonyl band in the IR spectrum (Fig. 31) at 1710 cm$^{-1}$. In structure (124) the carbonyl group is conjugated both with the oxygen and the nitrogen atoms and carbonyl absorption should thus be characteristic of vinylogous amides which absorb at 1660 cm$^{-1}$. According to (123) the compound is a vinylogous carbamate and 1710 cm$^{-1}$ is close to the value reported for carbamates. While the structure (123) has good spectroscopic support it is difficult to formulate a mechanism for reduction of the initially formed pyridine (123a).
Reaction of 3-formylchromone

3-formylchromone chemistry has been the subject of much recent interest and its synthetic applications have led to several heterocycles not easily accessible through conventional methods. In the context of present studies it appeared of interest, therefore, to examine its behaviour towards triacetic acid lactone and 4-hydroxycoumarin after a survey of literature showed that such reaction have not been investigated. Two interesting examples of its reactivity is provided by the reaction with iodohydrin\textsuperscript{66} under mild basic conditions and its Diels-Alder addition to ethyl vinyl ether\textsuperscript{67}.

![Chemical structures](image)

Reaction of 3-formylchromone with triacetic acid lactone

When an equimolar amounts of 6-methyl-4-hydroxy-2H-pyran-2-one was added to an alcoholic solution of
the solution turned yellow and the colour deepened on warming. After it had been refluxed for an hour and allowed to stand overnight it deposited a yellow crystalline material which was labelled AMZ-1.

**AMZ-1**

M'\^{+}292, m.p. 175-80°C gave a positive ferric chloride reaction and its nmr spectrum, which unexpectedly did not show any singlet at higher field for the methyl group of the lactone, was similar to that of chalcones. M'\^{+} at m/z 292 also does not favour coupling of the lactone with chromone or formyl chromone and indicates rather the combination of two chromone units (146x2=292). Structure (125) which follows from these observations fits the mass spectrum, in which, apart from M'\^{+}, the only other significant peak is at m/z 171 corresponding to loss of the hydroxybenzoyl group. This compound and its tautomer (125) were first reported by Schönberg\textsuperscript{68} to be the products of base attack on chromone.
Its formation in the present case points to prior decomposition of formylchromone to 2'-hydroxy-2-formylacetophenone (127). Support for this comes from the reaction of 3-formylchromone with o-hydroxyacetophenone which gave the same product over a longer reaction period and in poor yields. Taking these facts into consideration the following mechanism seems probable for the reaction.

\[ \text{(125) } + \text{H}_2\text{SO}_4 \rightarrow \text{(126)} \]
Alternatively the lactone could just be acting as a protic acid, particularly as formylchromone was found to give (127) on refluxing the ethanol/H₂O solution after addition of a drop of acetic acid.
Crucial to the structure elucidation is the position of the doublet at 66.12 with J=1.5 Hz. It is best assigned to an allylic proton under oxygen with long range coupling to an olefinic proton. On this basis and evidence of mass spectral (Fig. 34) fragmentation, which can be analysed as shown (Scheme-12), the most likely structure for AMZ-2 is (128).
(128)

m/z 464 (M$^+$)

-1H$^+$

m/z 463 (19.8)

-145

m/z 319 (60.4)

m/z 463 (19.8)

-\text{CO}

m/z 291 (17)

-\text{CO}

m/z 263 (100)

m/z 120 (80)

m/z 343 (4)

Scheme 12
The only peak in the mass spectrum for which there is no really satisfactory pathway is that at m/z 162 which must belong to modified 4-hydroxycoumarin moiety. However, allylic cleavage to (128) should be facile and the resulting ion can decompose further with hydrogen transfer.

Mechanistically (128) can arise if 4-hydroxycoumarin attacks position 2 of the formylchromone, as do other nucleophiles and possibly the triacetic acid lactone in the reaction discussed earlier, the initial product of this reaction should be (129), which may exist in tautomeric equilibrium with (130) and (131).
Hydrolytic loss of the formyl group can occur at this stage or later on reaction with another molecule of formyl-chromone to give ultimately (132) which then rearranges to (128).

While agreement with spectral data is thus complete mechanistically the situation is not as happy for the dehydration product (132) would have been expected to react chiefly, if not exclusively, with involvement of the 4-hydroxy group to give (133).
Structure (133) is, however, made impossible by the infrared spectrum and formation of (128) therefore requires some mechanistic justification which though available and is shown in (Scheme-13) is not of a compelling nature. Since 2-hydroxy-2-formylacetophenone is a key intermediate in the acetic acid catalysed conversion of 3-formylchromone to the dimer (125) its involvement here is possible because acidity of 4-hydroxycoumarin is of the same order as that of acetic acid so that formylchromone may suffer partial decomposition to (127).
Scheme-13

134

\(- \text{H}_2\text{O} \)

127

(128)
It seemed surprising, however, that 4-hydroxycoumarin itself does not add to the reactive double bond of (134) and this cast doubt on the validity of the above mechanism as well as structure (128) assigned to the compound. To gain further insight into the course of the reaction- and confirm structure (128) formylchromone was treated with 5,7-dimethyl and 6,7-dimethyl-4-hydroxycoumarin. If the underlying assumption of the involvement of two formylchromone and one 4-hydroxycoumarin molecules were correct- the product of the above reaction should have had M+ at m/z 492- but instead it was found to have a mass of 520 amu indicating involvement of only one formylchromone and two 4-hydroxycoumarin units. The nmr spectrum (Fig.35) of the product obtained from 6,7-dimethyl-4-hydroxycoumarin showed a 12 H singlet 62.25 whereas that of the product from 5,7-dimethyl-4-hydroxycoumarin showed 6H singlets at 62.4 and 62.75. The coincidence of methyl singlets indicated that they are in similar chemical environment so that either both aromatic rings are part of chromone or of coumarin moieties of the compound.

The product on this basis could have had structure(135) arising through attack of 4-hydroxycoumarin on the formyl groups of chromone and finally dehydration as shown in(Scheme-14).
Scheme 14

$$R'' = R''' = CH_3$$
$$R' = H$$
The ir spectrum and presence of ferric colour cannot, however, be reconciled with this structure. Moreover the allylic proton of (135) occurs in similar compounds at δ 5.5 and not at δ 6.13. If, however, the intermediate (134) is retained and addition of 4-hydroxycoumarin to it occurs, as one would expect, the product, besides having the wrong mass, carries two different ring systems and the methyl resonances should therefore not coincide. The 4-hydroxycoumarin unit of (136) must therefore have rearranged to chromone as shown in (Scheme-15). This is not
unexpected as formylation can occur through either the hydration of formylchromone to 2'-hydroxy-3-formylchromanone or by intervention of 2'-hydroxy-2-formylacetophenone (127) formed through its decomposition.
Methylation of AMZ-2

The conversion of two 4-hydroxycoumarin molecules to chromone moieties in AMZ-2 while mechanistically feasible is none the less unusual. Further evidence for the assigned structure was, however, forthcoming from the result of methylation which was carried out conveniently with Ag$_2$O/CH$_3$I in chloroform and supplied AMZ-2 Me.

AMZ-2 Me

$M^+$ 510, m.p. >300°C shows in its ir spectrum bands due to hydroxyl and carbonyl groups the latter at a value characteristic of coumarins (Fig.36). Its mass and nmr spectra identify it as a dimethyl ether formation of which is possible only if the pyranochromone ring system of (128) suffers hydrolytic cleavage. The difference in the molecular weight of (137) and AMZ-2 amounts to 46 amu (510-464=46). This works out exactly for addition of water and two methyl groups. The mass spectrum further shows losses of methanol and methyl groups by peaks at m/z 478 and 463.

The nmr spectrum (Fig.37) but for the presence of two methyl singlets is similar to that of AMZ-2. The 1H singlet at 66.2 is approximately at the same position as in AMZ-2 and should, therefore, have also arisen from a proton under oxygen. Combination of these spectral features leads to (137).

The singlet at 68.2, assigned to the C-2 hydrogen of the chromone moiety is not clearly visible in the nmr spectrum
of AMZ-2 probably due to different solvents (DMSO$_{d6}$ for AMZ-2 and TFA for AMZ-2 Me) used for measuring the two spectra. The mass spectrum (Fig. 39) of AMZ-2 Me can be rationalized as shown (scheme-16).

![Scheme-16](image-url)
MASS SPECTRUM: (3)+(4)
SAMPLE: ME-3
NOTE: DR. A. SHOEER, 12/10/88
BASE PEAK: M/E 78.0 INT. 122.0

FIG. 38
The initial point of attack of the base must be the phenolic hydrogen and it is apparent that the resulting anion can exist in tautomeric equilibrium with small amounts of (138) and (139).
In presence of CH$_3$I (138) is captured by methylation and water always present in traces in commercial chloroform adds to the double bond followed by opening of the chromanone ring and methylation.