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The desulphurisation of thiocarbonyl compounds

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THE DESULPHURISATION OF THIOCARBONYL COMPOUNDS

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I hereby declare that the work described in this thesis has not been submitted for a higher degree to any other University or Institution.

R. A. SCHIBECI

SUMMARY

The desulphurisation of thioesters by mercury (II) carboxylate salts was shown to give aliphatic acid anhydrides in high yield. The reaction is rapid at room temperature, giving a mixture of mercuric sulphide, ester and anhydride. The mercuric sulphide is removed by filtration and the ester by distillation. An intramolecular mechanism involving two cyclic transition states was proposed for this desulphurisation reaction, and attempts were made to gather evidence for this mechanism.

The desulphurisation of thioesters by active W-2 Raney nickel was shown to give saturated ethers in good yields. Thiobenzoates gave alcohols, due to hydrogenolysis of the intermediate benzyl ether.

The desulphurisation of thiophenylacetates by deactivated W-2 Raney nickel gave enol ethers in moderate yields. The enol ethers were identified by their mass spectra, and by their methanolysis in the presence of an acid catalyst. Thioesters other than thiophenylacetates gave a mixture of products.

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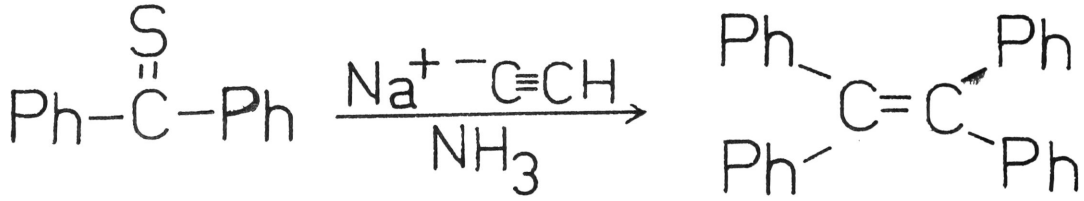
1. INTRODUCTION

1.1 THE THIOCARBONYL GROUP

The chemistry of organic sulphur compounds is similar in many ways to the chemistry of their oxygen analogues. Such differences as do exist may be explained by their respective electronic structures (oxygen, $1s^2\ 2s^2\ 2p^4$ and sulphur, $1s^2\ 2s^2\ 2p^6\ 3s^2\ 3p^4$). Although the distribution of the outer shell s and p electrons is the same, the chemical reactivity of sulphur is modified by the distance of the valence electrons from the nucleus, the screening effect of the second shell electrons, and the possibility of expansion of the outer shell by hybridisation using the normally vacant 3d orbitals. These factors contribute to the lower electronegativity of sulphur compared with oxygen. Also, because the sulphur atom is larger than the oxygen atom, the outer shell is more polarisable: this makes sulphur a stronger nucleophile than oxygen.

In the case of thiocarbonyl compounds, the most important feature is that the larger size of the sulphur atom greatly reduces the stability of the carbon-sulphur π bond compared with the carbon-oxygen π bond. The overlap of a 2p orbital of carbon is greater with a 2p oxygen orbital than with a 3p sulphur orbital. Thus, whereas thiols (R-SH) are chemically similar to alcohols, thioketones ($R_2C{=}S$) and



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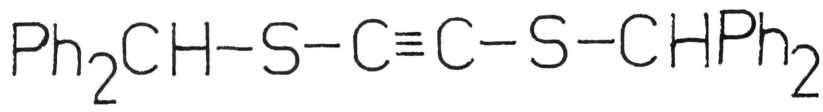


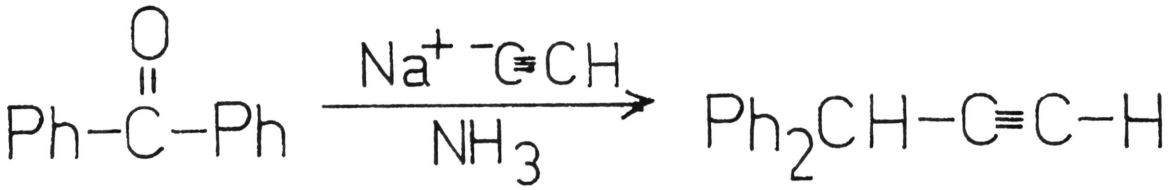


Figure 1

thioaldehydes (R-CS-H) are rare, and far more reactive than the corresponding carbonyl compound. For example, thioacetophenone can be isolated at temperatures in the range -80° to -40° only.[1]

The instability of the thiocarbonyl group compared with the carbonyl group is also illustrated by the fact that typical nucleophilic reagents such as hydroxylamine attack the carbon of a thiocarbonyl group more readily than the carbon of a carbonyl group.[2] In cycloaddition reactions, the thiocarbonyl group has been found more reactive than the carbonyl group.[3] The weakness of the π bond in the thiocarbonyl group of these compounds may often lead to the formation of single C-S bonds by polymerisation.[4,5] The greater reactivity of the thiocarbonyl group compared with the carbonyl group is also shown by the different reaction of sodium acetylide with benzophenone and thiobenzophenone[6] (Figure 1).

Thio derivatives of carboxylic acids (thioesters R-CS-OR' and thioamides, R-CS-NR'_2) are more stable, particularly when the π electrons are delocalised by conjugation with an aromatic ring or other extended π system. Thiobenzoylthioglycollic acid, for example, can be kept indefinitely at room temperature.[7]

The aim of the present work was to exploit the inherent reactivity of the thiocarbonyl group by desulphurising thioesters, and to assess the value of this reaction as a source of intermediates for organic synthesis.

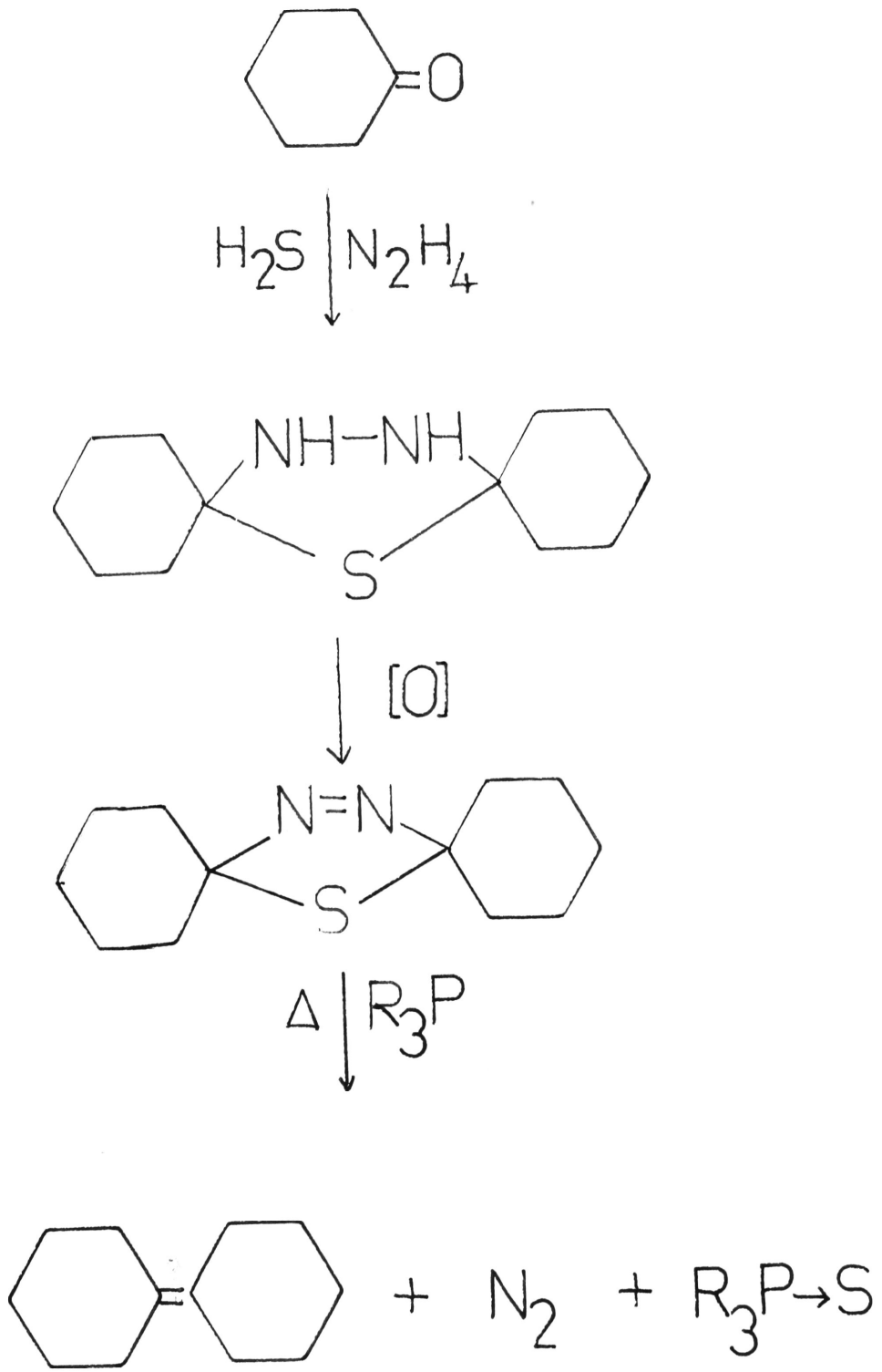


Figure 2

1.2 DESULPHURISATION OF THIOCARBONYL COMPOUNDS

Block,[8] in his review of the use of organosulphur compounds in synthesis, points out that the classical methods of organic synthesis, while satisfactory for simple molecules, are often unsatisfactory for complex systems. The search in modern organic synthesis is for reagents that are selective, stereospecific, efficient and (very often) economical. In his search for such reagents, the modern synthetic organic chemist has turned to a variety of organic compounds, including organosulphur compounds. Organically bound sulphur can be introduced into a molecule, modified easily to a number of valence states, and subsequently removed by a variety of methods.

Desulphurisation reactions have been used for many synthetic purposes, including:

1. Formation of carbon-carbon double bonds, either by clean replacement of a sulphonyl group with a double bond,[9] or by a "two-fold extrusion" process such as that shown in Figure 2;[10]
2. Formation of carbon-carbon single bonds, especially in cyclisation reactions such as the formation of dithiane derivatives by the interaction of carbonyl compounds with 1, 3-propanedithiol,[11] or by the reaction of sulphur ylids;[12]

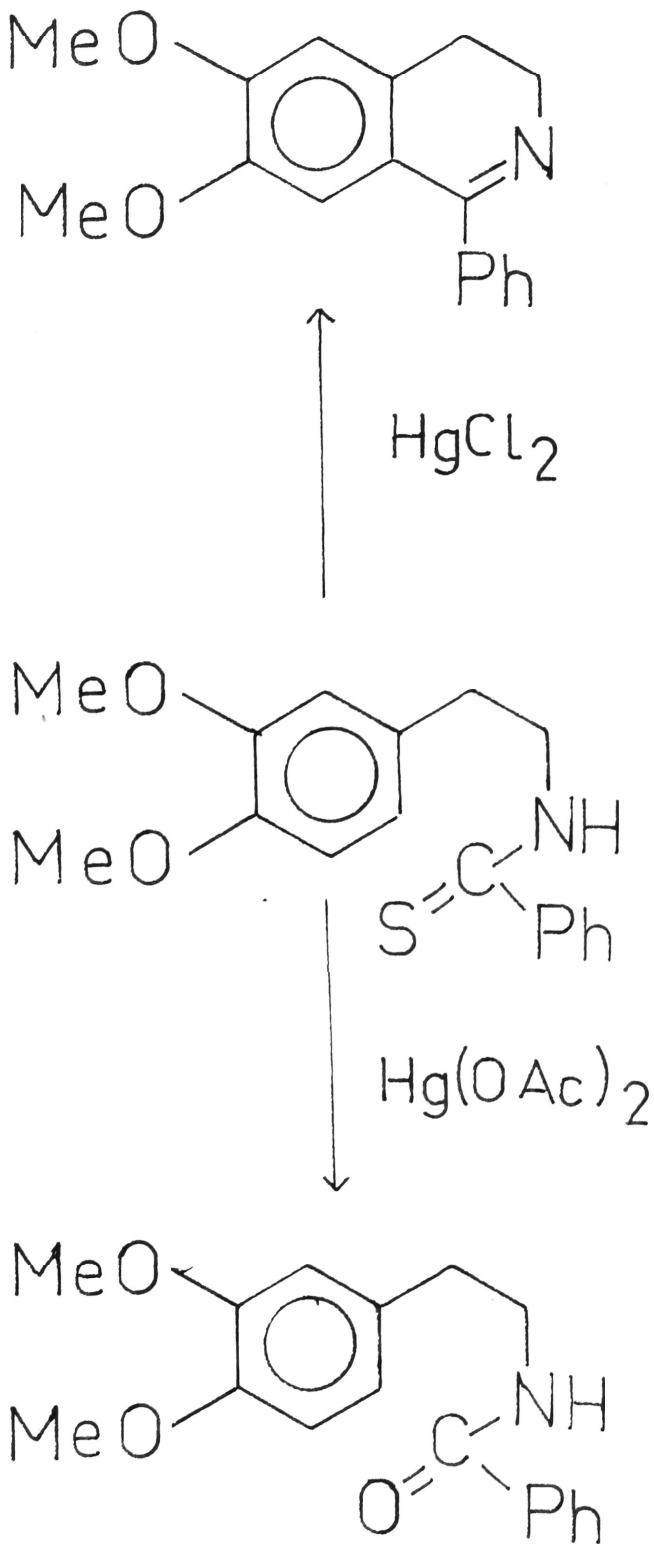
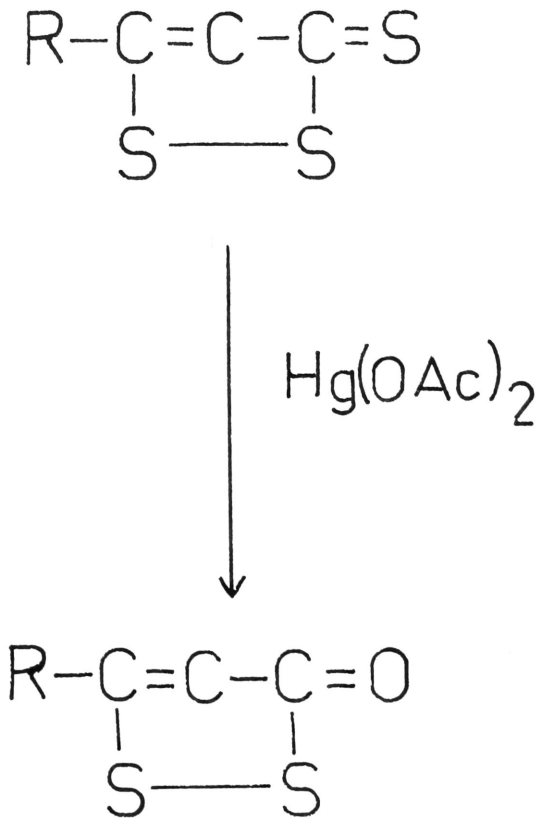


Figure 3

3. Formation of polycyclic hydrocarbons by pyrolysis of sulphones;[13]
4. Mild method for the cleavage of ethers;[14]
5. Cis-trans isomerisation of double bonds;[15]
6. The conversion of ROH to RH in allylic and benzylic alcohols;[16]
7. Cleavage of methyl esters;[17]
8. Dehydration of alcohols.[18]

Among the organosulphur compounds, thiocarbonyl compounds have been increasingly used in organic synthesis. The thiocarbonyl group can be introduced through enamines,[19] through the amino group,[20] through ketone semicarbazones,[21] and by use of thiophosgene.[22] More recently, Imaeda and coworkers[23] found bis(diethylaluminium) sulphide useful in converting the carbonyl group of ketones, amides, lactams and isocyanates to the thiocarbonyl group; esters formed 1:1 adducts.

The desulphurisation of thiocarbonyl compounds by mercuric salts has been used in cyclisation reactions, such as the preparation of tetrachlorothiirane by the desulphurisation of thiophosgene with phenyl (bromodichloromethyl) mercury.[24] The desulphurisation of N-homoveratryl-aldehyde (Figure 3) by mercuric chloride (but not by mercuric acetate) also results in ring closure.[25]



(R= Ph–, p-methoxyPh–)

Figure 4

Many metal salts desulphurise thiocarbonyl compounds to the corresponding carbonyl compound. This conversion has been observed in the reaction of: trithiones with mercuric acetate (Figure 4);[26] xanthate esters by heavy metal salts;[27] thiocarbonyl sugar derivatives with silver nitrate;[28] thioureas with mercuric oxide.[29]

It can be seen that mercuric salts (especially mercuric carboxylates) have played a prominent part in the desulphurisation of thiocarbonyl compounds. Other metal salts have played a less significant role. The metal is the sulphur acceptor and in many instances the metal sulphide is precipitated, while the organic products remain in solution. Thus, lead acetate desulphurises o-chlorophenylthiourea to o-chlorophenylcyanamide, with lead sulphide precipitating out of solution.[30]

Raney nickel has also been used widely as the sulphur acceptor in desulphurisation reactions. Its use has been reviewed by Pettit and Van Tamelen,[31] Hauptmann and Walter,[32] Brouty and Pallaud,[33] Challenger[34] and Fieser and Fieser.[35] Seven types of Raney nickel (designated W-1 to W-7) are listed by Fieser and Fieser.[35] Many authors do not specify the type of Raney nickel used, so it is often difficult to

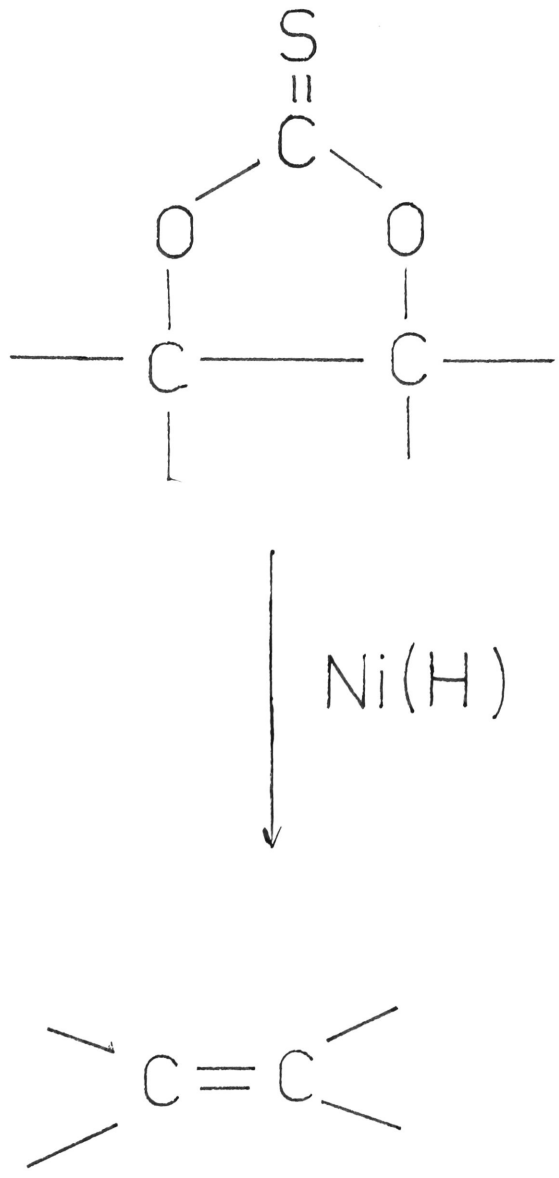


Figure 5

generalise about reactions. Usually, however, the activated catalyst results in hydrogenation, whereas the deactivated catalyst allows side reactions to occur: substitution of sulphur by oxygen, dimerisation and the formation of double bonds.

The desulphurisation of thiocarbonyl compounds by Raney nickel has been used in organic synthesis. The Raney nickel desulphurisation of cyclic thiocarbonates has led to a new, stereospecific olefin synthesis (Figure 5) by loss of carbon dioxide *via* a concerted rearrangement of a carbene.[36] *Trans*-α,β-dimethylstilbene has been prepared by the desulphurisation of thioacetophenone with W-2 Raney nickel;[37] the presence of the double bond indicates the partial deactivation of the catalyst. Di-(4-methoxyphenyl)-acetylene has been prepared by the desulphurisation of lead p-methoxydithiobenzoate with a modified W-2 catalyst.[38]

Photodesulphurisation of thiocarbonyl compounds also offers many synthetic possibilities. The photochemistry of thiocarbonyl compounds has not been investigated as thoroughly as that of carbonyl compounds, despite the fact that many thiocarbonyl compounds have more widely separated absorption bands than their oxygen analogues. Thiobenzophenone, for example, has three well-separated absorption

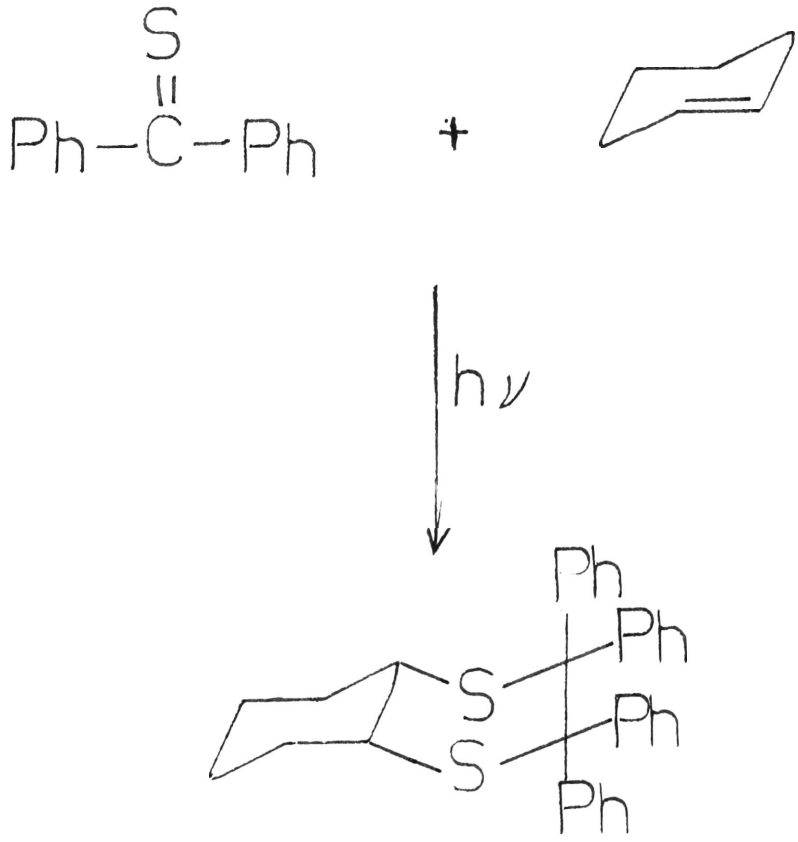


Figure 6

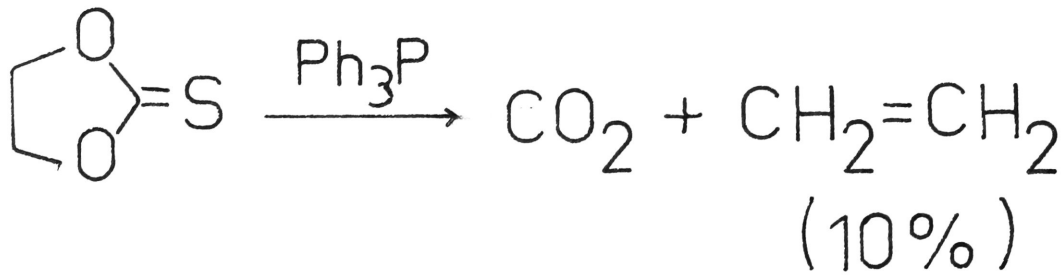
bands (π-π^*, 235 nm; π-π^*, 316.5 nm; n-π^*, 599 nm), so that it can be raised to one of these excited states without interference from others.[39]

The photocycloaddition of olefins to thiobenzophenone (reviewed by Ohno[39] and Tsuchihashi[40]) has been used to prepare a wide variety of thietanes; an example is given in Figure 6. The corresponding photocycloaddition of carbonyl compounds to olefins yields only oxetanes.[39]

Another synthetic method resulting from a photodesulpurisation reaction is the preparation of α-diketones from S-acyl xanthates. Thus, O, O-diethyl-S, S-glutaryldixanthate yields 1, 2-cyclopentanedione.[41]

The instability of the thiocarbonyl group is illustrated by the fact that many thiocarbonyl compounds are unstable to oxygen in the presence of light: xanthene-9-thione and 4, 4-dimethoxythiobenzophenone, for example.[42] Other thiocarbonyl compounds which are easily photodesulphurised are adamantanethione,[43] thiourea[44] and thiophosgene.[45]

Trivalent phosphorus has also been used as a sulphur acceptor, because of the ability of phosphorus to expand its outermost shell by using its unoccupied 3d orbitals. A variety of phosphorus (III) compounds has thus been used in desulphurisation reactions, including: tri-n-butylphosphine,[46] triethylphosphite,[47] trimethylphosphite,[36]



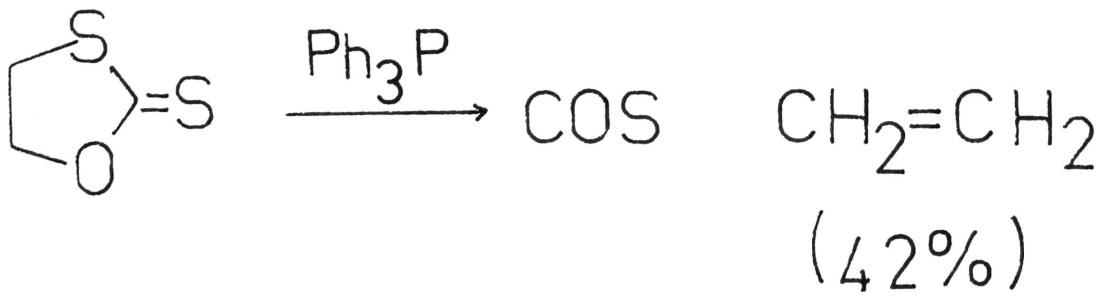


Figure 7

tris(diethylamino) phosphine,[48] triphenylphosphine.[49] For example, triphenylphosphine desulphurises ethylene thiocarbonate and 1, 3-oxathiolane-2-thione (Figure 7).[49]

A number of miscellaneous reagents have been used to desulphurise thiocarbonyl compounds to the oxygen analogue, including the desulphurisation of thioureas by hydrogen peroxide,[29] and the desulphurisation of thioamides by dimethylsulphoxide.[50]

Field[51] has reviewed recent developments in synthetic organic sulphur chemistry, including the use of sulphur chemistry to synthesise final products containing no sulphur.

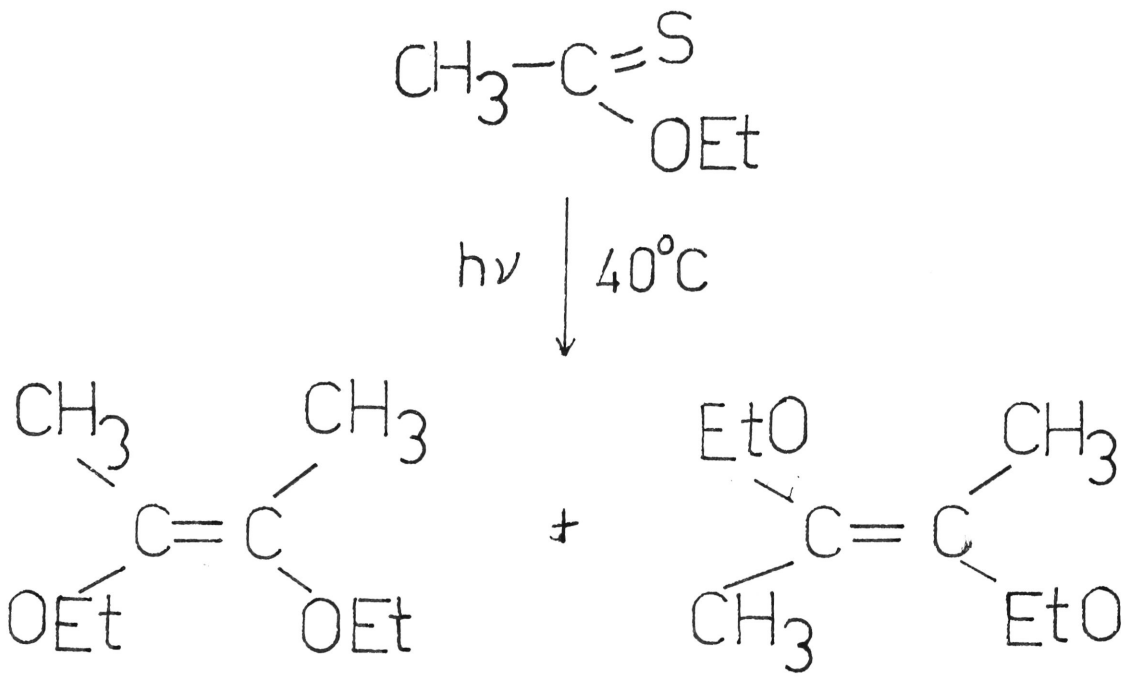


Figure 8

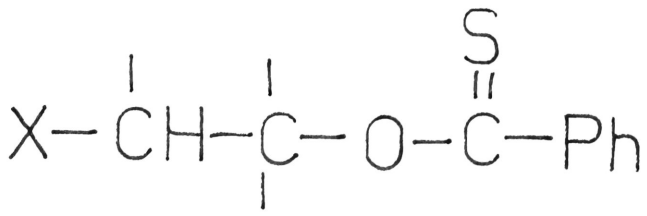


Figure 9

1.3 REPORTED DESULPHURISATIONS OF THIOESTERS

While the desulphurisation of thiocarbonyl compounds has, in general, been extensively studied, the desulphurisation of thioesters is virtually an unexplored field. In fact, very few reactions of thioesters have been studied. One exception is the thermal rearrangement of the -CS-O- group to the -CO-S-group in thiobenzoates. This rearrangement which has been extensively studied in a variety of thiocarbonyl compounds, has been reviewed by Oishi.[52]

A few thioesters have been photodesulphurised. Ethyl thioacetate was irradiated with u.v. light (λ = 254 nm) to give 2, 3-diethoxy-2-butene in 63% yield (Figure 8). The ratio of cis:trans isomers was 2:3. A small amount of 2, 3-diethoxy-2, 3-dimethylthiirane was also found. Under similar conditions, ethyl thiopropionate gave 3, 4-diethoxy-3-hexene in 60% yield.[53] In each case, photoepimerisation at the thiocarbonyl group is the primary reaction, followed by breakdown of the dithietanes.[54]

Barton and coworkers[55,56] have recently reported the photodesulphurisation of some thiobenzoates (Figure 9) to the corresponding olefin and thiobenzoic acid. Cholesteryl thiobenzoate, for example, yielded cholesta-3, 5-diene in very high yield; nopol thiobenzoate gave nopodiene in 80%

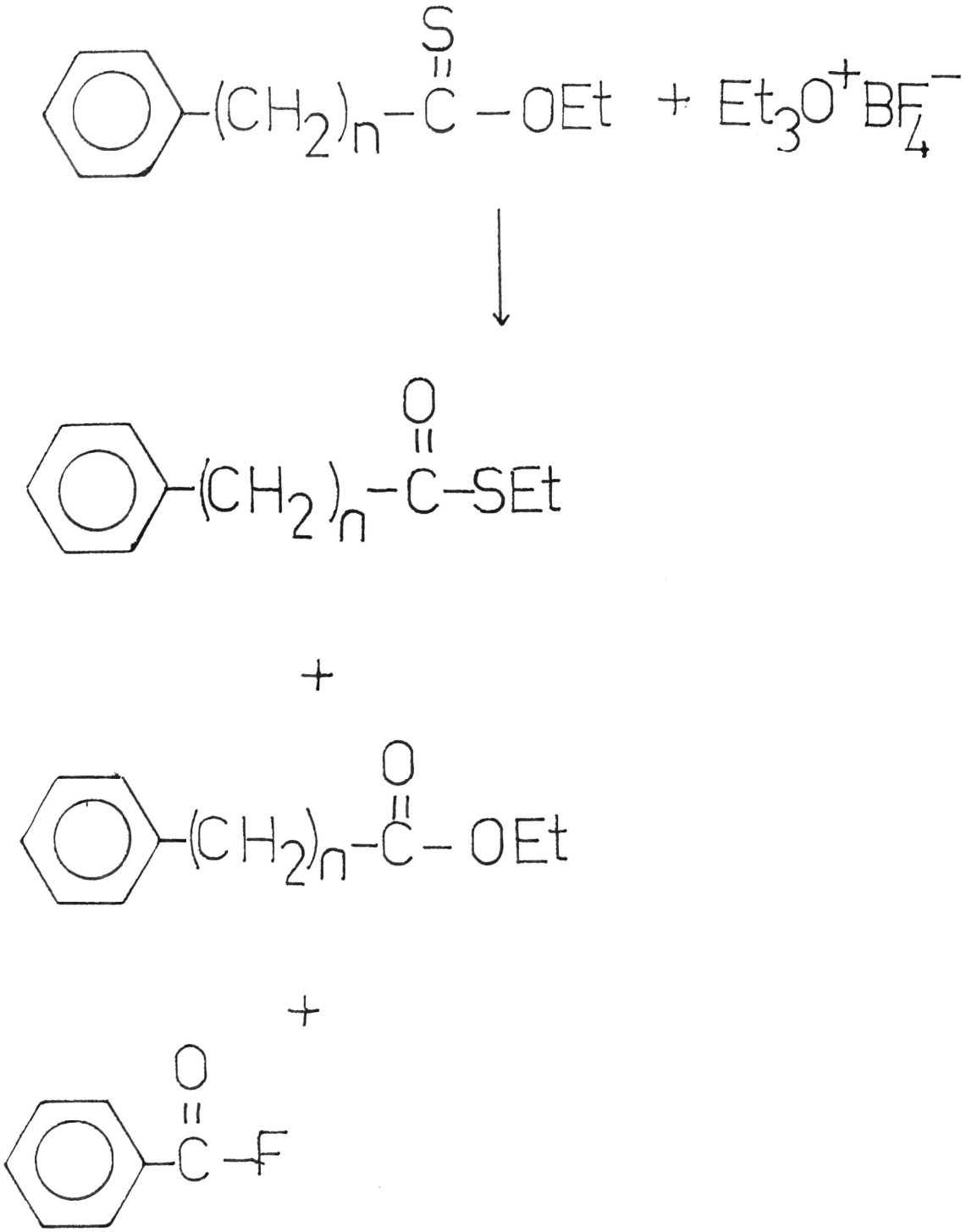


Figure 10

yield; o-phenylethyl thiobenzoate gave styrene in 90% yield. If the X function was not in potential conjugation, photolysis was slow, giving a mixture of products. Thus 4, 4-dimethylcholesteryl thiobenzoate photolysed slowly giving no characteristic elimination products; cholestanyl thiobenzoate gave the 3α-thiolbenzoate (21% yield) and the 3β-thiolbenzoate (17% yield). This photoelimination of thiobenzoates affords a neutral, mild method for dehydrating homoallylic alcohols.

Ohno and coworkers[57] have explored the synthetic applications of the photocycloaddition reactions of thiobenzoates to olefins. Phenethyl phenyl ketone, for example, was prepared by the reaction of methyl thiobenzoate with allylbenzene. These photocycloadditions, which proceed <u>via</u> thietane derivatives, occur only if an allylic methylene group is present in the olefin.

Two other investigations on thioesters have been reported. Oishi has reported studies of the alkylation of thioesters to thiolesters by Et_3O^+-BF_4^- catalysis[58] (Figure 10) and by diethoxycarbonium hexantimonate[59] catalysis. Smith[60,61] has reported kinetic studies on the acidic and alkaline hydrolysis of ethyl thiobenzoate to ethyl thiolbenzoate and ethyl benzoate.

Apart from the studies described in this section,

the desulphurisation of thioesters is an unexplored field, with rich possibilities for organic synthesis.

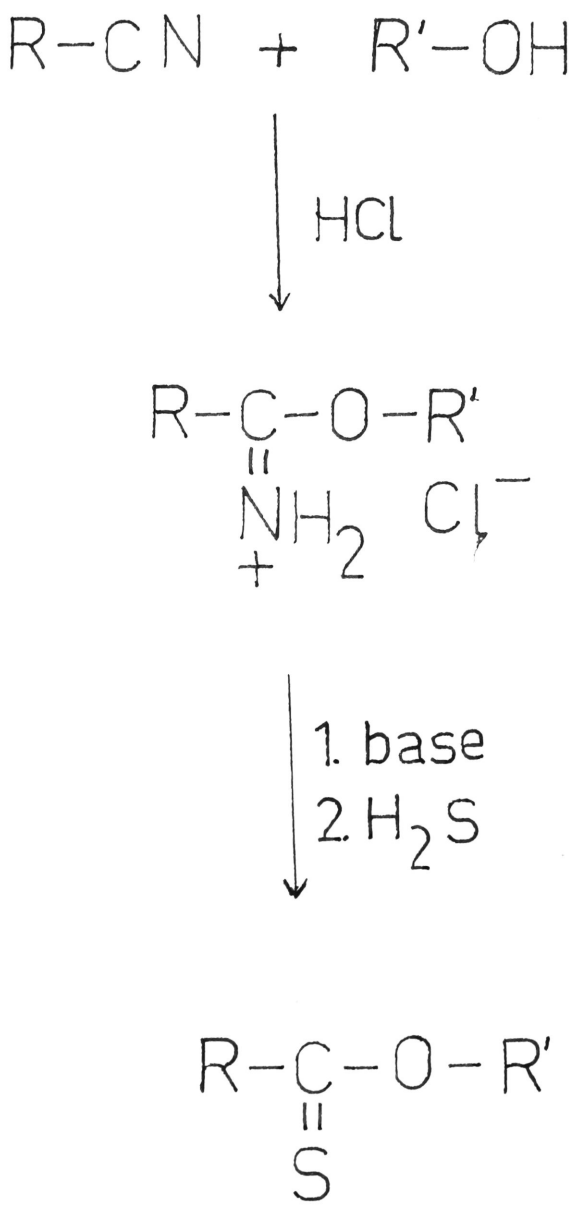


Figure 11

1.4 SYNTHESIS OF THIOESTERS

As a result of the investigations described in the previous section and also for the purpose of making spectral investigations (including i.r., n.m.r., m.s. and u.v. studies), a number of thioester syntheses have been reported in the literature.

(a) The Pinner synthesis

One of the earliest methods reported for the synthesis of thioesters is the reaction of iminoesters with hydrogen sulphide (the Pinner synthesis).[62] An alcohol is condensed with a nitrile in the presence of dry hydrogen chloride to form an iminoester hydrochloride. The free iminoester may be freed by shaking the hydrochloride with a basic aqueous solution,[63] or by treatment with dry ammonia;[64] the thioester is formed by saturating the iminoester with hydrogen sulphide (Figure 11).

Thioamides often form in this synthesis.[65] To avoid this, Schmidt[66] passed hydrogen sulphide into a solution of the iminoester hydrochloride in pyridine. This modification of the Pinner synthesis was used to prepare most of the thioesters used in this project.

Iminoester hydrochlorides are extremely hygroscopic substances. Reaction of the iminoester hydrochloride with water yields the normal oxygen ester. Any ester formed in

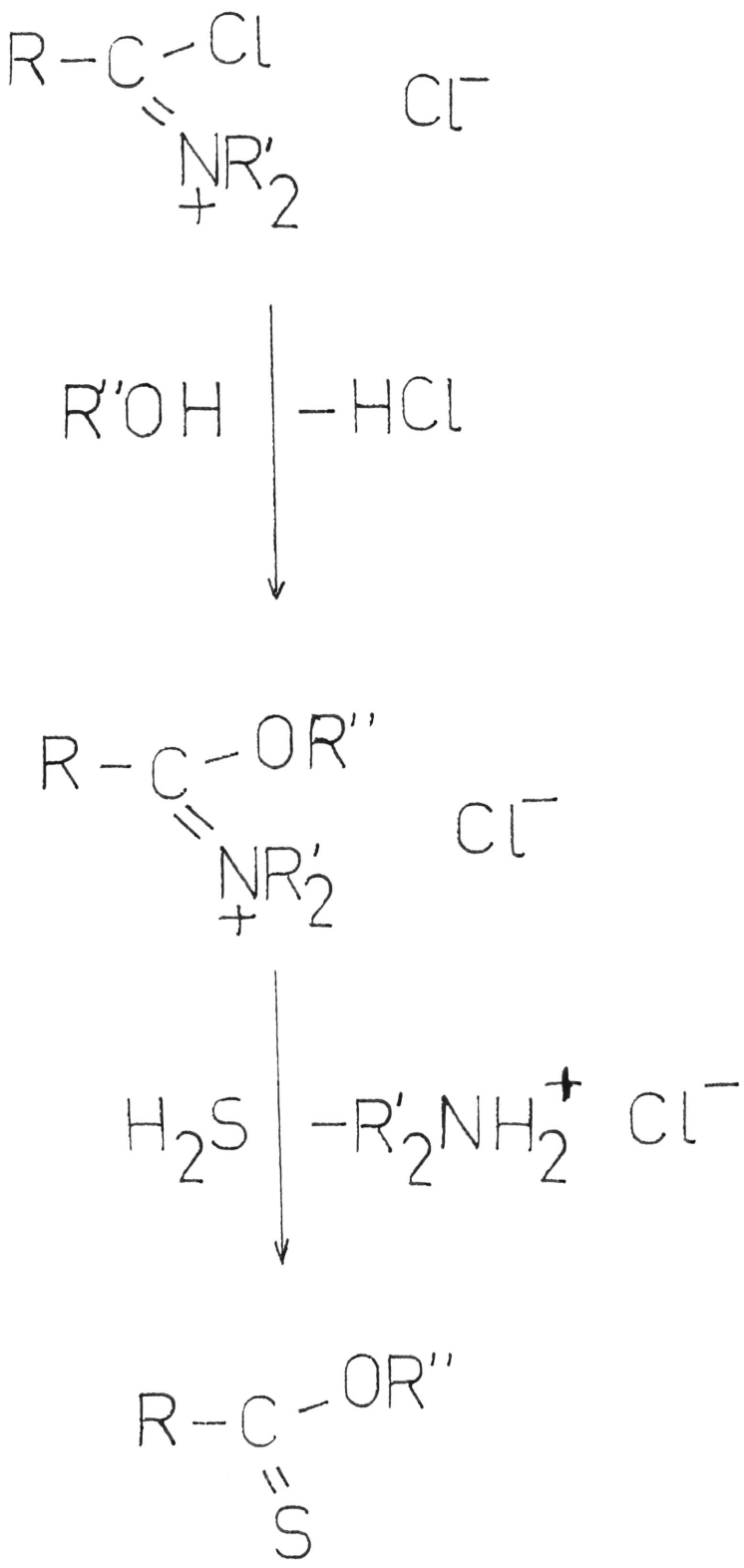


Figure 12

this synthesis can be separated on a column of silica gel (not alumina, since thioesters are oxidised to esters on an alumina column), with petroleoum spirit as the eluting solvent.

A related synthesis is the reaction of immonium-type salts (Figure 12) with hydrogen sulphide.[67] This reaction of N, N-disubstituted carboxamide chlorides has been used to prepare a variety of compounds, including thioesters, dithioesters, thioamides, orthoesters and many others.

(b) Thioacylation of an alcohol

The thioacylation of an alcohol leads to thioesters.[68] Phenyl thiobenzoate,[69] other aryl thiobenzoates,[70] allylic thiobenzoates,[71] and some steroidal thiobenzoates[55] have been prepared by this method.

Thioacyl chlorides are prepared from dithioacids.[72] Aryl dithioacids can be prepared by the action of carbon disulphide on phenylmagnesium halides.[73] Aliphatic dithioacids are not accessible by this method;[72] this is another example of the instability of the thiocarbonyl group when not stabilised by an aromatic system. Dithiobenzoic acid has been prepared from methyl dithiobenzoate, which is available from thiobenzomorpholide methiodide.[74]

(c) Reaction with phosphorus pentasulphide

Trebaul and Teste[75] have successfully converted heterocyclic esters to the corresponding thioesters by refluxing in xylene with phosphorus pentasulphide. Yields ranged from 35% to 55%. This conversion had previously been attempted unsuccessfully by Renson and Bidaine.[76]

Varying success has been reported in the conversion of a carbonyl to a thiocarbonyl group with this reagent: amides have been converted to thioamides;[77] aliphatic enamino ketones have been converted to the corresponding thioketones in 10-18% yields;[78] ethyl thiobenzoate has been prepared in 50% yield from ethyl benzoate;[79] the muscle relaxant 1-methyl-6-(trifluoromethyl) thiocarbostyril has been converted to thiofenchone.[81] Attempts to convert benzoyl chloride, phenyl benzoate and cholestanyl benzoate to the corresponding thiocarbonyl compounds with phosphorus pentasulphide in this project were unsuccessful.

The varying success reported with phosphorus pentasulphide has been partially explained by a study of the conversion of adamantone to adamantanethione. In this study, Greidanus[82] found that adamantanethione could be prepared in 90% yield if the right conditions are found. In particular, a large excess of phosphorus pentasulphide must be avoided.

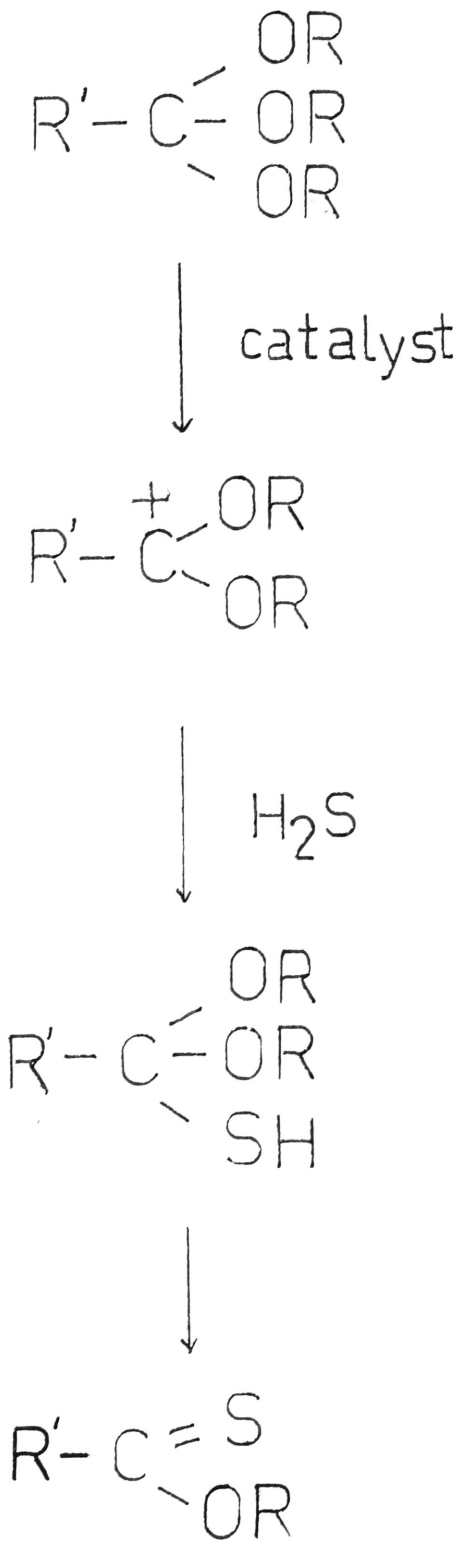


Figure 13

This is especially true at high temperatures, as secondary reactions can occur.

Phosphorus pentasulphide may thus be a useful reagent in converting carbonyl groups to thiocarbonyl groups if the proper conditions can be found.

(d) Use of thiobenzoylthioglycollic acid

Thiobenzoylthioglycollic acid is a useful thiobenzoylating agent. Kurzer[7] has reviewed its use. This reagent is available through a number of routes:

1. potassium dithiobenzoate and alkali chloroacetate;[83]
2. benzaldehyde and hydrogen polysulphides;[84]
3. benzotrichloride and potassium hydrogen sulphide;[85]
4. reaction between benzaldehyde, sulphur and piperidine (the Willerodt-Kindler reaction), followed by chloroacetic acid and hydrogen sulphide.[74,86]

To prepare the thioester, the alcohol is first converted to the sodium alkoxide by treatment with sodium hydride in glyme. This is followed by treatment with thiobenzoyl-thioglycollic acid. A number of steroidal thiobenzoates,[55,56] have been prepared by this method.

(e) Other syntheses

Thioesters have been prepared by the action of hydrogen sulphide on orthoesters in the presence of a catalyst (Figure 13).[87] A similar, recently-reported synthesis is

the action of boron sulphide on orthoesters, but no yields for the reaction were given.[88]

Finally, thioesters have been prepared by the action of Grignard reagents on chlorothiocarbonic esters (R-O-CS-Cl); these esters have been prepared by the reaction between thiophosgene on an alcohol or phenol.[89] Because these esters are particularly unstable, this method frequently gives poor yields.[90]

2. DISCUSSION

2.1 DESULPHURISATION OF THIOESTERS BY MERCURY (II) CARBOXYLATE SALTS

(a) Previous observations with cholestanyl thioacetate

Previous work carried out in this laboratory[91] showed that the course of desulphurisation of the thioester, cholestanyl thioacetate, is dependent on the anion of the mercury salt used as the sulphur acceptor. Mercuric chloride desulphurised cholestanyl thioacetate very slowly, giving a mixture of cholestane, cholestanyl acetate, cholestanone and cholestanol. The relative proportions of the products varied with the solvent used (acetic acid, propionic acid, ethanol, ether or pyridine). When cholestanyl thioacetate was treated with mercuric benzamide in pyridine, it did not react. Mercuric benzamide in acetic acid, however, reacted rapidly to give cholestanyl acetate. This fast reaction in acetic acid may be attributed to partial or complete formation of mercuric acetate by attack of the stronger acid, acetic acid on the mercuric salt of the weaker acid, benzamide. Mercuric acetate in acetic or propionic acid reacted rapidly to give cholestanyl acetate and a black precipitate of mercuric sulphide.

These experiments suggested that the carboxylate group is the source of oxygen in the conversion of the thiocarbonyl

group of the ester. This suggestion was confirmed by the fact that mercuric acetate reacted rapidly with cholestanyl thioacetate in pyridine under a nitrogen atmosphere.

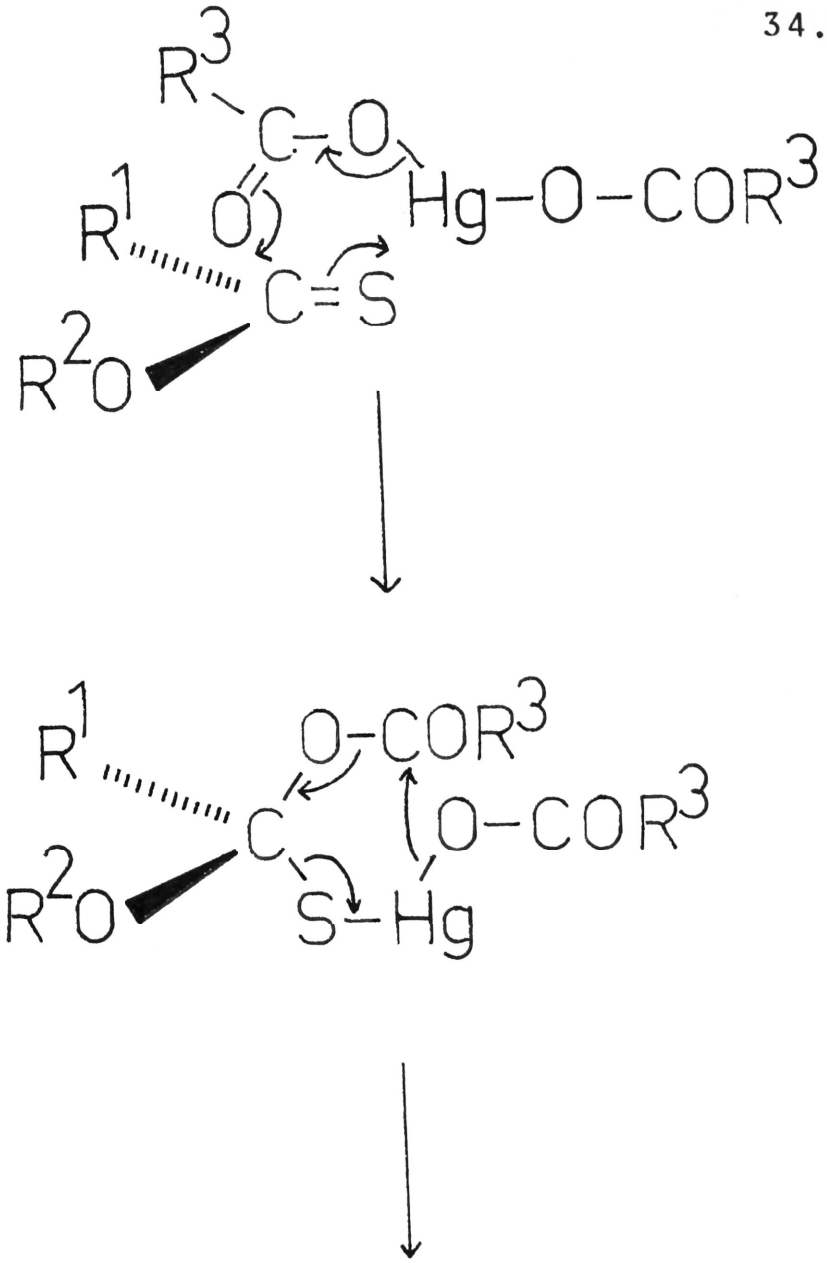
Two mechanisms for the replacement of sulphur by oxygen were possible:

(1) There could be direct attack on the thiocarbonyl group: the sulphur atom only is removed, followed by replacement with oxygen. By this mechanism, cholestanyl thioacetate would give cholestanyl acetate when desulphurised, regardless of solvent.

(2) There could be O-alkyl or O-thioacyl cleavage, followed by condensation of the steroidal fragment with an acetoxy group from acetic acid solvent or mercuric acetate. By this mechanism, cholestanyl propionate would be the major product if propionic acid were used as the solvent.

Desulphurisation of cholestanyl thioacetate in propionic acid as solvent was shown by n.m.r. to give cholestanyl acetate (singlet at δ 2.0 due to $C\underline{H}_3$-CO-O-), not cholestanyl propionate (which would give a quartet at δ 2.3 due to CH_3-$C\underline{H}_2$-CO-O-). The reaction clearly involved direct attack on the thiocarbonyl group with replacement of sulphur by oxygen.

In earlier studies by other workers on the desulphurisation of thioacetamide, it was found that mercuric chloride



$$(R^3CO)_2O + HgS + R^1-CO-OR^2$$

Figure 14

reacts with thioacetamide to produce stable complexes, which slowly hydrolyse to mercuric sulphide.[92] On the other hand, Taylor and Smith[93] found thioacetamide reacts rapidly with mercuric acetate at room temperature. The results of this experiment indicate that the rate of precipitation of mercuric sulphide is not controlled by hydrolysis, but by direct reaction. This kinetic study showed that the reaction is first order in mercury (II), and is independent of ionic strength, which is consistent with the thioacetamide reacting as an uncharged species.

(b) A novel anhydride synthesis

The experiments described above led us to propose a mechanism for the desulphurisation of thioesters by mercury (II) carboxylate salts (Figure 14).[94] This mechanism suggests the initial formation of a 1:1 complex of thioester and mercuric salt, which then rearranges *via* a cyclic transition state to give an ester and anhydride as the principal organic products.

The generality of the reaction was established by desulphurising cyclohexyl thioacetate and ethyl thiobenzoate with a variety of mercury (II) carboxylate salts in chloroform, dichloromethane or pyridine as solvent. In all cases, a fast reaction was observed, with rapid precipitation of mercuric sulphide. The precipitate was

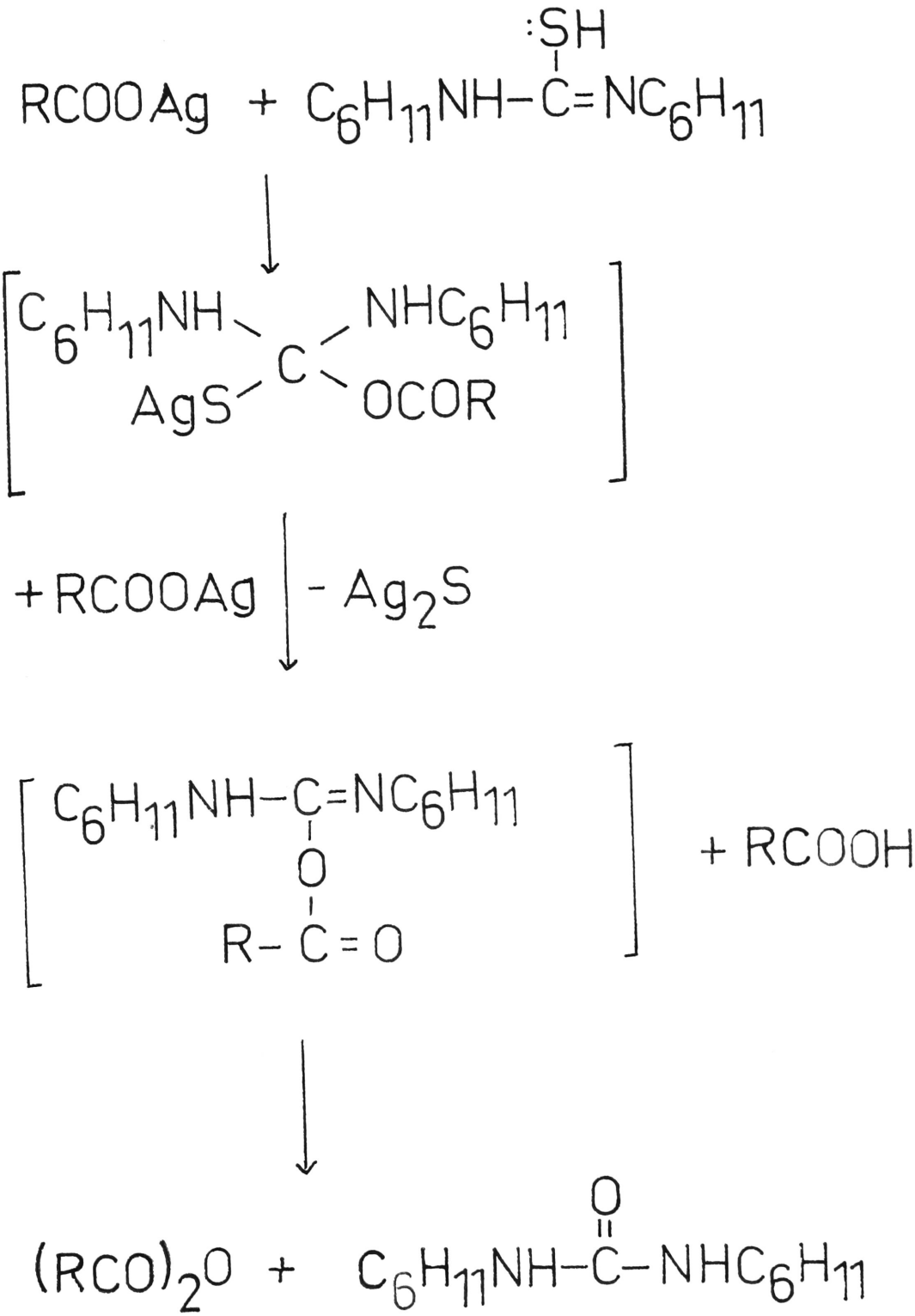

RCOOAg + C6H11NH–C(:SH)=NC6H11
C6H11NH
NHC6H11
AgS
C
OCOR
+RCOOAg
- Ag2S
C6H11NH–C=NC6H11
O
R–C=O
+ RCOOH
(RCO)2O + C6H11NH–C(=O)–NHC6H11

Figure 15

filtered off and the organic products examined by g.l.c.. The results of these desulphurisation experiments are shown in Table 1.

The rapid precipitation of mercuric sulphide shows that the mercury salt is the source of oxygen as well as the sulphur acceptor. The results obtained in Table 1 indicate that the reaction is a general one, obeying the stoichiometry:

$$R^1\text{-CS-}OR^2 + (R^3COO)_2Hg \rightarrow R^3CO\text{-}O\text{-}COR^3 + R^1\text{-CO-}O\text{-}R^2 + HgS$$

This equation requires a one-to-one ratio of ester to anhydride. Loss of anhydride by hydrolysis results in a slight deviation from this expected one-to-one ratio.

The desulphurisation of thioesters by mercury (II) carboxylate salts bears a superficial resemblance to the recently reported synthesis of anhydrides by the desulphurisation of N, N-dicyclohexylthiourea by silver carboxylates (Figure 15).[95] It can be seen that this mechanism is different from ours, and the reaction time for preparation of propionic anhydride (15 hours at room temperature) is far longer than in our reaction (5 minutes at room temperature).

The desulphurisation of thioesters by mercury (II) carboxylate salts affords a new synthesis of aliphatic acid anhydrides and has certain advantages when compared with other anhydride syntheses. The methods presently available

THIOESTER	MERCURIC SALT	SOLVENT	YIELDS (%) Anhydride	Ester	MOLAR RATIO Anhydride:Ester
cylclohexyl thioacetate	acetate	γ-picoline	75	82	1:1.1
	butyrate	chloroform	84	95	1:1.1
	valerate	dichloromethane	89	100	1:1.1
	pivalate	chloroform	87	100	1:1.2
	laurate	pyridine	96	95	1:1.0
ethyl thiobenzoate	propionate	dichloromethane	86	98	1:1.1
	valerate	dichloromethane	84	100	1:1.2
	laurate	pyridine	82	89	1:1.1

DESULPHURISATION OF THIOESTERS BY MERCURY (II) CARBOXYLATE SALTS

Table 1

for the synthesis of anhydrides include:

1. Reaction of an acyl halide with a sodium salt of a carboxylic acid.[96] The preparation of both the sodium carboxylate and acyl halide is time-consuming.

   $RCOCl + RCOONa \rightarrow (RCO)_2O + NaCl$

2. Reaction of a carboxylic acid with ketene.[96] The preparation of ketene by pyrolysis of acetone at 700° requires specialised equipment.

   $RCOOH + CH_2=C=O \rightarrow (RCO)_2O + CH_3COOH$

3. Reaction of an acyl halide with a carboxylic acid in the presence of pyridine.[96] The preparation of the acyl halide is time-consuming.

   $RCOCl + C_5H_5N + RCOOH \rightarrow (RCO)_2O + C_5H_5N.HCl$

4. Reaction of diphenylmercury, carboxylic acid and tri-n-butylphosphine:[97]

   $Ph_2Hg + (n\text{-}C_4H_9)_3P + 2RCOOH \rightarrow$

   $Hg + (RCO)_2O + 2C_6H_6 + (n\text{-}C_4H_6)_3P=O$

   This preparation initially involves the formation of phenylmercuric carboxylates by the reaction between diphenylmercury and acid.[98] This anhydride synthesis requires refluxing for 2-4 hours, and gives yields of 74-80%.

5. Reaction of mercurous and mercuric carboxylates on triethylphosphite on tertiary phosphines:[99]

$$(R'COO)_2Hg + R_3P \rightarrow Hg + (RCO)_2O + R_3P{=}O$$

(R = EtO-, n-C_4H_9-, or C_6H_5-)

This synthesis requires heating for 1 hour at 69° or 100°, and gives yields of 51-82%.

6. Reaction of thallium (I) carboxylates with a stoichiometric amount of acyl or aroyl halide:[100]

$$RCOCl + R'COOTl \rightarrow (RCO)_2O + TlCl$$

Symmetrical anhydrides can also be prepared by the action of the thallium (I) carboxylates and thionyl chloride:

$$2RCOOTl + SOCl_2 \rightarrow (RCO)_2O + SO_2$$

The desulphurisation of thioesters by mercuric carboxylates is a new, useful synthesis of aliphatic acid anhydrides. The mercury salts are prepared in a few minutes by warming the carboxylic acid with mercuric oxide; unreacted acid may be recovered. The preferred thioester is methyl thioacetate, since the methyl acetate produced is very voltatile (b.p. 56°).

The reaction between the thioester is unusually rapid for an organic reaction at room temperature. The anhydride is obtained in near-quantitative yield. The mercuric

sulphide is removed by filtration, and the solvent and ester by distillation.

It has been shown in this work that this synthesis is a general one and readily forms the anhydrides of such sterically hindered acids as pivalic acid. There appears to be very little steric hindrance to attaining the two cyclic transition states of the proposed mechanism. It was hoped to extend the usefulness of this reaction by using a readily available thiocarbonyl compound which would give a gaseous desulphurisation product. Carbon disulphide, thiophosgene and carbonyl sulphide were tried, but all three proved unreactive.

This new synthesis of symmetrical anhydrides is comparable in efficiency with the thallium salt method of Taylor and MacKillop.[100] Unlike the latter, however, it cannot be used for the preparation of mixed anhydrides.

2.2 MECHANISM OF THE DESULPHURISATION OF THIOESTERS BY MERCURY (II) CARBOXYLATES

The proposed mechanism for the oxidation of thioesters by mercury (II) carboxylates involves the formation of a 1:1 complex, followed by intramolecular rearrangement *via* a cyclic transition state. While this mechanism is consistent with kinetic studies for the related reaction between mercuric acetate and thioacetamide[93] described in the previous section, it was desirable to gather more evidence supporting the proposed mechanism.

The mechanism, being an intramolecular rearrangement, requires that the reaction of a thioester with a total of one molar equivalent of two different mercuric carboxylates should yield two symmetrical anhydrides only, and no mixed anhydrides. If an intermolecular mechanism operated, a mixture of all three anhydrides would be formed. The absence of any mixed anhydride in the products from such an experiment would constitute strong support for the proposed desulphurisation mechanism.

The success of such a "crossed products" experiment depends on two factors:

1. the mixed anhydride, if it forms, must be reasonably stable;

2. there must be an adequate analytical method for detecting the mixed anhydride.

The literature on mixed anhydrides was examined in detail in the context of these two criteria.

(a) Preparation and detection of mixed anhydrides

A number of methods for the preparation of mixed anhydrides have been reported:

1. The reaction between ketene and an aliphatic or aromatic acid gives mixed acetic anhydrides:[101]

   $RCOOH + CH_2=C=O \rightarrow RCO\text{-}O\text{-}COCH_3$

2. The reaction between an acid halide and a sodium salt gives mixed anhydrides:[102]

   $RCOONa + R'COCl \rightarrow RCO\text{-}O\text{-}COR' + NaCl$

3. The reaction of thallium (I) carboxylates with an acyl or aroyl halide has recently been used to prepare a mixed anhydrides in high yields:[100]

   $RCOCl + R'COOTl \rightarrow RCO\text{-}O\text{-}COR' + TlCl$

4. The reaction of an acid halide and an acid in the presence of a base:[103]

   $RCOOH + R'COCl + C_6H_5N \rightarrow RCO\text{-}O\text{-}COR' + C_6H_5N.HCl$

The very existence of mixed anhydrides was for a long time doubted because of their tendency to disproportionate to the two symmetrical anhydrides when distilled at

atmospheric pressure. Close examination of the literature on mixed anhydrides reveals many inconsistencies. The most extensive series of mixed anhydrides in the literature is the series of acetic anhydrides prepared by Dunbar and Garven,[104] by the action of ketene on carboxylic acids. The criteria used by them for the purity of these mixed anhydrides were: a "specific" test described by Whitford;[105] the absence of effervescence with cold sodium carbonate solution;[106] elemental analysis, refractive index and density.

The procedure devised by Whitford[105] relates to the dehydration of oxalic acid by acetic anhydride in pyridine solution, the volume of liberated carbon monoxide and carbon dioxide being used for the estimation of the anhydride. The only mixed anhydride referred to in this paper is a postulated 1:1 complex between acetic anhydride and oxalic acid, which is not a mixed anhydride in the sense meant by Dunbar and Garven. Any anhydride, mixed or symmetrical, would be expected to dehydrate oxalic acid in this way.

The cold aqueous sodium carbonate test was first used by Behal[106] and subsequently by other workers.[104,107,108]

The symmetrical anhydride allegedly reacted vigorously with this reagent and the mixed anhydride reacted slowly only. It is difficult to see why a mixed anhydride should

be unreactive and the corresponding symmetrical anhydrides reactive to this reagent, as reported. The lack of effervescence of the mixed anhydride with sodium carbonate may possible reflect the low concentration of free carboxylic acid present in freshly distilled material, rather than the symmetry of the anhydride. This test was rejected as being unsuitable for the present purpose, since effervescence would be expected whether the reaction proceeded intramolecularly (giving symmetrical anhydrides only) or intermolecularly (giving both the symmetrical and mixed anhydrides).

The other characterisation techniques such as elemental analysis and neutralisation equivalent are inherently incapable of distinguishing between a mixed anhydride and an equimolar mixture of two symmetrical anhydrides.

The purity of many mixed anhydrides in the literature is doubtful, since the reaction conditions used for their preparation would seem certain to lead to disproportionation. Thus when acetic propionic anhydride (which was reportedly distilled[109] at 160°) was prepared as described in the literature and examined by g.l.c., two sharp peaks corresponding to acetic anhydride and propionic anhydride were obtained. It would seem that analytical methods used previously to confirm the identity of the mixed anhydride had in fact been

used on material which was simply an equimolar mixture of symmetrical anhydrides.

(b) Attempts to prepare and detect mixed anhydrides

No report has appeared in the literature describing the detection of mixed anhydrides by g.l.c. Mixed anhydrides were accordingly prepared and the organic products examined by g.l.c. The following preparations were carried out as described in the literature:

1. acetyl chloride/valeric acid/pyridine;
2. acetyl chloride/sodium valerate;
3. butyryl chloride/sodium acetate;
4. propionyl chloride/sodium acetate;
5. acetyl chloride/sodium propionate.

In all cases, the two symmetrical anhydrides, but no mixed anhydrides were detected. This was true even when the injection block temperature of the gas chromatograph was lowered to 100° to minimise disproportionation of any mixed anhydride.

Samples analysed by g.l.c. before distillation showed the same result as after distillation: sharp peaks of symmetrical anhydrides, but no mixed anhydrides.

An attempt was made to prepare and detect mixed anhydrides at room temperature using t.l.c., with the spots being visualised by aniline spraying followed by iodine

vapour adsorption, or by spraying with bromocresol purple in aqueous ethanol. Severe streaking precluded the use of the latter, while spots produced by iodine adsorption were too faint for positive identification.

A number of spectroscopic techniques were explored in view of the reported use of i.r. and n.m.r. to detect mixed anhydrides and establish their purity.[100,110] Taylor[100] in his synthesis of mixed anhydrides by the action of an acyl or aroyl halide on a thallium (I) carboxylate used i.r. and n.m.r. spectroscopy to check the purity of the mixed anhydrides. In this synthesis, the ether solvent was removed from the reaction mixture by distillation to give a mixed anhydride in near-quantitative yield, and contaminated by 1-3% of symmetrical anhydrides. The details of the spectroscopic method used to detect the impurities were not published.

In our hands, pivalic-lauric anhydride was prepared by the action of lauroyl chloride on thallium (I) pivalate. The n.m.r. spectrum of the product was simply the sum of the n.m.r. spectra of the respective symmetrical anhydrides, which suggested that spectroscopic methods are not always applicable.

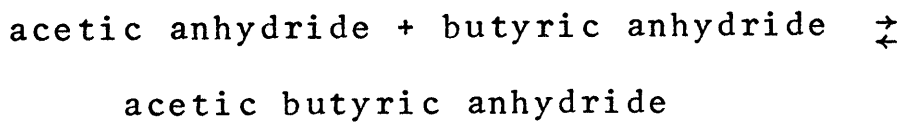
Taylor[111] subsequently confirmed this view in noting that n.m.r. spectroscopy was useful only for mixed aliphatic/

aromatic anhydrides. Thus, the n.m.r. spectrum (carbon tetrachloride) of benzoic pivalic anhydride showed the methyl protons at δ1.20. Similar small but significant differences were observed with other mixed benzoic/aliphatic anhydrides. In the case of a mixed anhydride prepared from two aliphatic carboxylic acids, direct comparison of the i.r. spectra of the (known) symmetrical anhydrides with the mixed anhydride was made. For example, the spectrum of isobutyric pivalic anhydride showed small doublets at 1395 cm^{-1} and 1385 cm^{-1}. Both symmetrical anhydrides showed the lower but not the higher peak. Also, the mixed anhydride lacked the 915 cm^{-1} peak characteristic of isobutyric anhydride. There was no rule-of-thumb: the i.r. spectrum of each mixed anhydride was compared with the i.r. spectra of the symmetrical anhydrides.

Since mercury benzoate cannot be prepared in a pure state,[112] use of n.m.r. was precluded. It was considered that the slight differences in the i.r. spectrum of a mixed anhydride prepared from two aliphatic carboxylic acids (compared with the symmetrical anhydrides) was not satisfactory as an analytical tool for identifying mixed anhydrides in the presence of the two symmetrical anhydrides. These differences may be due to loose association between the two symmetrical anhydrides (the literature refers to neat

liquids[100]) and not necessarily to a molecule which is a true mixed anhydride.

Brown and Trotter[110] reported an i.r. investigation which showed acetic anhydride and butyric anhydride gradually react to give acetic butyric anhydride. The evidence for the existence of this mixed anhydride was the appearance of bands not present in either of the two symmetrical anhydrides. Surprisingly, they did not record the i.r. spectrum of pure acetic butyric anhydride to support this interpretation of the observed spectral changes. Again, these new bands may arise because of a loose association between the two symmetrical anhydrides, rather than because of the presence of a mixed anhydride. In this report, the equilibrium constant for the reaction:



was given as 4, with no change in this value over the temperature range 20°-100°. The activation energy was calculated as 10.6 kcal/mole. If this figure is correct, thermal energy available at room temperature would quite rapidly transform any mixed anhydride into an equilibrium mixture.

With the exception of acetic formic anhydride, for which n.m.r.[113] and gas-phase electron diffraction data[114] have been published, no general spectroscopic method for characterising mixed anhydrides has been devised.

At first sight, mass spectroscopy (m.s.) would appear to be the ideal method for detecting mixed anhydrides. In practice, this method fails due to the absence of a molecular ion: only acyl cations could be detected, and these are of no value in distinguishing between mixed and symmetrical anhydrides.

In the absence of a satisfactory method for detecting mixed anhydrides *per se*, an indirect approach was explored. Pivalic caprylic anhydride, prepared by the method of Taylor,[100] was esterified with methanol and the mixture of methyl pivalate and methyl caprylate was examined by g.l.c. The esters were present in the ratio 1:3-1:4, which is to be expected in view of the steric hindrance associated with the pivaloyl carbonyl group compared with the caproyl carbonyl group. The experimental ratio of esters was very variable and at best indicated a comparatively low selectivity. Further, since an intermolecular desulphurisation mechanism would, on statistical grounds, give a 1:1 ratio of symmetrical to unsymmetrical anhydrides, it was not likely to be successful.

In the absence of a satisfactory method for the detection of mixed aliphatic acid anhydrides, and in view of the serious doubts associated with their stability, attemps to confirm an intramolecular mechanism by absence of crossed products were abandoned.

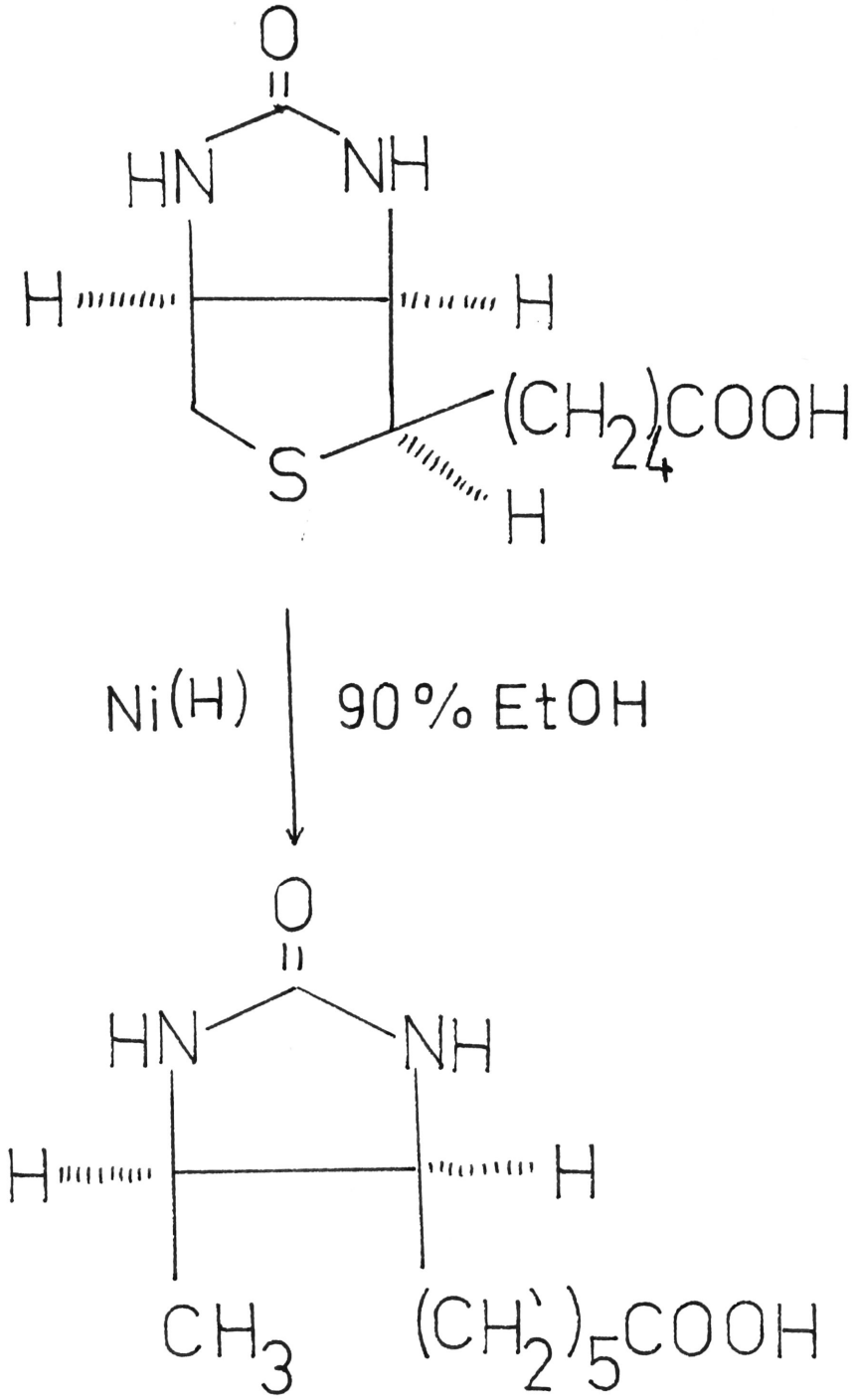


Figure 16

2.3 DESULPHURISATION OF THIOESTERS BY ACTIVE W-2 RANEY NICKEL

(a) Preparation and use of Raney nickel

During the investigation of the sulphur-containing vitamin, biotin (Figure 16), it was found that many sulphur compounds (sulphides, disulphides, sulphones, and sulphoxides) reacted with Raney nickel.[115] In these reactions, the sulphur atom was replaced by two hydrogen atoms. These investigations led to the desulphurisation of biotin with Raney nickel,[116] a key step in the structure elucidation of this vitamin.

Desulphurisation reactions with Raney nickel have subsequently been used for many purposes, including the quantitative determination of sulphur,[117] and the removal of sulphur impurities which poison other hydrogenation catalysts.[118] The main use for Raney nickel desulphurisation reactions is, however, for structure elucidation and in synthetic organic chemistry for: the removal of sulphur-containing protecting groups,[119] the removal of functional groups,[120] the interconversion of functional groups[38] and for carbon-carbon bond formation.[36,37]

Raney nickel catalyst is prepared by reacting a nickel-aluminium alloy with sodium hydroxide solution.

Hydrogen evolved by the reaction between aluminium and alkali is adsorbed on the nickel surface. The activated catalyst is used for hydrogenation and desulphurisation. The seven types of Raney nickel (designated W-1 to W-7) listed by Fieser and Fieser[35] differ in their activity, which in turn is related to the method of preparation. In this project, Raney nickel W-2[121] was used. The most powerful desulphurising agent appears to be Raney nickel prepared by digestion of Raney nickel alloy by strong alkali in situ.[122]

In desulphurising experiments, the catalyst is added in excess: about ten times the weight of the organo-sulphur compound. Occasionally, strong adsorption on the catalyst surface occurs. The product is removed by a suitable solvent in a Soxlhet extractor, or by dissolving the nickel in a mineral acid.

Nickel boride has recently been found[123] comparable in activity to Raney nickel W-2, with the advantage of being safer to handle (Raney nickel W-2 is highly pyrophoric). Nickel boride is also more selective than Raney nickel: in some cases it removes only one of two possible sulphur atoms.

(b) Previous desulphurisations with activated Raney nickel.

The reduction of a thiocarbonyl group to a methylene group by activated Raney nickel has been observed in a number

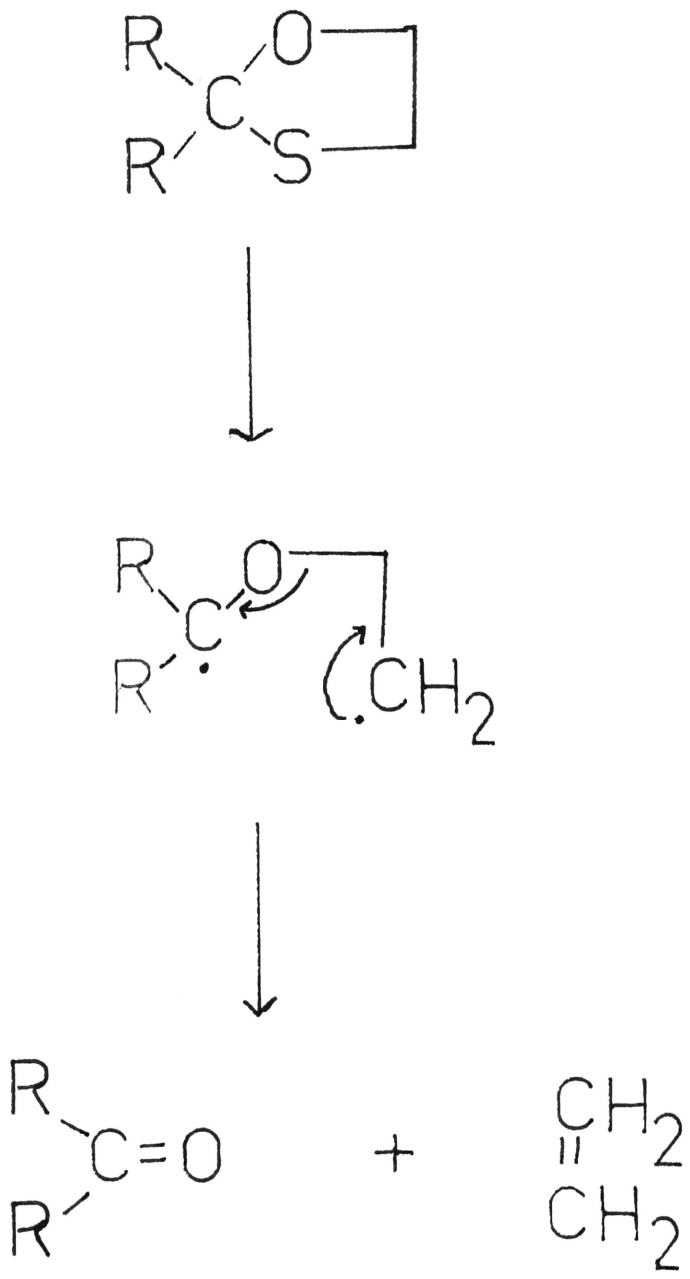


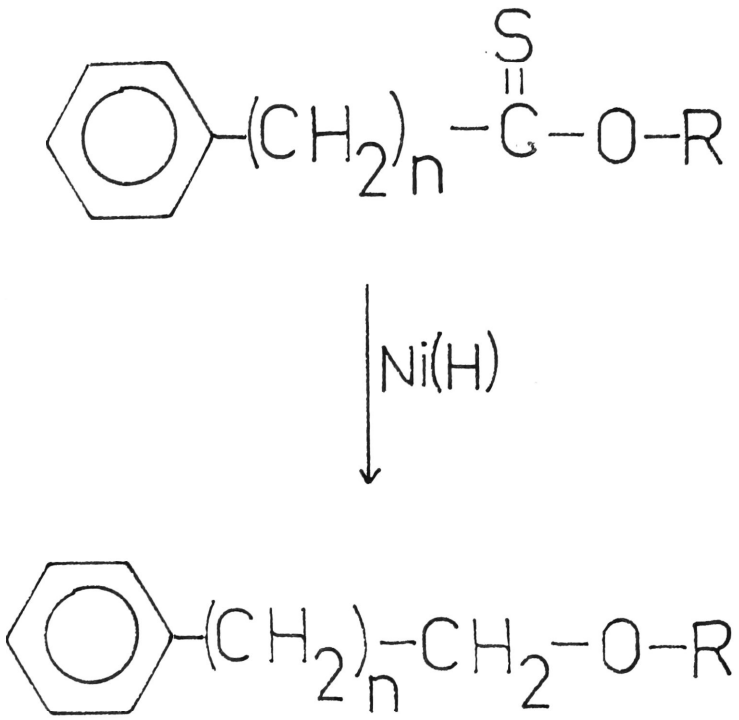
Figure 17

of compounds: thioamides,[77] pyrocatechol thiocarbonate,[124] thioacridone,[125] piperidine-2-thione,[126] 2-thiobarbituric acid derivatives,[126] and 2-thiouracil derivatives.[127] Picolyl secondary amines, a useful group of pharmaceuticals, have been prepared by this desulphurisation reaction.[128]

The mechanism of Raney nickel desulphurisations has been investigated. The source of hydrogen has been shown to be hydrogen bound to the nickel surface.[129] Although Bougault[130] suggested that a nickel mercaptide forms, which decomposes to give a hydrocarbon and nickel sulphide, later workers suggested radicals as intermediates. The first step is chemisorption of sulphur on the nickel surface;[131] this is followed by cleavage of the carbon-sulphur bond, which gives free radicals.[132]

As an example, Djerassi and co-workers[133] have suggested a free radical mechanism for the desulphurisation of cyclic hemithioketals (Figure 17). Hauptmann and Walter[32] list the following evidence for a free radical mechanism in desulphurisation reactions:

1. stereochemical considerations: desulphurisation results in racemisation;[134]
2. saturated aliphatic sulphur compounds give mixtures of olefins and paraffins;[135]
3. dimerisation[131,132] and cyclisation;[136]



(n= 1,2 ; R= 3β-cholestanyl-)

Figure 18

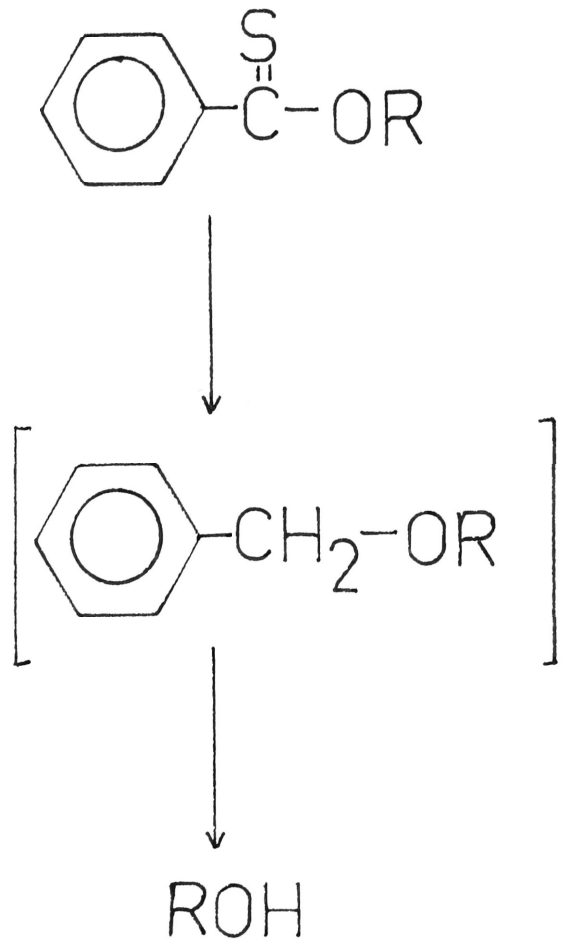
4. the formation of carbon monoxide when thiolesters are treated with degassed Raney nickel;[137]
5. The formation of cyclohexanone when 4, 5-bis(pentamethylene)-3, 6-dioxa-o-dithiane is desulphurised[138] by degassed Raney nickel at 200°.

(c) Desulphurisation of thioesters

The absence of any literature reference to the desulphurisation of thioesters with Raney nickel prompted us to examine this reaction using a series of thioesters with active and deactivated Raney nickel. By analogy with the desulphurisation of other thiocarbonyl compounds described previously, the thiocarbonyl group of the thioester would be expected to be reduced by activated Raney nickel W-2 to a methylene group. This expectation was verified when cholestanyl thiophenylpropionate gave 3β-(3'-phenylpropoxy)-cholestane in 77% yield and cholestanyl thiophenylacetate gave 3β-(2'-phenylethoxy)-cholestane in 72% yield (Figure 18).

Cholestanyl thiobenzoate gave cholestanol, and phenyl thiobenzoate gave phenol when desulphurised with active Raney nickel. This is presumed to be a result of hydrogenolysis (Figure 19) of an intermediate benzyl ether.

The results of the desulphurisation of thioesters with activated Raney nickel are summarised in Table 2.



(R= Ph–, 3β-cholestanyl–)

Figure 19

THIOESTER	AGE OF NICKEL	SOLVENT	REACTION TIME(hours)	PRODUCTS	YIELD (%)
cholestanyl thiophenylpropionate	8 days	benzene	1	3β-(3'-phenylpropoxy)-cholestane cholestanyl phenylpropionate cholestanol	77
cholestanyl thiophenylacetate	1 day	dichloromethane	$1\frac{1}{2}$	3β-(2'-phenylethoxy)-cholestane cholestanol	72
	16 days	ethanol	1	3β-(2'-phenylethoxy)-cholestane cholestanyl phenylacetate cholestanol	73
cholestanyl thiobenzoate	4 months	dichloromethane	1	cholestanol	75
phenyl thiobenzoate	9 days	ethanol	$1\frac{1}{2}$	phenol	68

DESULPHURISATION OF THIOESTERS WITH ACTIVE W-2 RANEY NICKEL

Table 2

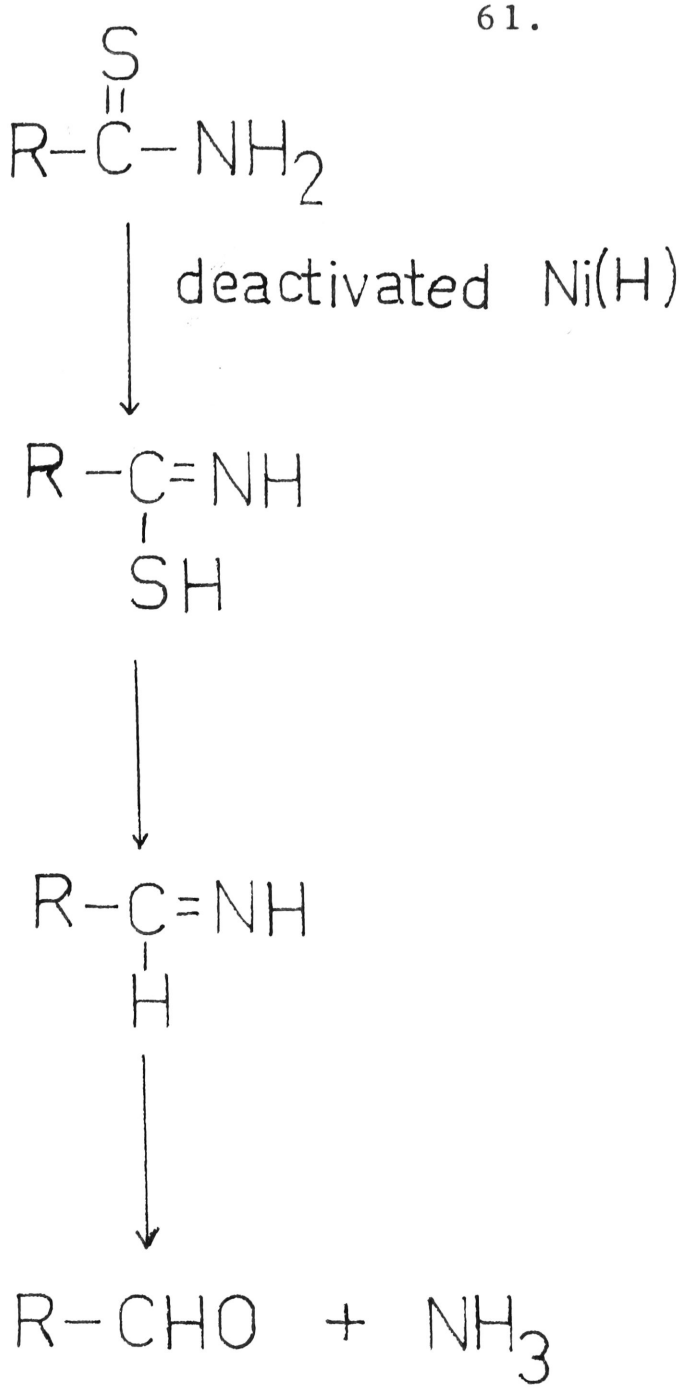


Figure 20

2.4 DESULPHURISATION OF THIOESTERS BY DEACTIVATED W-2 RANEY NICKEL

The active, hydrogen-rich catalyst can be deactivated by refluxing it in acetone.[139] The deactivated catalyst is more selective in its action, preserving olefinic bonds[140] or carbonyl groups[141] which would otherwise be reduced.

Whereas the thiocarbonyl group of thioamides is reduced to a methylene group by the active catalyst, the deactivated catalyst desulphurises thioamides to aldehydes (Figure 20). Benzaldehyde, for example, has been prepared by this method.[142] Bougault[130] found that thiourea gives methane and hydrogen when desulphurised.

It can thus be seen that the deactivated catalyst offered the possibility for desulphurising thioesters to useful synthetic intermediates, especially in view of its reported use for intermolecular coupling reactions such as the conversion of thioacetophenone to trans-α,β-dimethyl-stilbene.[37]

Cholestanyl thiophenylpropionate and cholestanyl thiobenzoate were desulphurised with Raney nickel catalyst which had been deactivated by refluxing in acetone. These two thioesters gave a variety of cholestane derivatives, which are shown in Table 3.

THIOESTER	REACTION TIME (hours)	SOLVENT	PRODUCTS	YIELD(%)	IDENTIFICATION
cholestanyl thiophenylpropionate	24	benzene	cholestanone	34	t.l.c., i.r.
			cholestanyl phenylpropionate	32	t.l.c., i.r.
			cholestanol	20	t.l.c., i.r.
			cholestene	13	t.l.c., i.r.
cholestanyl thiobenzoate	4	benzene	cholestanol		t.l.c.
			cholestanyl benzoate		t.l.c.
			cholestene		t.l.c.

DESULPHURISATION OF THIOESTERS WITH DEACTIVATED RANEY NICKEL W-2

Table 3

Cholestanyl thiophenylacetate gave a moderate yield (about 70% as shown by intensity of spots by t.l.c.) of a compound which had an R_f different from that of: the starting material, cholestanyl phenylacetate, cholestane, cholestene and cholestanol. When this compound was treated with acid and methanol at room temperature, cholestanol formed. The compound was presumed to be 2'-phenylethenyl cholestanyl ether, which, being an enol ether, would be expected to hydrolyse easily by protonation of the β-carbon of the double bond, followed by cleavage to the alcohol and formation of phenylacetaldehyde dimethylacetal. In order to establish the optimum conditions for this reaction, it was decided to use more volatile thioesters, and to examine the products by g.l.c./m.s.

Accordingly, cyclohexyl thiophenylacetate and n-butyl thiophenylacetate were desulphurised with deactivated Raney nickel W-2 to the corresponding enol ethers. Both the cyclohexyl 2'-phenylethenyl ether (70% yield) and n-butyl 2'-phenylethenyl ether (75% yield) gave two peaks of similar retention time on g.l.c.; these were attributed to the two geometrical isomers of the cis-trans mixture. In agreement, their mass spectra were identical (Table 4), and on acid catalysed methanolysis, both peaks disappeared.

Labelled phenylacetaldehyde dimethylacetal and the correspond-

n-butyl 2'-phenylethenyl ether

m/e	%	
176	16	$M^{+\cdot}$
120	100	$Ph\text{-}CH_2\text{-}CH{=}O^{+\cdot}$
91	77	tropylium ion
77	12	Ph^{+}

cyclohexyl 2'-phenylethenyl ether

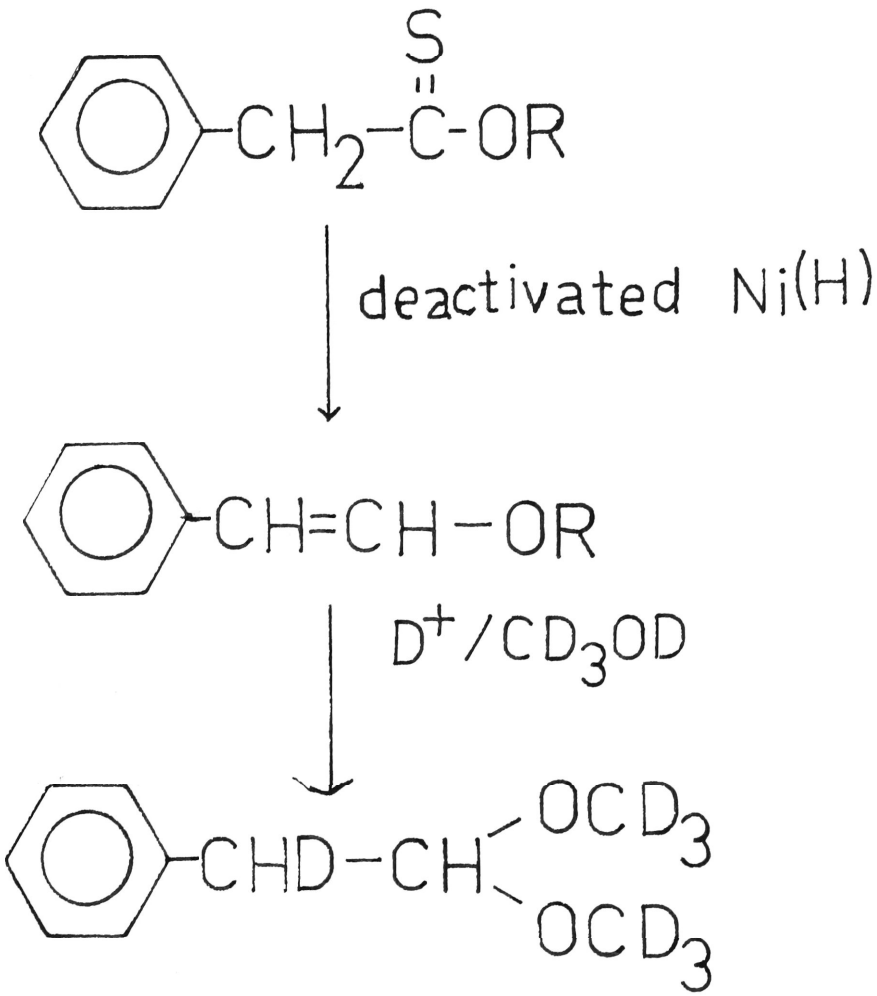
m/e	%	
202	3	$M^{+\cdot}$
120	100	$Ph\text{-}CH_2\text{-}CH{=}O^{+\cdot}$
91	41	tropylium ion
77	29	Ph^{+}

cholestanyl 2'-phenylethenyl ether

m/e	%	
504	-	$M^{+\cdot}$ not observed
120	100	$Ph\text{-}CH_2\text{-}CH{=}O^{+\cdot}$
91	77	tropylium ion
77	9	Ph^{+}

MASS SPECTRA OF ENOL ETHERS

Table 4



(R = 3β-cholestanyl–,
cyclohexyl–,
n-butyl–)

Figure 21

ing alcohol were obtained. The phenylacetaldehyde dimethylacetal was quantitatively labelled with one atom only of deuterium in the benzylic position (Figure 21); this is to be expected, since the facile acid catalysed hydrolysis of an enol ether proceeds by an initial protonation of the β-carbon of the double bond.

The mass spectrum of phenylacetaldehyde dimethylacetal has been reported by Danks and Hodges,[143] who observed a weak molecular ion (m/e 166, 0.5%). No molecular ion was observed for our Ph-CHD-$CH(OCD_3)_2$. The most intense peak reported for phenylacetalhedyde dimethylacetal was m/e 75 due to MeO-CH=OMe+; we observed the corresponding intense peak at m/e 81. The next most intense peak reported was due to the tropylium ion (m/e 91); the corresponding labelled tropylium ion at m/e 92 was the most intense peak in our spectrum. Important peaks in the reported mass spectrum of phenylacetaldehyde dimethylacetal and our labelled specimen are summarised in Table 5.

The different, and simpler, product distribution from thiophenylacetates as compared with other thioesters is attributed to the conjugation of the double bond of the enol ether with the benzene ring.

Phenylacetaldehyde dimethylacetal

m/e	%	
134	3.5	$C_9H_{10}O^{+\cdot}$
119	1.1	$C_8H_7O^+$
103	13	$C_8H_7^+$
91	49	tropylium ion
75	100	MeO-CH=OMe+
47	19	Me-OH-Me+
31	10	CH_2=OH+

Labelled phenylacetalhedyde dimethylacetal

m/e	%	
138	15	$C_9H_6D_4O^{+\cdot}$
120	4	$C_8H_6DO^+$
104	5	$C_8H_6D^+$
92	100	labelled tropylium ion
81	91	CD_3O-CH=OCD_3^+
53	27	CD_3-OH-CD_3^+
33	33	CD_2=OH+

COMPARISON OF MASS SPECTRA OF PHENYLACETALHEDEHYDE DIMETHYLACETAL AND LABELLED PHENYLACETALDEHYDE DIMETHYLACETAL

Table 5

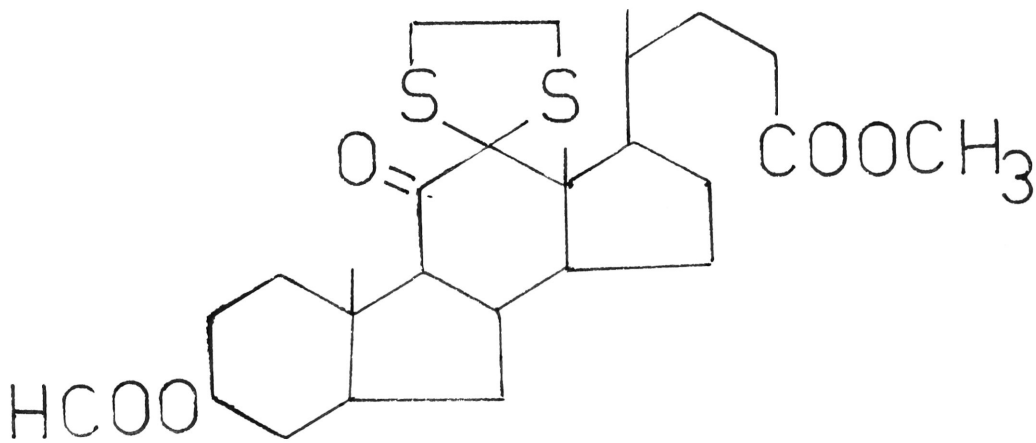


Figure 22

According to Pettit and van Tamelen[31] the reported conditions for many Raney nickel desulphurisations are more vigorous than necessary. They cite the desulphurisation of the thioketal (Figure 22). This thioketal is desulphurised to give 90% yield in boiling methanol, and 86% yield when shaken for 15 minutes at room temperature. It was found in the present work that if the thiophenylacetates were refluxed for too long (about 24 hours), then a complex mixture of products was obtained as shown by g.l.c. The reaction should be followed by g.l.c. or t.l.c. and stopped when 5-10% of the thioester still remains.

If prepared by a thioacylation-desulphurisation procedure, the 2'-phenylethenyl ether function could be used as a protecting group for the hydroxyl group. It can be introduced under mild conditions, it is inert to lithium aluminium hydride and is easily removed by acid hydrolysis.

2.5 SPECTRAL STUDIES OF THIOESTERS

During the course of this project, some new spectral data for thioesters was obtained.

The infra-red spectra of thioesters have been studied in detail.[76] The precise location of the thiocarbonyl stretching frequency proved troublesome initially; this was partly caused by the instability of many thiocarbonyl compounds. Rao[81] found it necessary to distinguish between thiocarbonyl compounds where the carbon atom is directly attached to a nitrogen atom, and those in which it is not. In the latter case, it was shown in a survey of thiocarbonyl compounds that the thiocarbonyl stretching frequency occurs in the region 1025-1225 cm^{-1}. Renson and Bidaine,[76] in a study of thioesters, located the thiocarbonyl vibration more precisely: for aliphatic thioesters, they located it in the range 1205-1218 cm^{-1}, and for aromatic thioesters at 1227 cm^{-1}.

In the present work, the i.r. spectra of thioesters and the corresponding esters were compared. Two strong bands were observed at 1230 cm^{-1} and 1050 cm^{-1} in ethyl thiobenzoate and cholestanyl thiobenzoate; these bands were absent from the oxygen analogues. All four thiophenylacetates prepared in this project (ethyl, n-butyl, cyclohexyl and cholestanyl) showed two characteristic

strong absorption bands at 1205 cm^{-1} and 1190 cm^{-1}. These bands are absent from the corresponding phenylacetates.

Very little n.m.r. data[73,87,88] has been reported for thioesters. The deshielding associated with the anisotropy of the thiocarbonyl group has been noted previously.[73]

The deshielding effect of the thiocarbonyl group is the sum of an inductive withdrawal of electrons due to the greater electronegativity of sulphur compared with carbon, and the diamagnetic anisotropy of the π bond. The inductive effect of the thiocarbonyl group is less than that of the carbonyl group, but its diamagnetic anisotropy is much greater. The total deshielding effects in esters, thioesters, dithioesters and thiolesters depends on the relative magnitude of these two effects. It has been established previously[73] that deshielding decreases in the order:

Ph-CS-O- > Ph-CO- > Ph-CS-S- > Ph-CO-S-

The present series of 3β-substituted thioesters (the first in which methylene protons separate the benzene ring and the thiocarbonyl group) extends the very limited data on proton chemical shifts of thiocarbonyl compounds and illustrates the relative anisotropic and inductive

deshielding by the carbonyl and thiocarbonyl groups respectively, as well as the additivity of deshielding by the benzene ring (Table 6).

While the carbonyl group of an ester deshields the 3-α methine proton by an additional 1.5 ppm relative to the corresponding ether, the thiocarbonyl group deshields it by a further 0.60-0.63 ppm. In the case of the thiobenzoate ester, the additional deshielding due to the benzene ring is not simply additive, but is greatly enhanced by its transmission through the thiocarbonyl rather than the carbonyl group. The 3-α methine proton signal of cholestanyl thiobenzoate is 0.30 ppm downfield of that of cholestanyl thiophenylacetate. In the case of the corresponding esters, the difference is only 0.19 ppm. The effect of the phenyl group is apparent only when it is adjacent to the carbonyl or thiocarbonyl group; the 3-α methine proton signal for the acetate, phenylacetate, phenylpropionate is virtually the same (δ 4.67-4.70), which is true for the thioacetate, thiophenylacetate and thiophenyl-propionate (δ 5.30).

The n.m.r. spectrum of cholestanyl thiophenylacetate gives us the chemical shift for methylene protons flanked by both a phenyl group and a thioacyl group (δ 3.94).

$Ph-CH_2-CH_2-X-O-cholestane$

o,m,p a b c d(3α-H)

	THIOESTER X = -CS-	ESTER X = -CO-	ETHER X = $-CH_2-$
Ph-X-O-cholestane	H_o 8.20 $H_{m,p}$ 7.35 H_d 5.60	H_o 7.98 $H_{m,p}$ 7.35 H_d 4.86	--
$Ph-CH_2-X-O-cholestane$	$H_{o,m,p}$ 7.24 H_d 5.30 H_a 3.94	$H_{o,m,p}$ 7.25 H_d 4.67 H_a 3.55	$H_{o,m,p}$ 7.23 H_d 3.20 H_a 2.85 H_c 3.62
$Ph-CH_2-CH_2-X-O-cholestane$	$H_{o,m,p}$ 7.18 H_d 5.30 $H_{a,b}$ 2.95	$H_{o,m,p}$ 7.24 H_d 4.68 H_a 2.92 H_b 2.52	$H_{o,m,p}$ 7.22 H_d 3.18 H_a 2.72 H_b 2.48
$CH_3-X-O-cholestane$	H_d 5.30 H_b 2.50	H_d 4.70 H_b 2.02	H_d 3.19 H_c 3.50 H_b 1.18

N.M.R. SPECTRAL DATA FOR 3β-CHOLESTANYL THIOESTERS, ESTERS & ETHERS

Table 6

For the oxygen analogue, the chemical shift is δ 3.55. Thus the thioacyl shifts this signal by a further 0.39 ppm compared with the acyl group. In both cases, a singlet is observed, showing the protons are magnetically equivalent. In the thiophenylpropionate and phenylpropionate, the methylene protons adjacent to the thioacyl group are deshielded by 0.43 ppm relative to the protons adjacent to the acyl group. The chemical shift of the benzylic protons in both esters is virtually identical (δ 2.95 and δ 2.92). Comparison of this shift with that for the benzylic protons of 3β-(3'-phenylpropoxy)-cholestane gives an estimate of the deshielding of a methylene group by a β carbonyl or thiocarbonyl group, namely about 0.2 ppm.

When the benzene ring is conjugated with the thiocarbonyl group, the deshielding effect of the thioacyl group extends to distant protons and all aromatic protons are shifted from their normal positions at δ 7.18-7.22 in the thiophenylpropionate and phenylpropionate esters and 3β-(3'-phenylpropoxy)-cholestane. The ortho protons are most affected, being at δ 8.20 in the thiobenzoate and δ 7.98 in the benzoate. The remaining aromatic protons are at δ 7.35 and 7.32 respectively, a downfield shift of ca 0.1 ppm relative to an unsubstituted benzene ring.

The deshielding of a methylene group due to a thioacyl

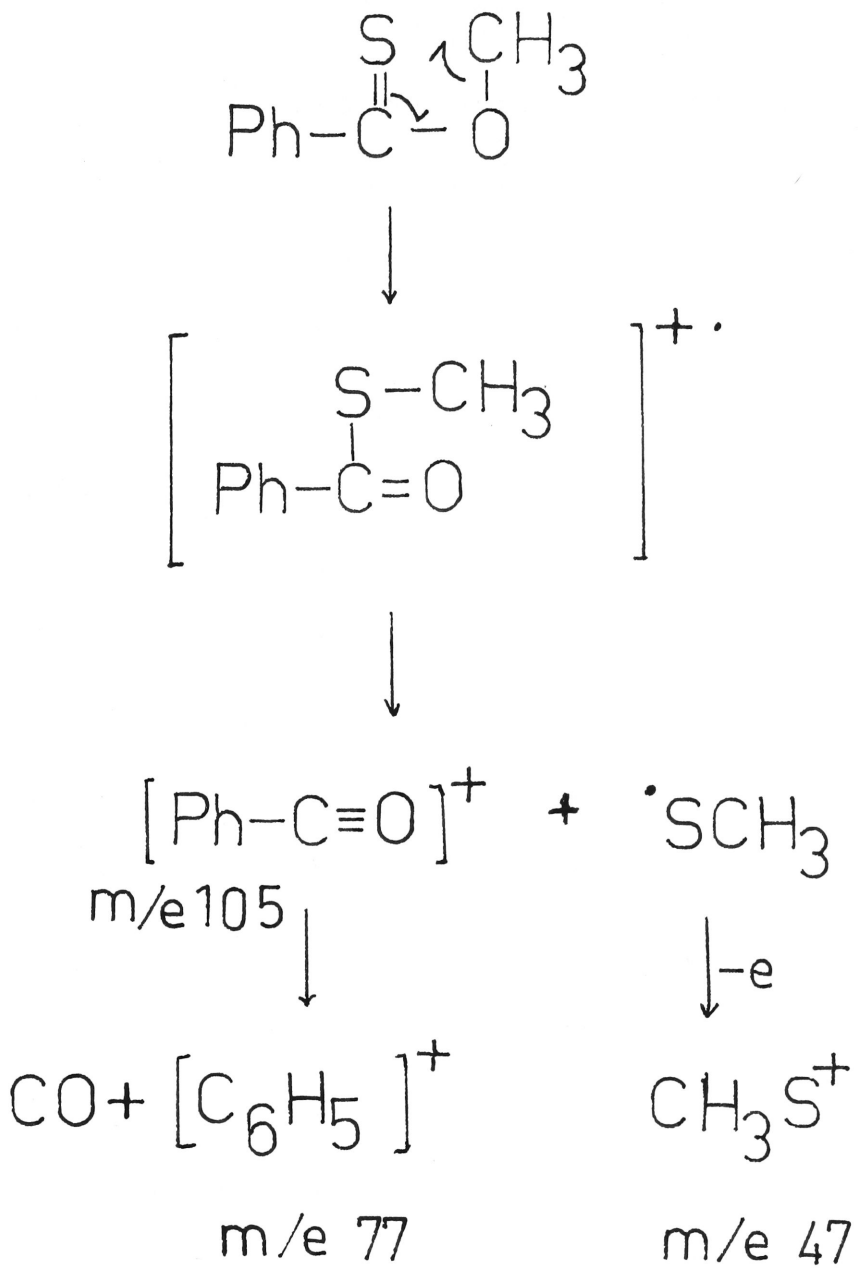


Figure 23

group alone can be approximated by examination of chemical shifts of benzylic protons of the thiophenylacetate and the 3β-(2'-phenylethoxy ethers. In the thiophenylacetate, the benzylic protons give a signal at δ 3.94, a downfield shift of 1.22 ppm relative to the ether. The deshielding effect of the thiocarbonyl group alone may be estimated by subtracting the benzylic proton shifts of 3β-(2'-phenylethoxy)-cholestane from that of cholestanyl thiophenylacetate (δ 3.94-2.85 = 1.09 ppm). The difference (0.13 ppm) between this shift and that of the thioacyl group agrees closely with the literature value[144] for the deshielding of a methylene proton by a β oxygen atom.

The mass spectral cracking patterns of thiobenzoates and thioacetates have been reported.[145-147] As with aromatic esters, the principal charged fragments originate from the acyl portion of the molecule. Thioester mass spectra contain a number of prominent ions arising from the rearrangement of the original ion molecule as shown in Figure 23. Alkyl migration from oxygen to sulphur results in the ion $[R\text{-}C \equiv O]^{+\cdot}$ In thioacetates, this ion is the base peak of the spectrum.[146] In the present work, this peak was observed in cholestanyl, n-butyl and cyclohexyl thiophenylacetates at m/e 119, $[Ph\text{-}CH_2\text{-}C \equiv O]^{+\cdot}$ A peak for the other fragment $[R'\text{-}S]^{+\cdot}$ was reported by Ohno,[145] but

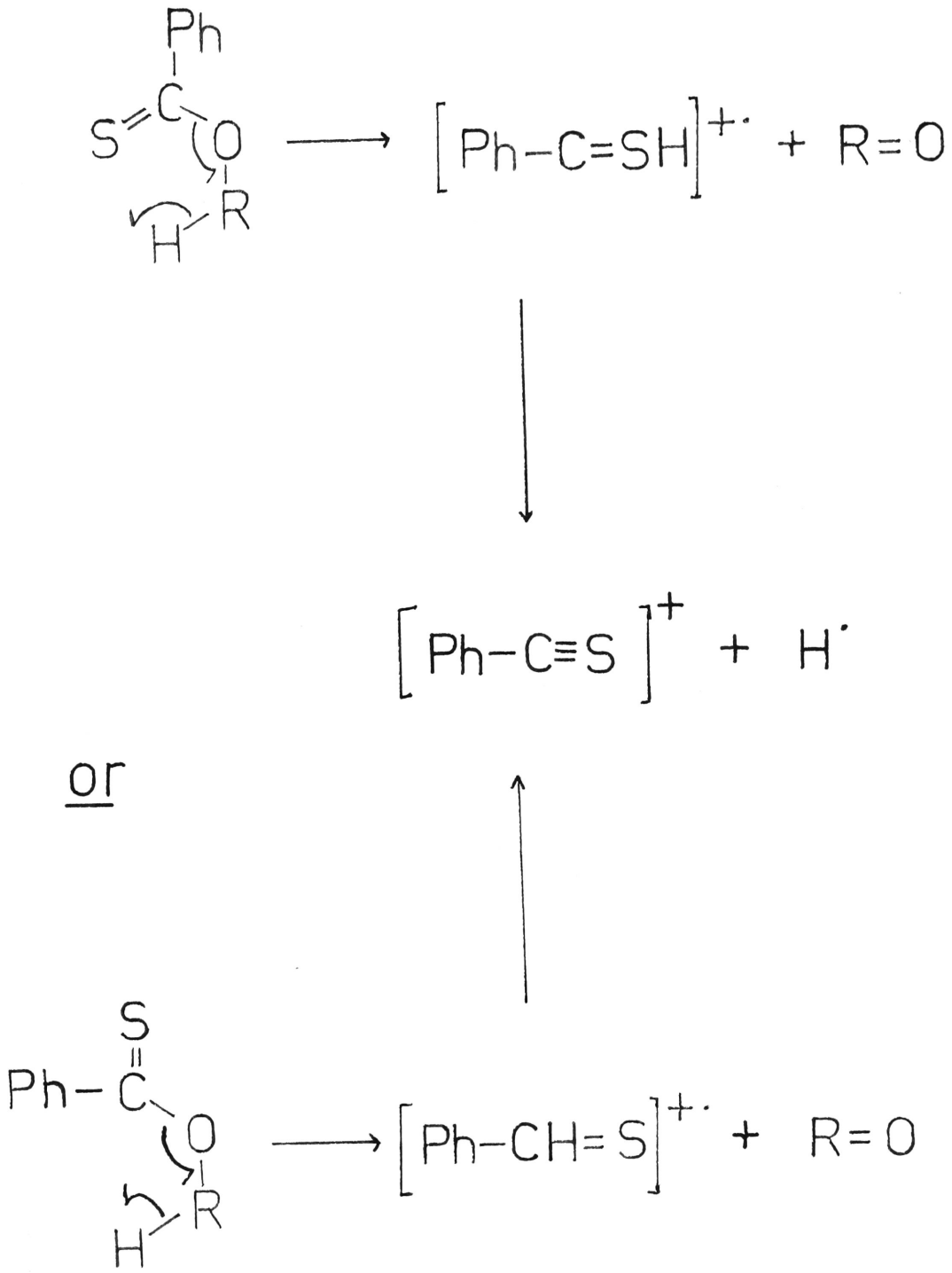


Figure 24

reported to be very weak (< 0.5%) by Bentley.[147] Peaks corresponding to this ion were not observed in the present work.

Unlike the McLafferty rearrangement of esters, a further rearrangement of alkyl thiobenzoates can take place even with methyl thioesters as shown in Figure 24. It was found that the elimination of a sulphyhydryl radical from alkyl thiobenzoates is much more important than the elimination of a hydroxyl radical from benzoates:

$$[Ph\text{-}CS\text{-}OR]^{+\cdot} \rightarrow [C_7H_4OR]^{+} + {}^{\cdot}SH$$

The criteria for the above rearrangements to occur were collected under a generalised scheme by Bentley and Johnstone:[147] for the rearrangement

$$[A{=}B\text{-}C\text{-}D]^{+\cdot} \rightarrow [D\text{-}A\text{-}B{=}C]^{+\cdot}$$

(i) when A is oxygen, C must be nitrogen;

(ii) when A is sulphur, C can be nitrogen or oxygen;

(iii) B can be carbon, phosphorus or nitrogen;

(iv) rearrangement is negligible when C is sulphur.

All esters and thioesters in the present work had small parent peaks, and an intense peak at m/e 91 due to the tropylium ion. A prominent peak at m/e 152 was observed

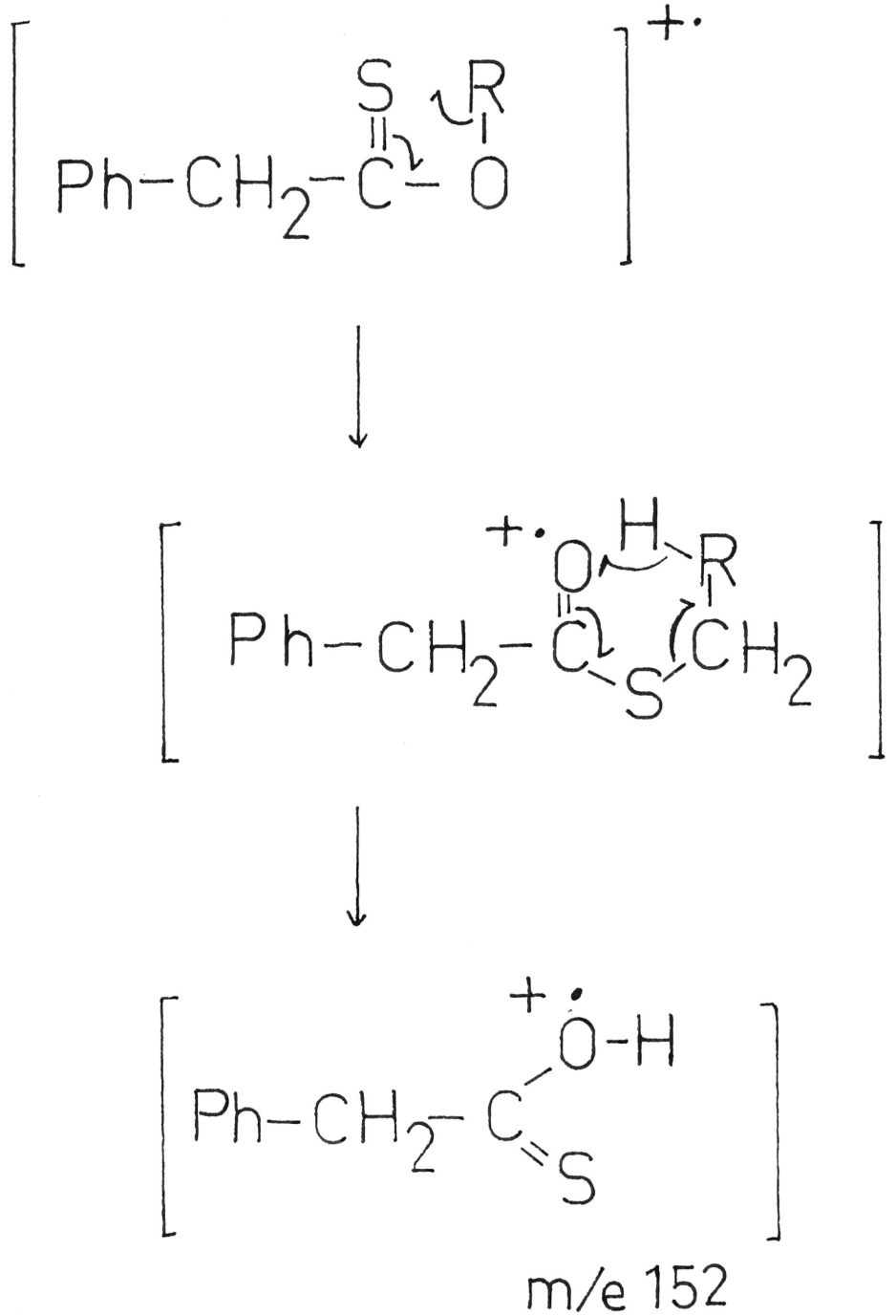


Figure 25

in n-butyl and cyclohexyl thiophenylacetates due to $[Ph\text{-}CH_2\text{-}CS\text{-}O + H]^{+\cdot}$. This ion, which is much less prominent in cholestanyl thiophenylacetate, could arise as shown in Figure 25; this rearrangement has been observed in esters.[148] The peak at m/e 135 could be formed by breakage of the carbon-oxygen bond to give $[Ph\text{-}CH_2\text{-}CS]^{+\cdot}$. In esters, fragmentation of the O-R bond can be accompanied by transfer of two hydrogen atoms to the oxygenated fragment;[148] a peak at m/e 137 corresponding to $[Ph\text{-}CH_2\text{-}CO\text{-}O + 2H]^{+\cdot}$ was observed in the present work, and the corresponding ion $[Ph\text{-}CH_2\text{-}CS + 2H]^{+\cdot}$ at m/e 153 observed in thiophenylacetates.

3. EXPERIMENTAL

GENERAL

Melting points were determined in glass capillaries and are uncorrected. An electrically-heated Gallenkamp melting point apparatus was used.

All temperatures are expressed in degrees Celsius.

G.l.c. was carried out using a six foot column with 5% OV-17 on silanised chromosorb W stationary phase, nitrogen carrier gas and flame ionisation detector. A temperature program of 10°/minute was normally used.

Anaesthetic ether was dried over sodium and filtered as required.

Pure hydrogen chloride and hydrogen sulphide were obtained from cylinders (Matheson Co.).

Combined organic phases were dried over anhydrous magnesium sulphate.

Dry methanol and "super-dry" ethanol were prepared according to the method described in Vogel.[96]

Pyridine (SpectrAR, Malinkrodt) was dried by refluxing over sodium hydroxide, distilled and stored over potassium hydroxide.

Carboxylic acid anhydrides were commercial specimens (Fluka); their purity was checked by g.l.c.

Ultra-violet spectra were recorded in hexane on a Perkin-Elmer model 137 spectrophotometer.

Infra-red spectra were recorded on a Perkin-Elmer model 357 recording spectrophotometer. Thin films were used for liquids, and nujol mulls for solids. Peaks are described as strong (s), medium (m), or weak (w).

Mass spectra were obtained on an EAI QUAD 300D instrument. This instrument was coupled to the gas chromatograph described earlier for g.l.c./m.s. work.

N.m.r. spectra were recorded on a Varian A60 spectrometer, using solutions in deuterochloroform with tetramethylsilane as internal standard.

Optical rotations were measured in a Hilger instrument in a 10 cm tube using a 1% solution is chloroform.

Thin layer plates were prepared by dipping microscope slides (2" x 1") into a suspension of silica gel (< 0.08 mm, Merck, Germany) in chloroform with ca 1% methanol, and slowly withdrawing the slides. Steroids were visualised by spraying with a sulphuric acid/acetic anhydride mixture (1:1) and warming. Other compounds were visualised by exposure to iodine vapour.

Alumina for column chromatography was Woelm, basic, activity grade 1. Silica gel for column chromatography was "Merck Kieselgel".

Petroleum spirit refers to the fraction with b.p. 60-80°.

Micro-analyses were carried out by Dr. E. Challen of the University of N.S.W., or by the Australian Micro-analytical Service, Melbourne.

DESULPHURISATION BY MERCURIC CARBOXYLATES

Preparation of mercuric carboxylates

Mercuric acetate was a commercial specimen (B.D.H.), purified by recrystallisation from acetic acid. The other mercuric carboxylates were prepared from mercuric oxide and the appropriate acid by the method of Bunce,[112] and purified by crystallisation from carbon tetrachloride to give:

mercuric propionate, m.p. 111-112° (lit.[94] 112°);

mercuric butyrate, m.p. 102-103° (lit.[94] 103°);

mercuric pivalate, m.p. 230-232° (lit.[149] 235°);

mercuric valerate, m.p. 87-88.5° (lit.[112] 93-95°);

mercuric caprylate, m.p. 111-112°;

mercuric laurate, m.p. 121-122° (lit.[150] 100°).

Preparation of thioesters

Thioesters were prepared by the condensation of the appropriate alcohol with the nitrile by the method of Schmidt[66] and purified by chromatography on silica gel. Elution with petroleum spirit gave the thioester, which was purified by crystallisation from methanol, or by fractional distillation under nitrogen to give:

cholestanyl thiophenylacetate, m.p. 105-106°, $[\alpha]_D$ + 31°; λ_{max} 248 and 380 nm (ε 10 200 and 50); n.m.r.δ 7.24 (5H, s; Ar-H), 5.30 (1H, m; 3α-H), 3.94 (2H, s; Ph-CH_2); ν_{max} (cm^{-1}) 1235 (m), 1285 (s), 1185 (m), 1120 (s), 1000 (m); (Found: C,80.4; H, 10.3; S, 6.1. $C_{35}H_{54}OS$ requires C, 80.4; H, 10.4; S, 6.1%).

cholestanyl thiophenylpropionate, m.p. 121-122°, $[\alpha]_D$ + 21°; λ_{max} 247 and 377 nm (ε 9 100 and 26); n.m.r. δ 7.18 (5H, s; Ar-H), 5.30 (1H, m; 3α-H), 2.95 (4H, s; Ar-CH_2 and CH_2-CS-O); ν_{max} (cm^{-1}) 1330 (s), 1300 (s), 1285 (s), 1250 (s), 1235 (s), 1185 (s), 1130 (s), 1075 (s); (Found: C, 80.5; H, 10.5; S, 6.0. $C_{36}H_{56}OS$ requires C, 80.2; H, 10.4; S, 5.8%).

cyclohexyl thiophenylacetate, b.p. 120-121°/1 mm; λ_{max} 249 and 381 nm (ε 10 700 and 50); n.m.r. δ 7.22 (5H, s; Ar-H), 5.34 (1H, m; 3α-H), 3.98 (2H, s; Ar-CH_2); ν_{max} (cm^{-1}) 2940 (s), 2860 (s), 1455 (s), 1305 (s), 1205 (s), 1190 (s), 1015 (s), 735 (s); (Found: C, 72.1; H, 8.0; S, 13.4. $C_{14}H_{18}OS$ requires C, 71.8; H, 7.7; S,13.7%).

n-butyl thiophenylacetate, b.p. 108-110° (lit.[151] 155-160°/36 mm); λ_{max} 242 and 378 nm (ε 14 000 and 45); n.m.r. δ 7.28 (5H, s; Ar-H), 4.43 (2H, t; J 6.3 Hz; -O-CH_2-CH_2), 4.04 (2H, s; Ar-CH_2-CS-O);

ν_{max} (cm^{-1}) 2960 (s), 2930 (s), 1310 (s), 1250 (s), 1200 (s), 1190 (s), 1195 (s), 700 (s); (Found : C, 69.6; H, 7.7; S, 15.7. $C_{12}H_{16}OS$ requires C, 69.2; H, 7.7; S, 15.4%).

ethyl thiophenylacetate, b.p. 80-82°/1 mm (lit.[64] 133°/22 mm; ν_{max} (cm^{-1}) 1205 (s), 1190 (s), 1095 (s), 865 (m), 810 (w).

methyl thioacetate, b.p. 80-90° (lit.[76] 89°).

The known thioester, cholestanyl thiobenzoate, was prepared by condensation of cholestanol with thiobenzoylthioglycollic acid as described in the literature.[55] The thiobenzoylthioglycollic acid required was prepared by condensing benzaldehyde, sulphur and piperidine to give thiobenzomorpholide, which was treated with bromoacetic acid, followed by hydrogen sulphide. This preparation is a slight modification of the method described in the literature.[74,86] Treatment of cholestanol with sodium hydride, followed by thiobenzoylthioglycollic acid gave: cholestanyl thiobenzoate, m.p. 140-141° (lit.[55] 141-142°); n.m.r. δ 8.20 (2H, m; o-Ar-H); 7.35 (3H, m; m, p-Ar-H); 5.60 (1H, m; 3α-H).

The known thioester, phenyl thiobenzoate, was prepared by the method of Araki[70] to give yellow-orange needles, m.p. 39-40° (lit.[70] 40.0-40.5°). The preparation of the thiobenzoyl chloride required is described below.

Thiobenzoyl chloride was prepared according to the method of Staudinger.[152] Thus magnesium turnings (12 g) were placed in a 1 litre round-bottom flask containing 200 ml sodium-dried ether. A few small crystals of iodine were added, followed by a few drops of bromobenzene. The mixture was reluxed for $2\frac{1}{2}$ hours. After this time, a vigorous reaction ensued. Bromobenzene (80 g) was added slowly, the reaction being kept under control in a chilled water bath. When reaction was complete, the mixture was refluxed gently for 30 minutes. The mixture was then cooled, chilled and carbon disulphide (38.7 g) added all at once. The reaction mixture was left standing for 24 hours. A red precipitate formed and gentle shaking induced further precipitation. The mixture was left in the freezer for a further 12 hours. Chilled 2.5 M hydrochloric acid (150 ml) was added to the cooled mixture. The ether layer was washed twice with distilled water and dried over magnesium sulphate. Thionyl chloride (100 ml) was added and the mixture refluxed for $2\frac{1}{2}$ hours. Excess thionyl chloride was

removed and ether removed by distillation under reduced pressure.

Thiobenzoyl chloride was obtained as a deep purple oil, which was purified by vacuum distillation under nitrogen: b.p. 104-109°/1.5 mm (lit.[71] 53-55°/0.2 mm). This compound needs to be distilled as quickly as possible at the lowest possible temperature, otherwise it polymerises. Characteristic absorption in i.r. (cm^{-1}): 3003 (w), 1580 (w) 1460 (m), 1445 (s), 1245 (s), 1180 (m), 1050 (s), 845 (m), 765 (m), 740 (s), 700 (s).

Preparation of reference esters

Reference esters were prepared as follows: phenylacetyl chloride, b.p. 71-73°/1.8 mm, was prepared by the method of Fieser and Fieser[153] and reacted with the appropriate alcohol. The ester was purified by crystallisation from methanol, or fractional distillation, to give: cholestanyl phenylacetate, m.p. 91-92°; $[\alpha]_D$ + 20°; λ_{max} 283, 267, 263, 257, 252 and 247 nm (ε 445, 467, 538, 549, 511 and 489); n.m.r. δ 7.25 (5H, s; Ar-H), 4.67 (1H, m; 3α-H), 3.55 (2H, s; Ar-$C\underline{H}_2$); ν_{max} (cm^{-1}) 1720 (s), 1340 (s) 1250 (s), 1115 (s), 730 (s); (Found: C, 83.0; H, 10.7. $C_{35}H_{54}O_2$ requires C, 83.0; H, 10.7%).

cyclohexyl phenylacetate, b.p. 132-134°/2.5 mm (lit.[154] 180.5/2.5 mm).

n-butyl phenylacetate, b.p. 101-103°/1.7 mm (lit.[96] 256°/760 mm).

ethyl phenylacetate, b.p. 88-92°/3.5 mm (lit.[96] 228°/760 mm)

Cholestanyl phenylpropionate and cholestanyl benzoate were prepared by dissolving the thioester (200 mg) in acetic acid and warming for 15 minutes with 1.1 molar equivalents of mercuric acetate. The mixture was diluted with aqueous sodium sulphide and extracted with chloroform. The chloroform extract was washed with aqueous sodium hydrogen carbonate, water and dried. Methanol was added and the chloroform removed by distillation. Suspended sulphur was removed by filtration of the hot methanol solution, which on cooling deposited the ester:

cholestanyl phenylpropionate, m.p. 92-93°, $[\alpha]_D$ + 30°; λ_{max} 266, 263, 260, 257, 254 and 280 nm (ε 67, 71, 72, 72, 62 and 51); n.m.r. δ 7.24 (5H, s; Ar-H), 4.68 (1H, m; 3α-H), 2.92 (2H, t; J 6.0 Hz; Ar-CH_2), 2.52 (2H, t; J 6.0 Hz; -CH_2-CO); ν_{max} (cm^{-1}) 1725 (s), 1180 (s), 1290 (s), 1135 (m), 1000 (m), 755 (m); (Found: C, 82.6; H, 10.7. $C_{36}H_{56}O_2$ requires C, 83.0; H, 10.8%).

cholestanyl benzoate, m.p. 130-131° (lit.[155] 136-137°), $[\alpha]_D$ + 21°; λ_{max} 278, 272, 265 and 234 (ε 880, 1 020, 820 and 10 340); n.m.r. δ 7.98 (2H, m; O-Ar-H), 7.35 (3H, m; m, p-Ar-H), 4.86 (1H, m; 3α-H); ν_{max} (cm^{-1}) 1710 (s), 1270 (s), 1110 (s).

Phenyl benzoate was prepared by the reaction of phenol and benzoyl chloride. The ester had m.p. 66-68° (lit.[96] 69°).

Desulphurisation of thioesters by mercuric carboxylates

A solution of the mercury salt (0.5 mmol) in the appropriate solvent was treated with a solution of the thioester (0.5 mmol) and the mixture stirred for 5 minutes. Black mercuric sulphide formed within minutes. Unchanged mercury salt was destroyed by passing hydrogen sulphide through the solution. The solution was filtered through silica gel (< 0.08 mm, Merck) and excess solvent removed by distillation through a short fractionating column. The organic mixture was examined by g.l.c.

For each experiment, calibration curves were drawn, relating peak area of recorder to the mass of organic compound being examined. To enable absolute yields to be determined (Table 1, page 38), an internal standard was added in each desulphurisation reaztion. In each case, it was chosen so as to be well separated from solvent, ester and anhydride. In the case of the mercuric laurate desulphurisation of cyclohexyl thioacetate, the lauric anhydride was converted to methyl laurate with methanol, since lauric anhydride had an unmanageably long retention time.

SYNTHESIS OF MIXED ANHYDRIDES

(a) acetic valeric anhydride

A mixture of acetyl chloride (1 ml) and valeric acid (1.5 ml) in pyridine was stirred for 10 minutes in benzene. The mixture was filtered and examined by g.l.c. No mixed anhydride was detected.

(b) acetic butyric anhydride

Butyryl chloride (10.3 g) was added slowly to a mixture of sodium acetate (8.0 g) in ether. The mixture was warmed gently for 2 hours, and then filtered. One half was placed in the freezer for analysis, the other half was distilled. Four fractions were collected: 40-44°/5 mm, 44-47°/5 mm, 47-54°/5 mm, 54-65°/5 mm. G.l.c. analysis of the mixture before and after distillation showed no mixed anhydride, even when the injection block temperature was lowered to 100°.

(c) acetic propionic anhydride

Sodium acetate (4.0 g) was made into a paste with 10 ml ether, and propionyl chloride (4.0 g) added slowly to the cooled flask. The mixture was refluxed for 2 hours on a water bath, filtered and distilled at atmospheric pressure, as was done by Polya and Spotswood.[109] Three fractions were collected: at 140° (shown to be propionic acid), at 152-3°, and at 152-8°. The latter two fractions contained

propionic acid and propionic anhydride (shown by peak enhancement), but no mixed anhydride.

(d) acetic propionic anhydride

Acetyl chloride (3 ml) in ether was added slowly to sodium propionate (4.0 g) in ether in a cooled flask. The mixture was quickly filtered, and a sample analysed by g.l.c. No mixed anhydride was observed, even when the injection block temperature was lowered to 100°.

(e) pivalic caprylic anhydride

Thallium pivalate was prepared from thallium (I) ethoxide and pivalic acid by the method of Taylor.[100] To a suspension of thallium pivalate (350 mg) in ether (20 ml) was added a solution of caproyl chloride (160 mg) in ether (5 ml). The mixture was stirred for 1 hour, then filtered through silica gel.

(f) pivalic lauric anhydride

The method described above was used to prepare pivalic lauric anhydride from thallium pivalate (300 mg) and lauroyl chloride (190 mg).

N.m.r. spectra of this mixed anhydride and the two corresponding symmetrical anhydrides were recorded: pivalic lauric anhydride, δ 0.87 (3H, t; $C\underline{H}_3$-CH_2), 1.23 (9H, s; $C\underline{H}_3$-C), 1.27 (18H, s; 9x$C\underline{H}_2$), 2.38 (2H, t; CO-$C\underline{H}_2$).

pivalic anhydride, δ 1.23 (18H, s; $C\underline{H}_3$-C).

lauric anhydride, δ 0.89 (6H, t; $C\underline{H}_3$-CH_2), 1.28 (36H, s; 18 x $C\underline{H}_2$), 2.39 (4H, t; CO-$C\underline{H}_2$).

DESULPHURISATION BY ACTIVE W-2 RANEY NICKEL

Active Raney nickel (W-2) was prepared from Raney's alloy (nickel-aluminium 50-50, Hopkin and Williams) according to the method of Mozingo.[121] One-fifth of the quantities listed in Mozingo's paper were used. The catalyst was stored in a stoppered flask under absolute ethanol.

(a) Desulphurisation of cholestanyl thiophenylpropionate

Cholestanyl thiophenylpropionate (160 mg) was dissolved in benzene and excess active Raney nickel (8 days old) in absolute ethanol was added. The mixture was refluxed for 1 hour, cooled, the catalyst filtered off and excess solvent removed on the rotary evaporator.

The solid residue was dissolved in petroleum spirit and chromatographed on a column of alumina (7 g). The column was eluted with 20 ml portions of petroleum spirit, each portion containing an increasing amount of benzene (in 10% steps). 39 x 10 ml fractions were collected and examined by t.l.c. (benzene as developing solvent). Three compounds were isolated: starting material (2%), cholestanol (21%) and a saturated ether, which could not be purified by crystallisation from any solvent. A dichloromethane solution was allowed to evaporate to give a which solid (dried at 60° in vacuo for 5 hours):

3β-(3'-phenylpropoxy)-cholestane, m.p. 62-64°, $[\alpha]_D$ + 15°; λ_{max} 268, 264, 261, 259, 255, 252 and 247 nm (ε 390, 380, 410, 410, 380, 380 and 370); n.m.r. δ 7.22 (5H, s; Ar-H), 3.48 (2H, t; J 6.0 Hz; $-C\underline{H}_2-O$), 3.18 (1H, m; 3α-H), 2.72 (2H, m; $Ar-C\underline{H}_2$); $\nu_{max}(cm^{-1})$ 3015 (m), 1130 (m), 1110 (s), 750 (s); (Found: C, 85.1; H, 11.8. $C_{36}H_{58}O$ requires C, 85.3; H, 11.5%).

(b) Desulphurisation of cholestanyl thiophenylacetate

Cholestanyl thiophenylacetate (103 mg) in dichloromethane was refluxed with active Raney nickel (1 day old). The mixture was worked up as described for the previous experiment. 15 x 10 ml fractions were collected and two compounds isolated: cholestanol (28%) and an ether (72%). A dichloromethane solution of the ether was allowed to evaporate, as it could not be crystallised. A white solid remained:

3β-(2'phenylethoxy)-cholestane, m.p. 78.5-79°, $[\alpha]_D$ + 11°; λ_{max} 267, 264, 260, 258, 254, 253 and 247 (ε 290, 330, 350, 370, 300, 300 and 200); n.m.r. δ 7.23 (5H, s; Ar-H), 3.62 (2H, t; J 7.5 Hz; $-C\underline{H}_2-O$), 3.20 (1H, m; 3α-H), 2.85 (2H, t; $Ar-C\underline{H}_2$); ν_{max} (cm^{-1}) 3015 (m), 1130 (m), 1105 (m), 750 (s); (Found: C, 85.6; H, 11.7. $C_{35}H_{56}O$ requires C, 85.3; H, 11.5%).

(c) Desulphurisation of cholestanyl thiobenzoate

A sample of cholestany thiobenzoate (~2 mg) was refluxed with active Raney nickel for 1 hour. Intensity of spots on t.l.c. indicated 75% conversion to cholestanol.

(d) Desulphurisation of phenyl thiobenzoate

Phenyl thiobenzoate (40 mg) was refluxed with active Raney nickel for $1\frac{1}{2}$ hours. After this time, phenol (19 mg, 68%) only was isolated.

DESULPHURISATION BY DEACTIVATED RANEY NICKEL

Active Raney nickel W-2 (10 g) prepared by Mozingo's method[121] was refluxed in acetone for 3 hours to deactivate it. Water was removed by azeotropic distillation with benzene. The deactivated catalyst was stored under benzene.

Cholestanyl thiophenylpropionate (150 mg) was refluxed with deactivated Raney nickel under a nitrogen atmosphere for 24 hours. The reaction was followed by t.l.c. The products (cholestanone, cholestanyl propionate, cholestanol, cholestene) were isolated on a column of silica gel (0.05-0.2 mm, Merck), with a mixture of petroleum spirit and benzene (10:1) as eluting solvent. The compounds were identified by comparison with authentic specimens (t.l.c. and i.r. spectra).

Cholestanyl thiobenzoate (~10 mg) was refluxed with deactivated Raney nickel for 4 hours and the products (cholestanol, cholestanyl benzoate, and cholestene) identified by comparison of R_f with authentic specimens in a variety of solvents.

The three thiophenylacetates (cholestanyl, cyclohexyl and n-butyl) were refluxed in benzene with deactivated Raney nickel W-2 until only 5-10% of the thioester was unchanged, as shown by t.l.c. or g.l.c. Cyclohexyl and n-butyl 2'-phenylethenyl ethers were examined by g.l.c./m.s. The enol ethers were treated with phosphorus trichloride/tetradeuteromethanol; the mass spectrum of the phenylacetaldehyde dimethylacetal was recorded and compared with the reported mass spectrum of unlabelled phenylacetaldehyde dimethylacetal.

SPECTRAL STUDIES OF THIOESTERS

The n.m.r. spectrum of cholestanyl thioacetate has been reported.[94] For comparison, 3β-ethoxycholestane was prepared.

Cholestanol (40 mg) was treated with sodium hydride (1 equivalent) in warm diglyme. A slight excess of ethyl iodide was added, and allowed to stand. Chromatography on a column of alumina with petrol spirit with 10% ether) as eluting solvent gave:

3β-ethoxycholestane, m.p. 79-81° (lit.[156] m.p. 80-81°); n.m.r. δ 3.50 (2H, q; J 7.0 Hz; CH_3-$C\underline{H}_2$), 3.19 (1H, m; 3α-H), 1.18 (3H, t; $C\underline{H}_3$-CH_2).

3β-acetoxycholestane (authentic specimen), n.m.r. δ 4.70 (1H, m; 3αH), 2.02 (3H, s; $C\underline{H}_3$-CO).

Mass spectra of thioesters and corresponding esters are recorded below (ions at m/e values with intensities in brackets).

Butyl thiophenylacetate.-208 (4), 153 (14), 152 (52), 135 (27), 119 (91), 92 (86), 91 (100).

Butyl phenylacetate.- 192 (4), 137 (18), 136 (61), 119 (14), 92 (93), 91 (100).

Cholestanyl thiophenylacetate.- 215 (3), 161 (7), 152 (3), 147 (10), 135 (9), 119 (25), 107 (24), 105 (20), 92 (26), 91 (100).

Cholestanyl phenylacetate.- 388 (3), 374 (2), 355 (1), 331 (1), 262 (3), 234 (27), 233 (39), 215 (60), 201 (10), 165 (54), 147 (42), 137 (17), 123 (49), 121 (67), 119 (38), 108 (99), 107 (100), 92 (23), 91 (84).

Cholestanyl thiophenylpropionate.- 370 (2), 355 (1), 316 (2), 301 (1), 257 (3), 215 (13), 147 (21), 133 (31), 106 (96), 105 (100).

Cholestanyl phenylpropionate.- 371 (3), 370 (3), 355 (3), 316 (4), 301 (2), 257 (7), 215 (42), 161 (28), 150 (70), 121 (53), 107 (100), 105 (98), 104 (99).

Cyclohexyl thiophenylacetate.-234 (1), 174 (1), 153 (43), 152 (24), 135 (8), 119 (28), 92 (98), 91 (90), 67 (100), 65 (49).

Cyclohexyl phenylacetate. - 218 (1), 137 (23), 119 (2), 118 (2), 92 (59), 91 (100), 83 (98).

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