

THESIS

submitted to

GLASGOW UNIVERSITY

in fulfilment of the requirements

for the Degree of

DOCTOR OF PHILOSOPHY

by

DEREK J. DIJKSMAN

September, 1951.

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ACKNOWLEDGEMENTS

The author wishes to express his sincere thanks to Professor F. S. Spring for his supervision and interest. Thanks are also due to Dr. G. T. Newbold for his unremitting guidance in many theoretical and practical aspects of this work.

The author thanks Messrs. T. and H. Smith, Ltd., Edinburgh, for generous gifts of narcotine and opianic acid.

PART I

THE USE OF RHODANINE IN ORGANIC SYNTHESIS

1:2-Dihydro-1-keto-2-thianaphthalenes

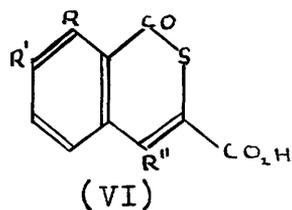
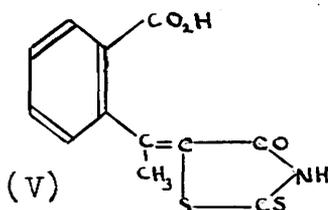
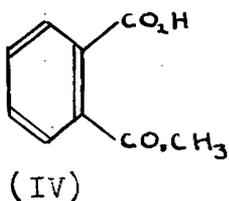
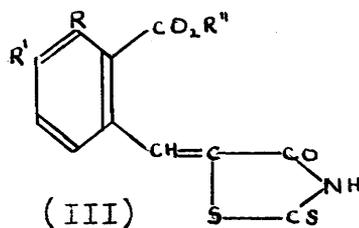
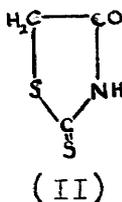
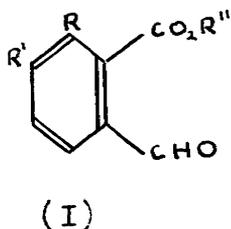
SUMMARY. PART I.

The work described in Part I of this thesis resulted from some exploratory studies leading towards the synthesis of morphine.

The condensation of rhodanine with aromatic o-carboxyaldehydes and with an o-carboxy-ketone has been studied. α -Methyl opianate (I; R = R' = OMe, R'' = Me) was condensed with rhodanine (II) to give 5-(2'-carbomethoxy-3':4'-dimethoxybenzylidene)-rhodanine (III; R = R' = OMe, R'' = Me). Similarly α -methyl phthalaldehyde (I; R = R' = H, R'' = Me) and phthalaldehydic acid (I; R = R' = R'' = H) condensed with rhodanine to give o-carbomethoxy- (III; R = R' = H, R'' = Me) and o-carboxybenzylidenerhodanine (III; R = R' = R'' = H) respectively. o-Carboxyacetophenone (IV) on condensation with (II) gave o-carboxy- α -methylrhodanine (V). o-Carboxybenzylidenerhodanines titrated as dibasic acids to phenolphthalein. It has been shown that the imino-group of the rhodanine ring is responsible for the second acidic function.

Treatment of o-carboxybenzylidenerhodanines with sodium hydroxide gave 1:2-dihydro-1-keto-2-thianaphthalene-3-carboxylic acids (VI). Thus (III; R = R' = OMe, R'' = Me) gave 1:2-dihydro-1-keto-7:8-dimethoxy-2-thianaphthalene-3-carboxylic acid (VI, R = R' = OMe, R'' = H).

Both o-carboxy and o-carbomethoxybenzylidenerhodanine on treatment with alkali gave (VI; R = R' = R'' = H); similar treatment of (IV) gave 1:2-dihydro-1-keto-4-methyl-2-thianaphthalene-3-carboxylic acid (VI; R = R' = H, R'' = Me).



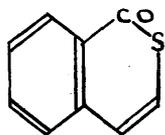
The thianaphthalene acids could be decarboxylated to give 1:2-dihydro-1-keto-2-thianaphthalenes (VII). The sulphur atom in these thianaphthalenes was readily eliminated by ammonia and primary amines with the formation of 1:2-dihydro-1-ketoisoquinoline derivatives (VIII). Thus (VI; R = R' = R'' = H) on heating with methylamine gave 1:2-dihydro-1-ketoisoquinoline-3-carboxylic acid (VIII; R = R' = H, R'' = Me).

Treatment of 7:8-dimethoxy-, 4-methyl-, and unsubstituted 1:2-dihydro-1-keto-2-thianaphthalene-3-carboxylic acid with Raney nickel gave respectively 6:7-dimethoxyindan-

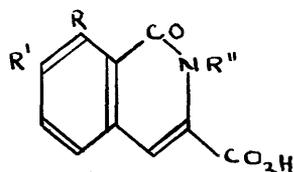
1-one (IX; $R = R' = \text{OMe}$, $R'' = \text{H}$), 3-methylindan-1-one (IX; $R = R' = \text{H}$, $R'' = \text{Me}$), and indan-1-one (IX; $R = R' = R'' = \text{H}$). The latter compound was also obtained by the action of Raney nickel on 1:2-dihydro-1-keto-2-thianaphthalene.

Treatment of 5-benzylidenerhodanine with Raney nickel gave (a) an unidentified product m.p. 189° , (b) N-methyl-hydrocinnamamide, and (c) hydrocinnamamide. 5-Benzylidene-3-methylrhodanine on similar treatment gave a mixture of N-methyl-, and N-dimethylhydrocinnamide. The product obtained from the action of Raney nickel on 5-benzylidenerhodanine benzoate was not identified.

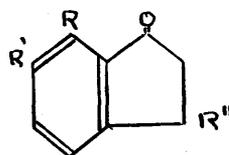
An attempt to prepare substituted benzthiophenes by the alkaline hydrolysis of o-bromobenzylidenerhodanines was unsuccessful.



(VII)



(VIII)



(IX)

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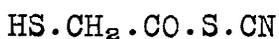
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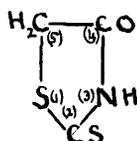
THE USE OF RHODANINE IN ORGANIC SYNTHESIS

INTRODUCTION

Rhodanine was first prepared by Nencki (1) in 1877 by the condensation of monochloroacetic acid with ammonium thiocyanate. Because of its strongly acidic character and his belief that his bright yellow product contained a thiocyanate grouping, Nencki named it rhodanic acid, and represented it as an open-chain compound (I). Shortly afterwards, Lieberman and Lange (2) on consideration of its mode of formation, its degradation products on hydrolysis, and its similarity to thiohydantoin showed that it is a five membered heterocyclic compound 4-keto-2-thioketothiazolidene (II).

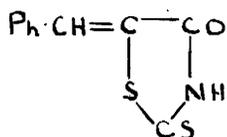


(I)

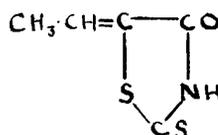


(II)

Nencki and Bourquin (3) showed that the reactive methylene group in rhodanine readily condensed with benzaldehyde and acetaldehyde on warming the components with concentrated sulphuric acid in ethanol, giving, respectively, 5-benzylidene- (III) and 5-ethylidene-rhodanine (IV).



(III)



(IV)

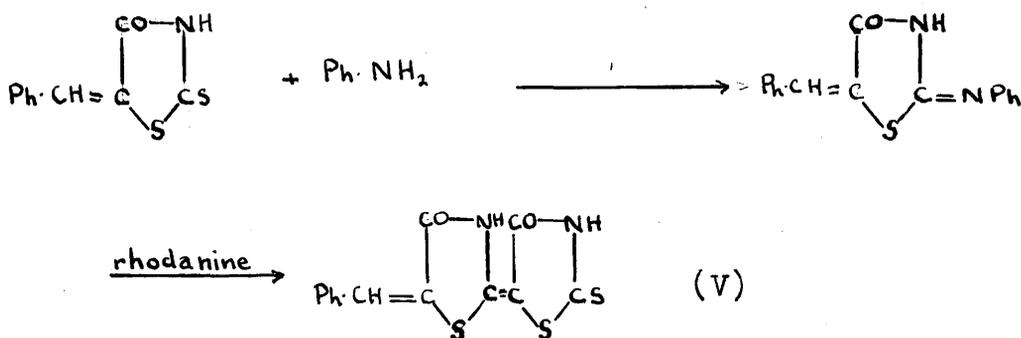
Nencki and Bourquin also found that these yellow condensation products of rhodanine dyed silk, wool and skin, and in general acted as vat dyestuffs. Although the colours obtained were not attractive, the possibility of obtaining a commercially valuable vat dyestuff, together with the facility of condensation, caused many chemists (4-14) to examine these rhodanine condensation products. While no success was forthcoming in the dyestuffs field, the interest in 5-substituted rhodanines has been maintained until today, when these products are being widely examined for their suitability as sensitizers in photographic emulsions and as fungicides. The result of this work has been that many new preparations for rhodanine have been published (15-20), of which the most important is the method proposed by Gränacher (21) and modified by Julian and Sturgis (22). Considerable work has also been carried out on the chemistry of the condensation products of aldehydes with N-alkyl and N-aryl homologues of rhodanine.

The Use of Rhodanine in Organic Syntheses.

(a) Condensation with Aldehydes.

Gränacher (13) showed that the alkylidenerhodanines react with aniline and phenyl-hydrazine to yield the corresponding anilides and phenylhydrazones, the sulphur of the thioketo group being eliminated as hydrogen

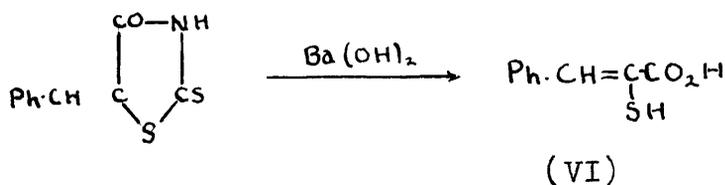
sulphide. As aniline is comparatively easily removed from these anilides, they can be used for condensing the rhodanine molecule with compounds containing a reactive methylene group. In this way Gränacher was able to condense 5-benzylidenerhodanine with a second molecule of rhodanine to obtain 5-benzylidene-5'-rhodanylidene-2-rhodanine (V).



With rhodanines containing the free methylene group, such as N-phenylrhodanine, reaction with aniline or phenylhydrazine proceeds in a totally different manner. In this case the sulphur of the thioketo group remains unaffected, and complete fission of the rhodanine ring occurs with formation of thiocarbamides or thiosemicarbazides. This reaction occurs so readily that it is a convenient method for the preparation of the latter class of substances.



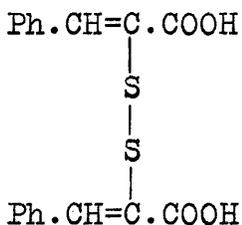
The rhodanine ring, in the intensely coloured condensation products with aldehydes, is very labile and in particular the ring system is readily decomposed by alkalis. Bondzinski (23) showed that the condensation product of benzaldehyde and rhodanine, on heating with aqueous barium hydroxide, can be almost quantitatively converted into α -thiolcinnamic acid (VI).



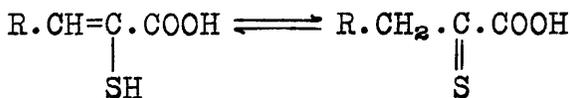
This result caused Gränacher (21) to investigate systematically the decomposition products of 5-substituted rhodanines. He showed that these decomposition products could be used as starting material for the relatively simple synthesis of several groups of compounds which were only obtainable with great difficulty by alternative routes. Gränacher and his co-workers found that the rhodanine ring could also be split by sodium amylate in amyl alcohol to give the same α -thiolacrylic acids. In certain cases, however, where the condensation product contained a free nitro or amino group, ring opening took place but at the same time secondary reactions occurred and no product could be isolated. Gränacher found that the simplest and best way of ring opening was the treatment of the condensation

products with either barium or sodium hydroxide.

Ginsberg and Bondzinski (24) had considered that the hydrolysis product of 5-benzylidenerhodanine was α -thiolcinnamic acid (VI) as it gave a deep green colour with ferric chloride (a reaction typical for the thiol group), and could be oxidised to a disulphide derivative of cinnamic acid (VII). Gränacher, however, came to the conclusion that the products did not possess the rigid formula of an α -thiol acid, but that they reacted tautomerically and showed the same reactions as if they were α -thioketocarboxylic acids (VIII).



(VII)

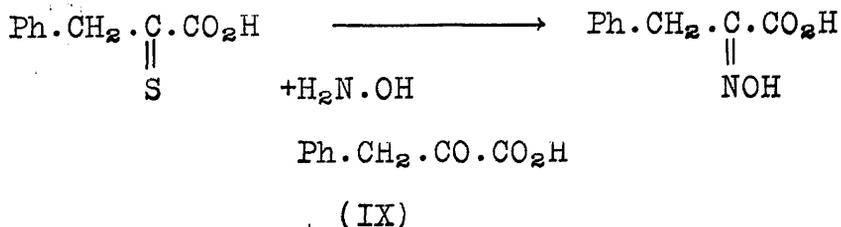


(VIII)

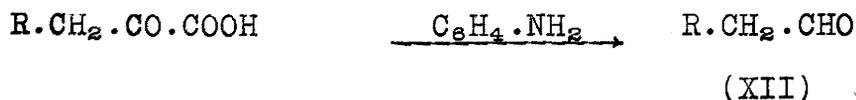
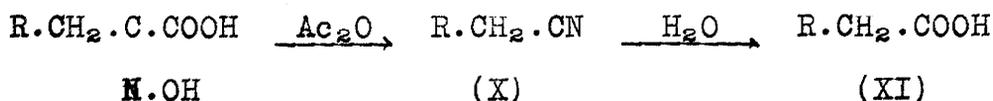
The hydrolysis products, in the thio keto form, readily react with nitrogenous bases with the elimination of the sulphur as hydrogen sulphide. Thus phenylthio-pyruvic acid on treatment with hydroxylamine, hydrazine, aniline and ammonia gives the corresponding derivatives of phenylpyruvic acid and this acid itself (IX).

Kitamura (25) has also shown that the alkylidene- and arylidenerhodanines can be hydrolysed in one step, with hydrogen peroxide, to substituted pyruvic acids. The oximes on treatment with formaldehyde and hydrochloric

acid (26) are converted into substituted pyruvic acids.

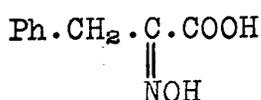


Since the α -keto oximes readily lose water and carbon dioxide, on heating in acetic anhydride, a synthetic method for the preparation of nitriles (X) possessing one carbon atom more than the starting aldehyde has been advanced by Gränacher (21). Hydrolysis of the nitriles with alkali gives an acid (XI) containing one carbon atom more than the starting material (22). Decarboxylation of the substituted pyruvic acids by warming with aniline (27) yields the homologous aldehydes (XII).

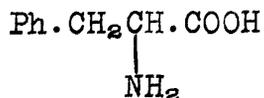
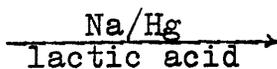


Alternatively, the α -keto acid oximes can be reduced, in weak acid solution, to the corresponding α -amino carboxylic acids possessing two carbon atoms more than the starting aldehydes. Thus phenylalanine (XIII) can be prepared from benzaldehyde through phenylpyruvic acid oxime (XIV) (21), and furfurylalanine (XV) can be

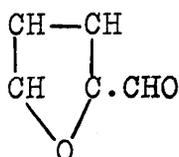
prepared from furfural (XVI) (22).



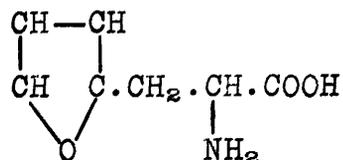
(XIV)



(XIII)



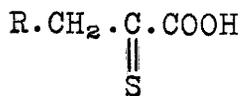
(XVI)



(XV)

This method is of considerable use in the synthesis of acid sensitive amino acids, as the whole synthesis can be carried out in the absence of mineral acids, the reduction being effected by sodium amalgam in lactic acid solution.

Reduction of the thiopyruvic (VIII) acids by Clemensen's method with zinc amalgam and hydrochloric acid (28) completely eliminates the sulphur atom and substituted propionic acids (XVII) containing two carbon atoms more than the starting material are obtained.



(VIII)

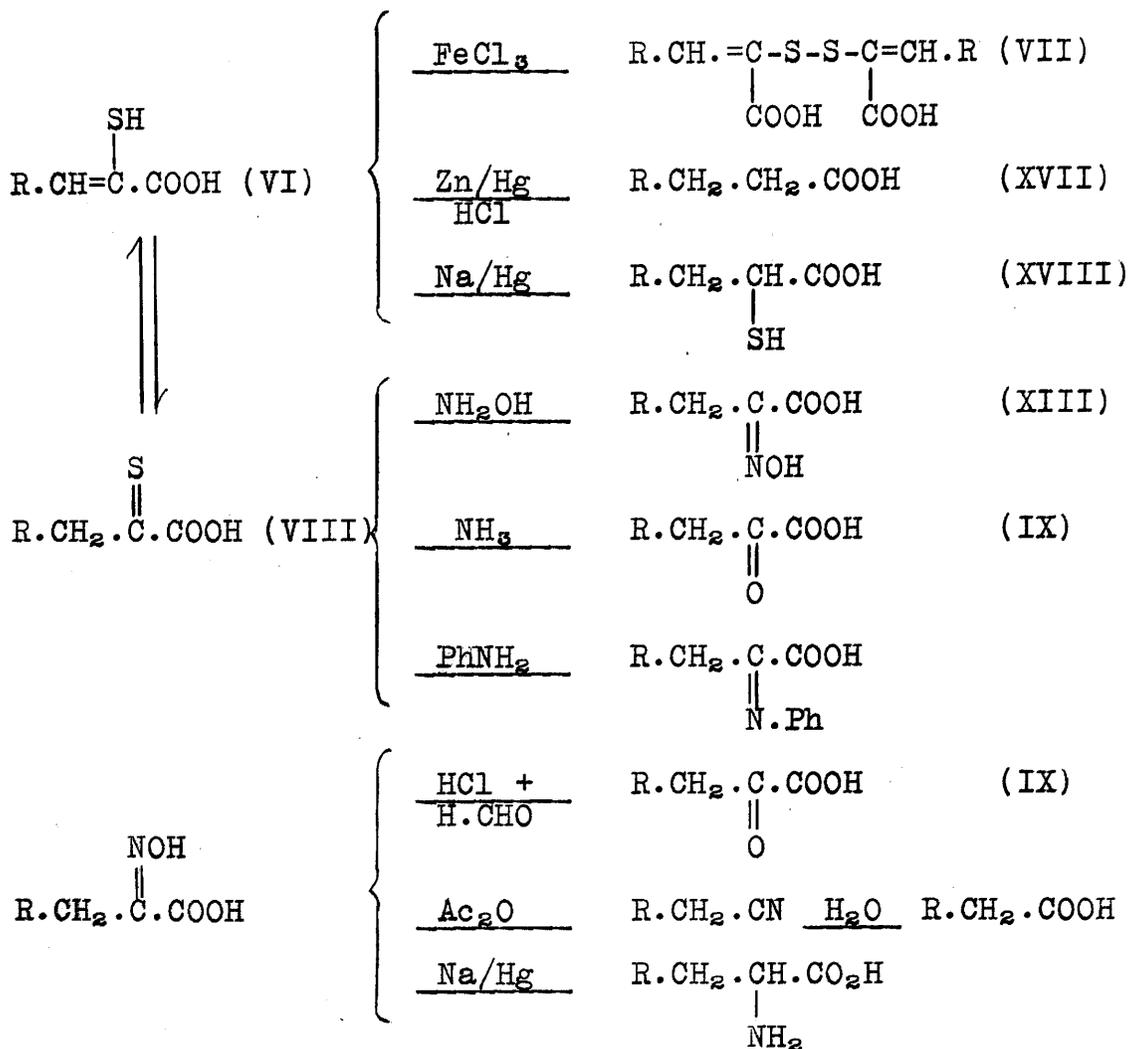


(XVII)

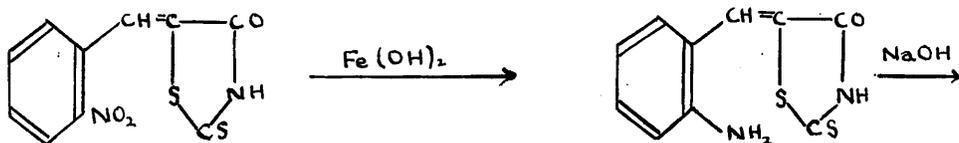
Reduction of the α -thiolacrylic acids with sodium amalgam in alkaline solution yields derivatives of β -substituted α -thiolpropionic acid (XVIII) (cf. Table I).

Syntheses derived from α -thiolacrylic acids and the tautomeric thiopyruvic acids are summarised in Table I.

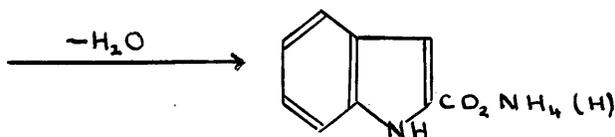
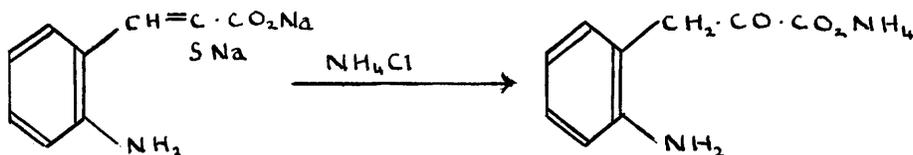
Table I



In a further communication Gränacher, Mahal and Gero (29) showed that by reducing *o*-nitrobenzylidenerhodanine (XIX) with alkaline ferrous hydroxide in the presence of ammonium chloride, simultaneous cyclisation and dehydration take place with the formation in high yield of indole-2-carboxylic acid (XX).

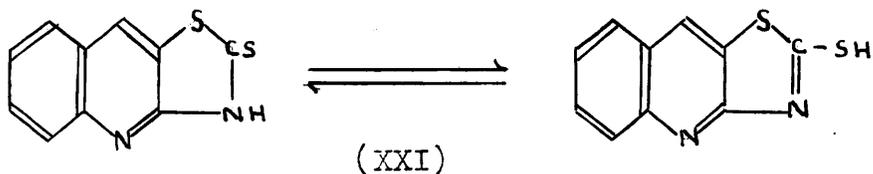


(XI)



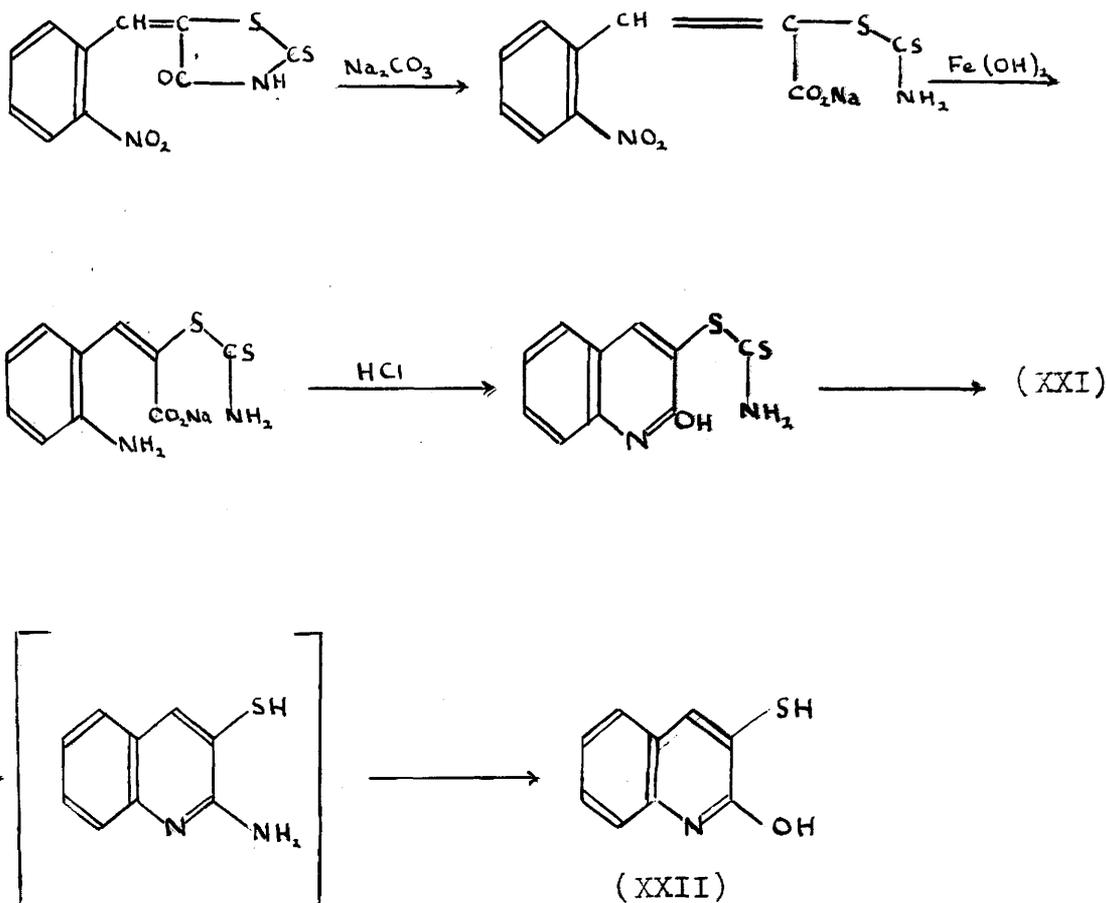
(XX)

Gränacher, Ofner and Kloppenstein (30) isolated, as a by-product in the above reaction, a compound containing a new heterocyclic ring system which they termed quinrhodine (XXI).



They found that quinrhodine could not be obtained, as appeared likely, by the internal condensation of *o*-aminobenzylidene-rhodanine, but owed its formation to the opening of the rhodanine ring by alkali when, after

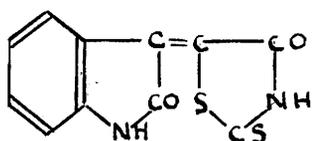
reduction of the nitro group to amino, the quinoline ring closes first followed by the closure of the rhodanine ring. Thus the best method of preparation consisted in partially hydrolysing the *o*-nitrobenzylidene-rhodanine with sodium carbonate, reducing with ferrous hydroxide and subsequently acidifying. *N*-substituted quinrhodines are obtained from the condensation products of *o*-nitrobenzaldehyde with *N*-substituted rhodanines. Fusion of quinrhodine with sodium hydroxide results in the formation of 2-hydroxy-3-thiolquinoline (XXII).



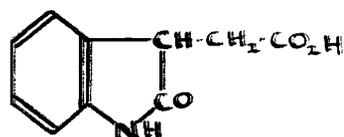
(b) Condensations with Ketones.

Although rhodanine condenses readily with aldehydes its reaction with ketones received little attention from the earlier workers in this field. Butscher (12), in 1911, had shown that rhodanine condensed with α - β -diketones, and other workers had reported rhodanine derivatives of these compounds (14,31,32).

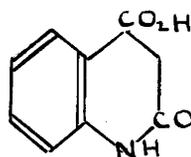
In 1923, Gränacher and Mahal (33) obtained 5-(2'-oxindolidene)-rhodanine (XXIII) by the condensation of isatin with rhodanine. 5-(2'-Oxindolidene)-rhodanine on hydrolysis and reduction gave a product which Gränacher and Mahal described as 2-oxindole acetic acid (XXIV), but which has been shown by Hill, Schultz and Lindwall (34) to be 2-keto-1:2:3:4-tetrahydroquinoline-4-carboxylic acid (XXV).



(XXIII)



(XXIV)

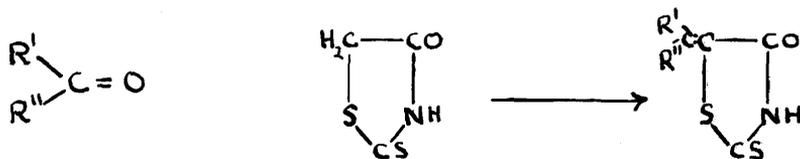


(XXV)

The synthesis of rhodanine oxindoles has also been studied by Andreasch (10) and Jones and Henze (32), while the condensation of rhodanine and N-substituted rhodanines

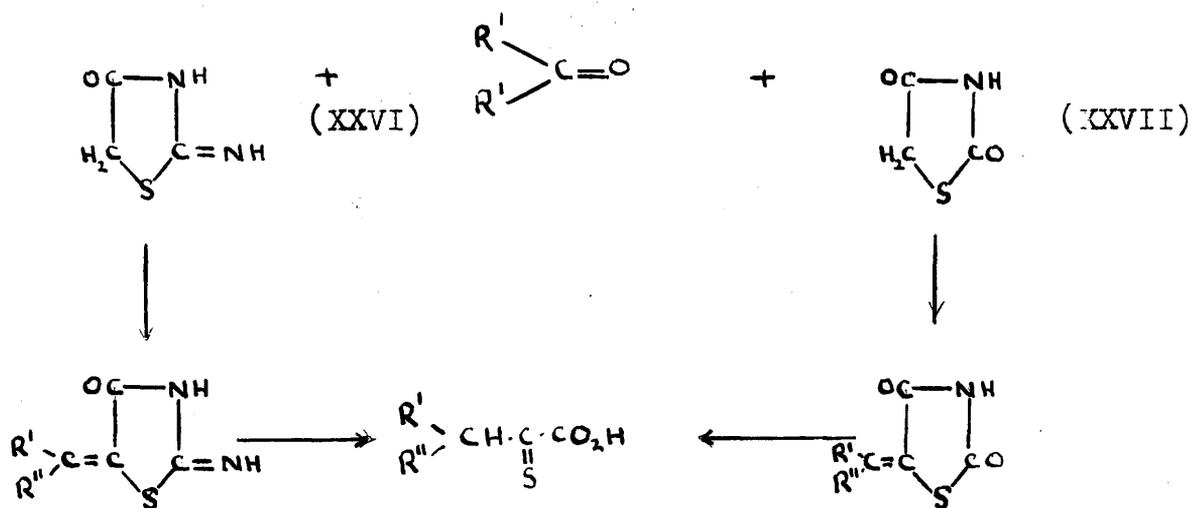
with isatin and nitroisatin has been examined by Hann (35) and by Jones and Hann (33).

Although Feigl (36) and Schwartz (37) stated that rhodanine could condense with simple ketones neither author gave any physical properties or analyses for their products. Brown, Bradsher, McCallum and Potter (38), however, in a recent communication have reported the successful condensation of a large variety of ketones with rhodanine using the method of Girard (39), in which condensation takes place in an ammonium hydroxide-ethanol medium containing ammonium chloride.



Condensation of Aldehydes with pseudoThiohydantoin.

This report would not be complete without mention of the work of Liebermann, Himbert and Hengl (40) on the condensation of aldehydes and ketones with 2-amino-4-keto-thiazolidene (pseudothiohydantoin) (XXVI) and with 2:4-diketothiazolidene (XXVII). The condensation products on hydrolysis with sodium hydroxide yield the same substituted thiopyruvic acids obtained by hydrolysis of the corresponding rhodanines.



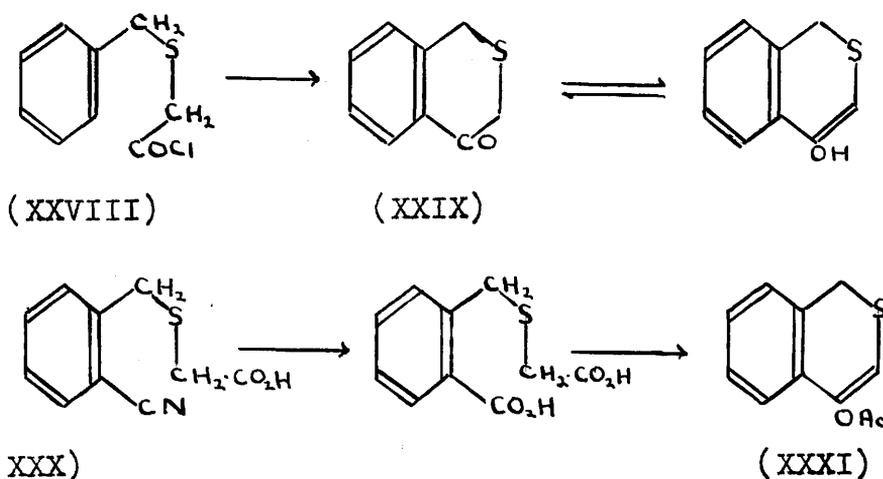
Liebermann et al. claim that the above method is more suitable for the large scale preparation of substituted thiopyruvic acids as it uses more readily available starting materials.

2-Thianaphthalenes.

The preparation and chemistry of 2-thianaphthalenes has received little attention in the past. Lesser and Mehrländer (41) synthesised 1:2-dihydro-4-keto-2-thianaphthalene (XXIX) by the internal condensation of benzylthioacetyl chloride (XXVIII) (from the condensation of benzyl mercaptan with monochloroacetic acid) with aluminium chloride in the presence of nitrobenzene.

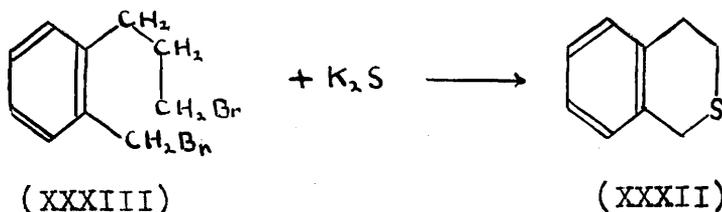
Lesser and Mehrländer also condensed ω -mercaptoacetic acid with o-cyanobenzyl chloride in the presence

of sodium hydroxide to give *o*-cyanobenzylthiolacetic acid (XXX), which on hydrolysis was converted by boiling acetic anhydride and potassium acetate into 4-acetoxy-1:2-dihydro-2-thianaphthalene (XXXI).



4-Keto-1:2:3:4-tetrahydro-2-thianaphthalene

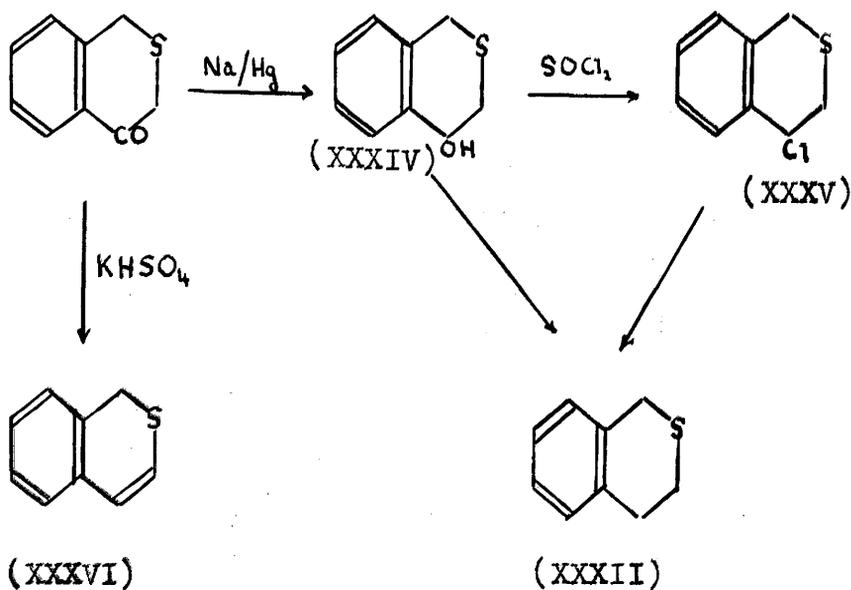
(XXXII) has been prepared by von Braun and Zobel (42) by refluxing dibromo-*o*-homoxylene (XXXIII) with potassium sulphide in alcohol.



Finally, von Braun and Weisbach (43) showed that

1:2-dihydro-4-keto-2-thianaphthalene on reduction with sodium amalgam gave 4-hydroxy-1:2:3:4-tetrahydro-2-thianaphthalene (XXXIV), which on treatment with thionyl chloride gave the corresponding chloride (XXXV). Both

(XXXIV) and (XXXV) give 1:2:3:4-tetrahydro-2-thianaphthalene (XXXII) on reduction with zinc and hydrochloric acid. 4-Hydroxy-1:2:3:4-tetrahydro-2-thianaphthalene on fusion with potassium hydrogen sulphate yields 1:2-dihydro-2-thianaphthalene (XXXVI).



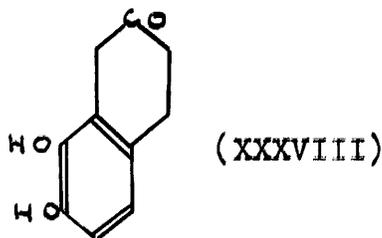
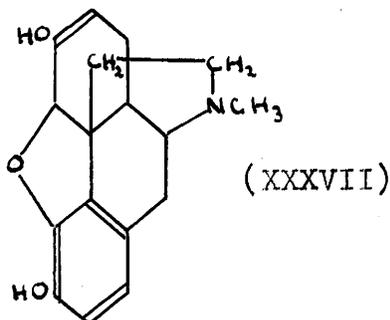
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Introduction.

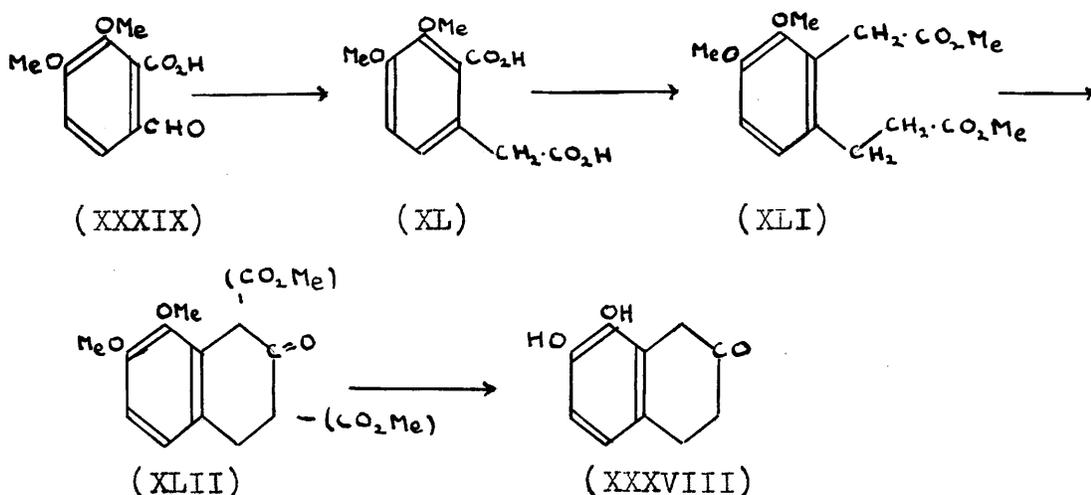
The work described in Part I of this Thesis resulted from some exploratory studies leading towards the synthesis of morphine (XXXVII).



It was desired to obtain as an intermediate the dihydroxytetralone (XXXVIII). A comparison of (XXXVIII) with the structure of morphine shows that it contains two of the ring systems present in the alkaloid, and the phenolic group of the morphine molecule. It was hoped to use the other hydroxyl group (a) present in the tetralone for the formation of the cyclic ether ring; the ketonic group of the tetralone would have been available for the addition of the fourth planar ring. Completion of the morphine molecule by addition of the nitrogen ring-bridge system was envisaged by a method similar to that reported by Baltrop (44) in his work on synthetic studies in the morphine series.

Opianic acid (XXXIX) provided a most suitable starting material for the preparation of the tetralone (XXXVIII).

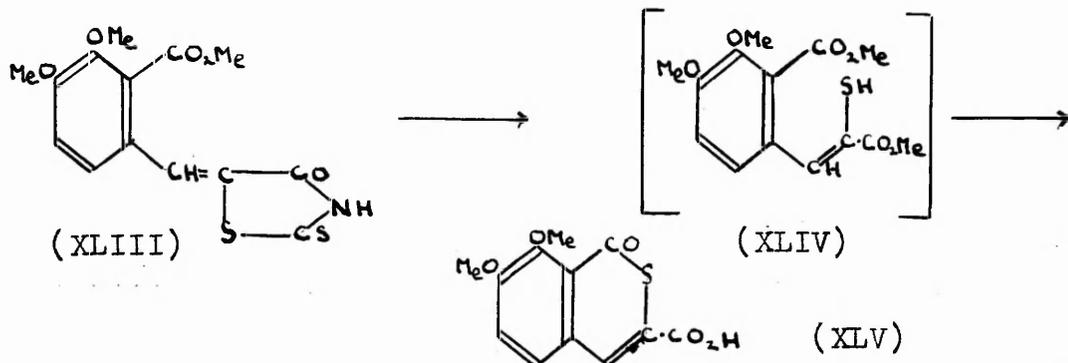
Thus conversion of the formyl group of opianic acid to an acetic acid grouping to give 2:3-dimethoxy-6-methylcarboxybenzoic acid (XL), followed by a double Arndt-Eistert reaction on the latter intermediate would yield a product (XLI) capable of cyclisation under Michael conditions to give (XLII). Hydrolysis and decarboxylation of (XLII) would yield the desired tetralone (XXXVIII).



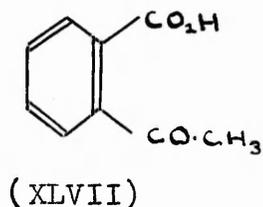
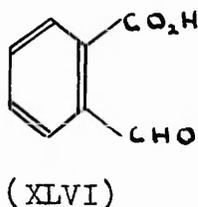
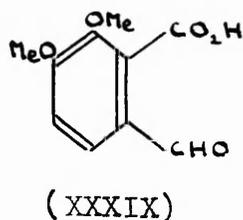
Normal methods for the lengthening of the aldehydic side chain in opianic acid (e.g. formation of the nitrile with hydrogen cyanide, Arndt-Eistert reaction) were unsuccessful, resulting in the formation of derivatives of the pseudo form of opianic acid or in resinous products. Attention was then turned to the use of rhodanine for the synthesis of homologous acids (22). α -Methyl opianate condensed with rhodanine to give 5-(2'-carbomethoxy-3':4'-dimethoxybenzylidene)-

rhodanine (XLIII); the latter product on hydrolysis with sodium hydroxide did not give the expected α -thiolcinnamic acid (XLIV) but a product which could be formulated as 1:2-dihydro-1-keto-7:8-dimethoxy-2-thianaphthalene-3-carboxylic acid (XLV).

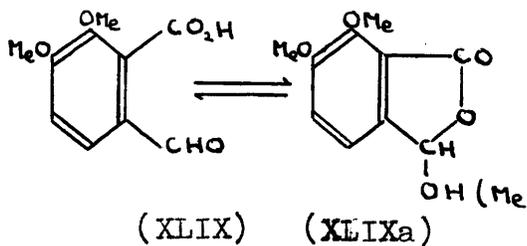
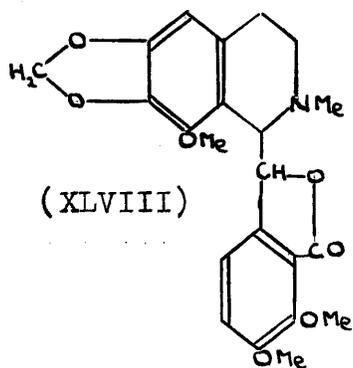
It was found that the above reaction was a general reaction for o-carbomethoxybenzylidene rhodanines. The nature and chemistry of these thianaphthalene derivatives was of such general interest that they have been studied to the exclusion of the work on the synthesis of morphine.



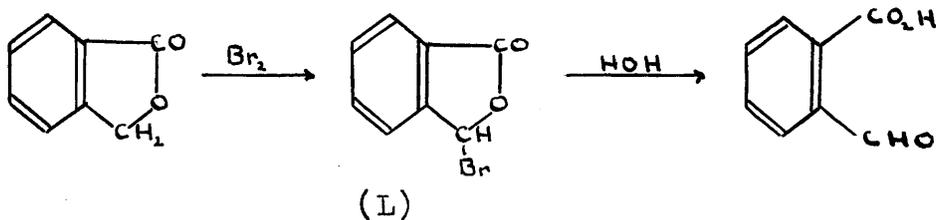
Three ortho-carbonyl benzoic acids were used in this study, either as the free acids or as the methyl esters, and their condensation with rhodanine and the chemistry of the o-carboxybenzylidenerhodanines and of their hydrolysis products is the main subject of this thesis. The carbonyl compounds used were opianic acid (XXXIX), o-phthalaldehydic acid (XLVI) and o-carboxyacetophenone (XLVII).



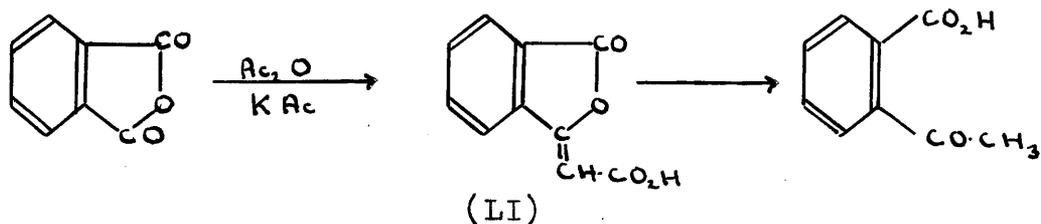
Opianic acid was prepared by the oxidation of narcotine (XLVIII) with manganese dioxide, and its α -methyl ester prepared from the silver salt by the method of Bain, Perkin, and Robinson (45) by refluxing with an ethereal solution of methyl iodide. The method of Wegscheider (46) for the preparation of the α -ester, by shaking the silver salt with methanol and methyl iodide, yielded only the pseudo-methyl ester, and this result is in agreement with the generally accepted view that the free acid exists in equilibrium with the tautomeric hydroxy lactone (LXIX). Support for this view was forthcoming when it was found that merely warming opianic acid with methanol resulted in the formation of the pseudo-methyl ester (XLIXa).



Phthalaldehydic acid was prepared by the hydrolysis of 2-bromophthalide (L) with hot water.

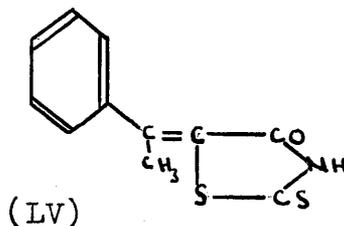
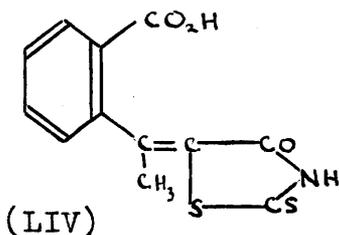
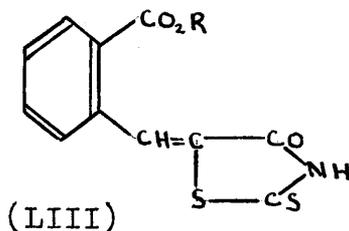
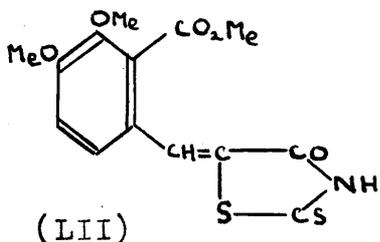


o-Carboxyacetophenone was prepared by heating phthalyl acetic acid (LI) with water at 200° for two hours, when simultaneous hydrolysis and decarboxylation take place. Phthalyl acetic acid was obtained from phthalic anhydride by means of the Perkin reaction (47).



Condensation of ortho-Carbonyl Benzoic Acids with Rhodanine.

α -Methyl opianate condensed smoothly with rhodanine on refluxing the two components together with sodium acetate in glacial acetic acid. The product, 5-(2'-carbomethoxy-3':4'-dimethoxybenzylidene)-rhodanine (LII) was isolated in good yield on pouring the warm reaction solution into water. Similarly, α -methyl phthalaldehyde condensed with rhodanine to give 5-(2'-carbomethoxybenzylidene)-rhodanine (LIII; R = Me); o-phthalaldehydic acid and o-carboxyacetophenone condensed to give 5-(2'-carboxybenzylidene)- (LIII; R = H) and 5-(2'-carboxy- α -methylbenzylidene)-rhodanine (LIV) respectively.

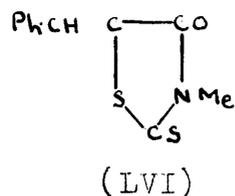
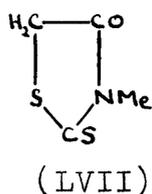
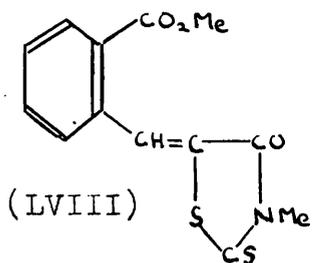


It was found that 5-(2'-carboxybenzylidene)-rhodanine and 5-(2'-carboxy- α -methylbenzylidene)-rhodanine gave sharp end-points with phenolphthalein, as dibasic acids, on titration against sodium hydroxide. As 5-benzylidenerhodanine and 5- α -methylbenzylidenerhodanine (LV) titrated sharply as monobasic acids under the same conditions, the second acidic function must be present in the rhodanine fraction of the condensation products. These results are in agreement with Holmberg's (18) observation that rhodanine itself could be titrated against sodium hydroxide using phenolphthalein as an indicator; the same author also determined the acidic strength of rhodanine as K_a at 25° 3×10^{-6} (cf. acetic acid K_a 1.845×10^{-5}). Thus the acidity of the readily accessible condensation products of rhodanine with aldehydes and ketones provides a useful

alternative method to the titration of carboxy- or sulphophenylhydrazones, suggested by Anchel and Schoenheimer (48) and by Willstätter, Schuppli and Mayer (49), for the determination of the molecular weights of carbonyl compounds. 5-(2'-Carbomethoxy-3':4'-dimethoxybenzylidene)- and 5-(2'-carbomethoxybenzylidene)-rhodanine, as expected, titrated as monobasic acids.

The position of the acidic function in the rhodanine moiety was determined by the action of diazomethane on 5-benzylidenerhodanine, when the only product isolated was 5-benzylidene-3-methylrhodanine (LVI) which was identical in physical properties with the product obtained by Andreasch and Zipser (6) from the condensation of 3-methylrhodanine (LVII) with benzaldehyde. This suggests that the principal acidic centre in 5-benzylidenerhodanine is the imino-group, and this view is supported by the fact that both 5-benzylidenerhodanine and 5-benzylidene-3-methylrhodanine possess identical absorption spectra. An attempt to obtain further confirmation that the acidity of the rhodanine molecule is contained in the imino group was, unfortunately, unsuccessful. 3-Methylrhodanine was condensed, with α -methyl phthalaldehyde to give 5-(2'-carbomethoxybenzylidene)-3-methylrhodanine (LVIII).

5-(2'-Carboxybenzylidene)- and 5-(2'-carbomethoxybenzylidene)-rhodanine were both treated with a large excess of an ethereal solution of diazomethane. Dissolution occurred immediately with vigorous evolution of nitrogen, but both reaction solutions on evaporation to dryness yielded intractable gums as products, which could not be resolved either by attempted crystallisation or by chromatographic techniques. If, however, these reactions had both yielded, as expected, 5-(2'-carbomethoxybenzylidene)-3-methylrhodanine (LVIII) identical in behaviour with the product obtained from the condensation of α -methyl phthalaldehyde with 3-methylrhodanine, no reasonable doubt could have existed as to the position of the acidic centres in o-carboxyrhodanines.



Opianic acid, itself, condensed with rhodanine to give not the expected 5-(2'-carboxy-3':4'-dimethoxybenzylidene)-rhodanine, but a sodium salt. The latter product was converted into the free acid, m.p. 237-240° (decomp.), on crystallisation from ethanolic hydrochloric acid. The sodium salt titrated to phenolphthalein giving

a value for the molecular weight of ca. 400, but did not give a sharp end-point. Analysis showed that the product was the tetrahydrate of the sodium salt of 5-(2'-carboxy-3':4'-dimethoxybenzylidene)-rhodanine; an examination of its ultraviolet light absorption spectrum in ethanol showed that it possessed slight differences from the spectral curve of the corresponding methyl ester, having a less detailed curve and greater absorption at ca. 2900 Å.

Similarly, α-methyl opianate did not condense normally with 3-methylrhodanine, but in this case two products were formed. The first, soluble in ethanol and chloroform, was present to the extent of 5% and was shown from analysis and molecular weight determinations to be 5-(2'-carboxy-3':4'-dimethoxybenzylidene)-3-methylrhodanine, hydrolysis of the carbomethoxy- group having taken place. As α-methyl opianate condenses with rhodanine to give the methyl ester, with 3-methylrhodanine condensation probably takes place first followed by hydrolysis to the free acid. The condensation product was extracted with chloroform, but the extract on evaporation to dryness again only yielded 5-(2'-carboxy-3':4'-dimethoxybenzylidene)-3-methylrhodanine and no methyl ester could be found. The residue from the chloroform extraction was found to be a sodium salt, which on crystallisation from ethanolic hydrochloric acid

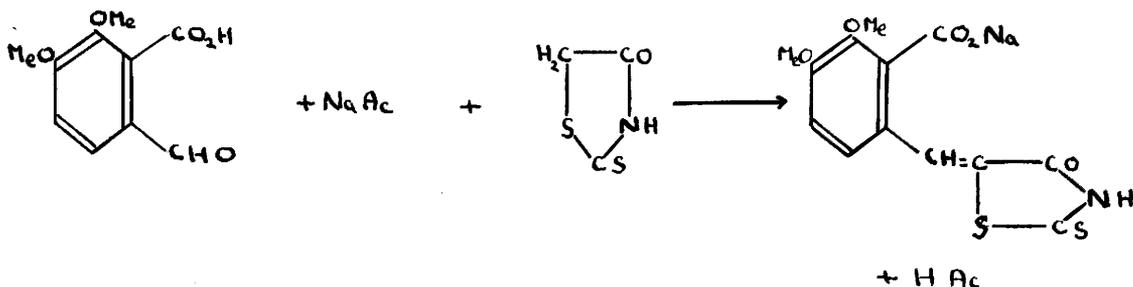
gave a product, m.p.199-200°, and which analysed for $C_{14}H_{13}O_5NS_2$ and titrated as a monobasic acid; the acid was therefore 5-(2'-carboxy-3':4'-dimethoxybenzylidene)-3-methylrhodanine.

An explanation of the behaviour of opianic acid on condensation with rhodanine is forthcoming from a comparison of the K_a^{25} values of opianic acid and phthalaldehydic acid with that of acetic acid (Table II).

Table II

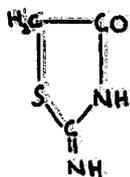
<u>Acid</u>	<u>K_a at 25°</u>
Opianic	8.82×10^{-4}
Acetic	1.845×10^{-5}
Phthalaldehydic	3.6×10^{-5}

It can be seen that while phthalaldehydic acid is of comparable acidic strength to acetic acid, opianic acid is much stronger; thus, it is to be expected that in solution with acetic acid and sodium acetate phthalaldehydic acid would condense normally with rhodanine, while in the case of opianic acid reaction with sodium acetate would occur simultaneously with rhodanine condensation.

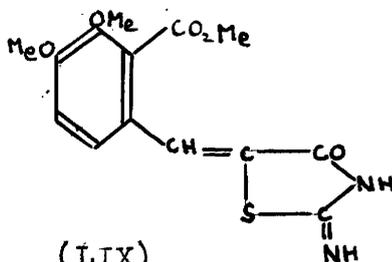


This explanation, however, does not attempt to explain the difference in behaviour of α -methyl opianate on condensation with rhodanine and 3-methylrhodanine, where in the former case condensation is quite normal with the formation of 5-(2'-carbomethoxy-3':4'-dimethoxybenzylidene)-rhodanine while in the latter case simultaneous hydrolysis of the carbomethoxy-group and condensation occur. This difference must in some way be due to the influence of the substituted imino group in the rhodanine ring, but this interesting problem was not further pursued as it is outwith the subject of this thesis.

In view of the claims of Liebermann, Himbert, and Hengl (40) that better yields of substituted thiopyruvic acids can be obtained through the 2-amino-4-keto-thiazolidenes than through the corresponding rhodanines, α -methyl opianate was condensed with pseudothiohydantoin (XXVI) to give 5-(2'-carbomethoxy-3':4'-dimethoxybenzylidene)-2-amino-4-ketothiazolidene (LIX).



(XXVI)



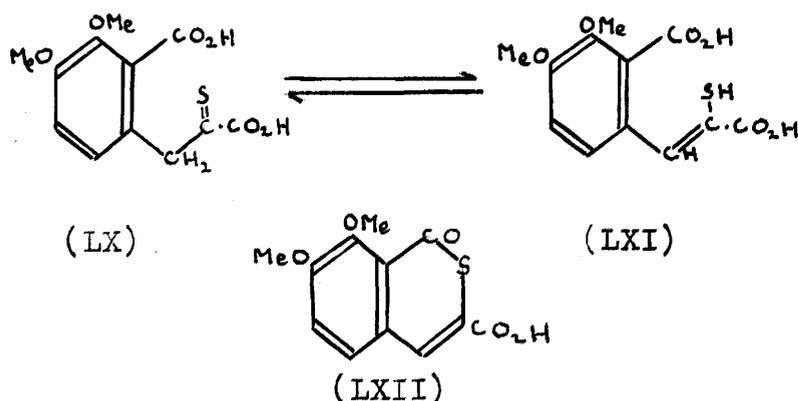
(LIX)

It was found that considerably more vigorous reaction conditions were necessary to obtain complete condensation, and that the product was isolated in relatively lower yield than the corresponding rhodanine derivative. The product was also considerably more difficult to handle than the rhodanine, and great difficulty was experienced in obtaining a crystalline specimen for analysis. In the case of α -methyl opianate, at least, it can be concluded that the rhodanine condensation product is obtained more readily and in better yield than the corresponding aminoketothiazolidene.

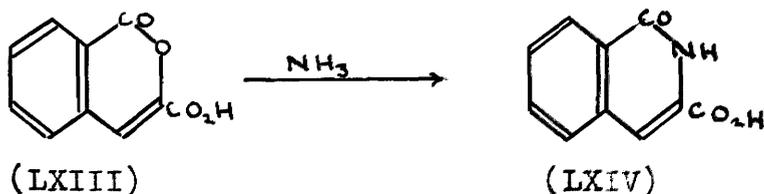
Hydrolysis of o-Carboxybenzylidenerhodanines into 1:2-Dihydro-1-keto-2-thianaphthalene-3-carboxylic acids.

5-(2'-Carbomethoxy-3':4'-dimethoxybenzylidene)-rhodanine was hydrolysed by warming on the water-bath for 30 minutes with dilute aqueous sodium hydroxide. On pouring the cooled reaction mixture into an excess of dilute hydrochloric acid an acidic material, m.p. 258°, was obtained. The product, which analysed for $C_{12}H_{10}O_5S$, and which titrated to phenolphthalein with sodium hydroxide as a monobasic acid, equivalent 264, was formed by the loss of water from the intermediate 2-carboxy-3:4-dimethoxyphenylthiopyruvic acid (LX) tautomeric with 2-carboxy-3:4-dimethoxy- α -thiolcinnamic acid (LXI), and can be formulated as 1:2-dihydro-1-keto-7:8-dimethoxy-2-

thianaphthalene-3-carboxylic acid (LXII).



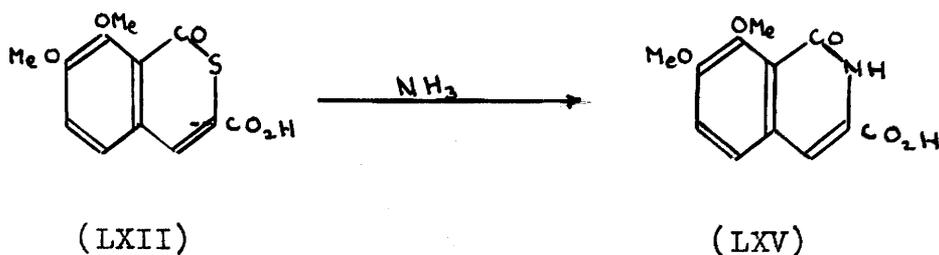
The similarity of this formula (LXII) to the isocoumarins suggested that confirmation of the position of the sulphur atom in the thianaphthalene molecule would be forthcoming from an examination of the product obtained on treatment of (LXII) with ammonia. Bamberger and Kitchelt (50) have shown that treatment of iso-coumarin-3-carboxylic acid (LXIII) with ethanolic ammonia under sealed tube conditions gives 1:2-dihydro-1-keto-isoquinoline-3-carboxylic acid (LXIV) in good yield.

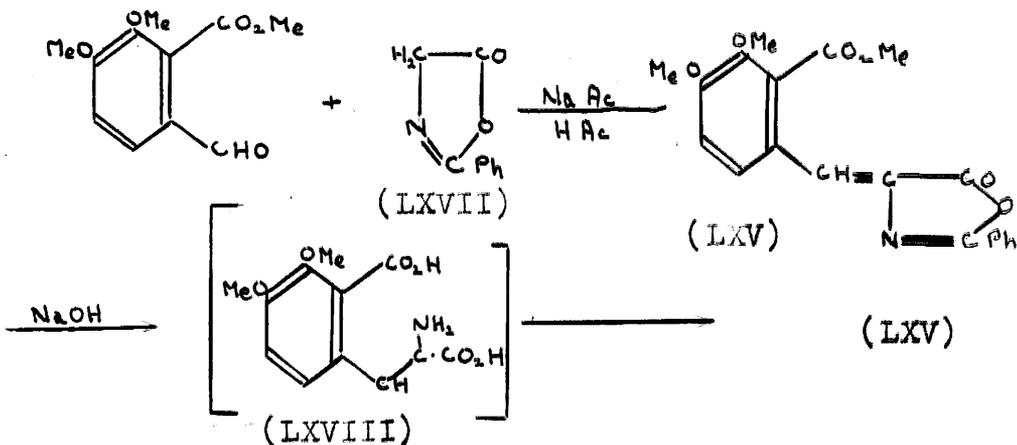


It was found that treatment of 1:2-dihydro-1-keto-7:8-dimethoxy-2-thianaphthalene-3-carboxylic acid with ethanolic ammonia at 130° for two hours gave a reaction mixture possessing a strong smell of hydrogen sulphide.

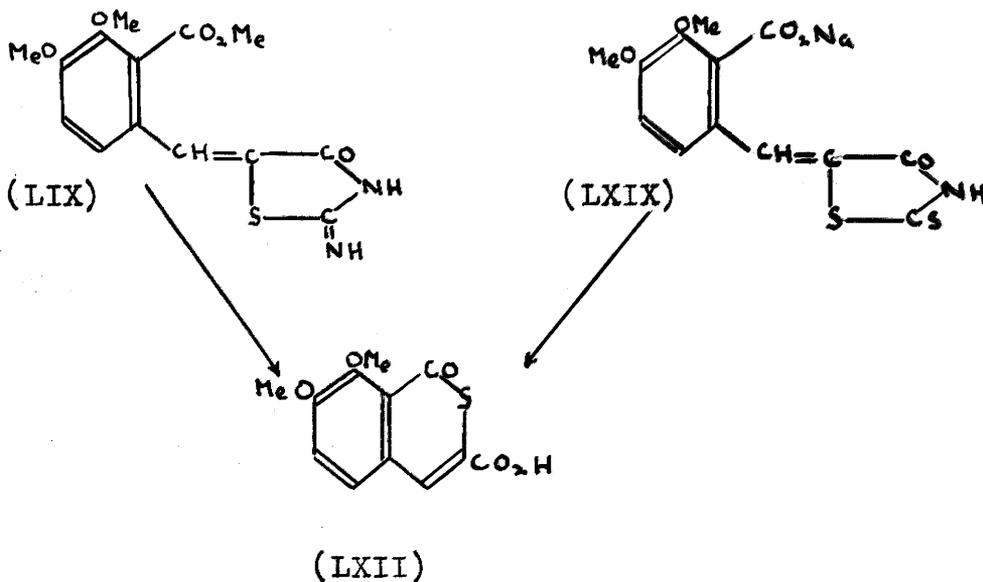
Removal of the solvent and acidification gave a colourless acid, m.p. 257°, which did not contain sulphur, and which was identical with 1:2-dihydro-1-keto-7:8-dimethoxy-isoquinoline-3-carboxylic acid (LXV) prepared by Bain, Perkin, and Robinson (45) by the alkaline hydrolysis of 5-(2'-carbomethoxy-3':4'-dimethoxybenzylidene)-2-phenyloxazol-4-one (LXVI). The preparation of 5-o-carbomethoxybenzylidene-2-phenyloxazol-4-ones by the condensation of aromatic orthocarbomethoxy aldehydes with hippuric acid (LXVII), and their hydrolysis to intermediate α -amino-o-carboxycinnamic acids which cyclise to 1:2-dihydro-1-ketoisoquinoline-3-carboxylic acids, very closely parallels the method described above for the formation of 1:2-dihydro-1-keto-2-thianaphthalene-3-carboxylic acids from o-carbomethoxybenzylidene-rhodanines.

The conversion of 1:2-dihydro-1-keto-7:8-dimethoxy-2-thianaphthalene-3-carboxylic acid into the corresponding isoquinoline identified beyond doubt the positions of the sulphur atom and the carboxylic acid group in the molecule.

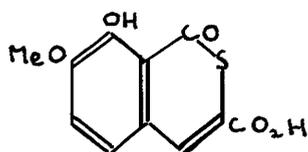




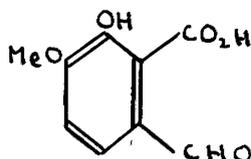
1:2-Dihydro-1-keto-7:8-dimethoxy-2-thianaphthalene-3-carboxylic acid was also obtained, by the same alkaline treatment, from 5-(2'-carbomethoxy-3':4'-dimethoxybenzylidene)-2-amino-4-ketothiazolidene (LIX) and from the sodium salt of 5-(2'-carboxy-3':4'-dimethoxybenzylidene)-rhodanine (LXIX). In the latter case hydrolysis proceeded under very mild conditions; dissolution in cold 20% sodium hydroxide and acidification giving the thianaphthalene acid in 70% yield.



1:2-Dihydro-1-keto-7:8-dimethoxy-2-thianaphthalene-3-carboxylic acid readily reacts with ethereal diazomethane to give a methyl ester. The free acid is partially demethylated on refluxing with constant boiling hydrobromic acid to give a monomethyl ether, which can be formulated as 1:2-dihydro-8-hydroxy-1-keto-7-methoxy-2-thianaphthalene-3-carboxylic acid (LXX); since opianic acid under similar conditions has been shown by Wegscheider (51), Liebermann (52), and by Schorigin, Issaguljanz, and Below (53) to give 2-formyl-6-hydroxy-5-methoxybenzoic acid (LXXI).



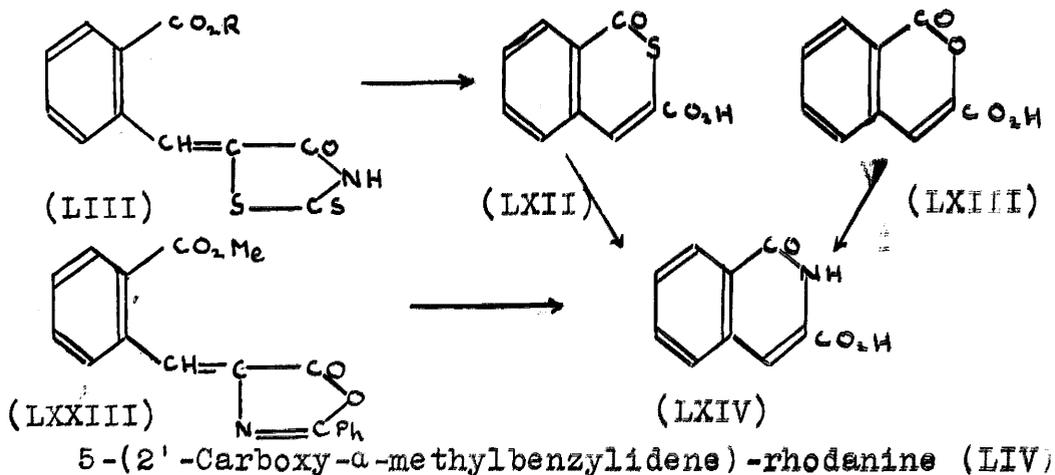
(LXX)



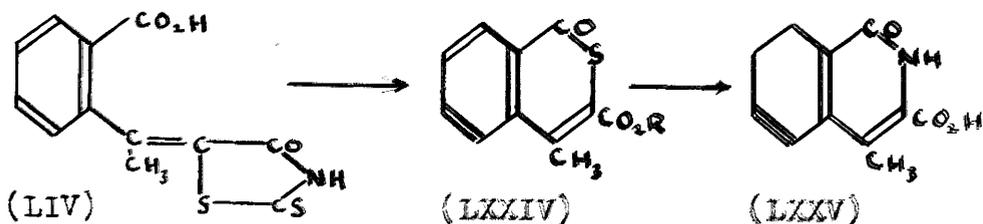
(LXXI)

Similarly, 5-o-carbomethoxybenzylidenerhodanine (LIII; R = Me) and 5-o-carboxybenzylidenerhodanine (LIII; R = H) on hydrolysis with hot dilute sodium hydroxide gave 1:2-dihydro-1-keto-2-thianaphthalene-3-carboxylic acid (LXXII; R = H) which readily formed a methyl ester (LXXII; R = Me) with diazomethane. 1:2-Dihydro-1-keto-2-thianaphthalene-3-carboxylic acid on treatment with aqueous concentrated ammonia at 130° gave in 80% yield 1:2-dihydro-1-ketoisoquinoline-3-carboxylic acid (LXIV), identical with the product obtained by Bamberger and

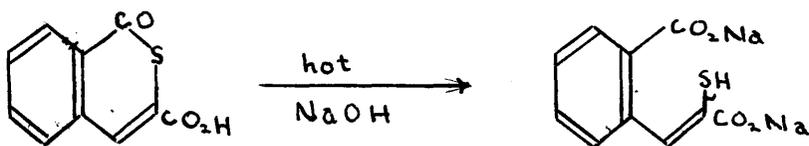
Kitschelt (49) by a similar process from isocoumarin-3-carboxylic acid (LXIII), and by Bain, Perkin and Robinson (45) by the alkaline hydrolysis of 5-o-carboxymethoxybenzylidene-2-phenyloxazol-4-one (LXXIII).



on treatment with dilute sodium hydroxide was converted into 1:2-dihydro-1-keto-4-methyl-2-thianaphthalene-3-carboxylic acid (LXXIV; R = H) which readily formed a methyl ester (LXXIV; R = Me) with diazomethane. The acid when heated at 130° with concentrated aqueous ammonia was smoothly converted, in good yield, into 1:2-dihydro-1-keto-4-methylisoquinoline-3-carboxylic acid (LXXV), which has not been previously reported in the literature.



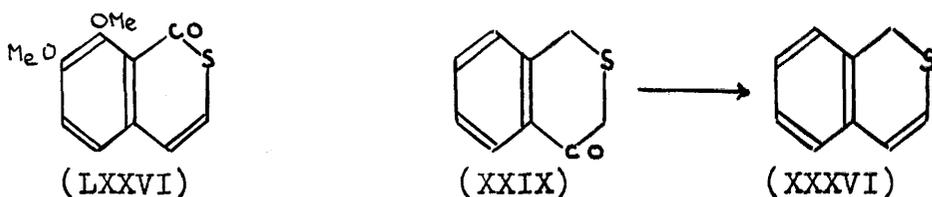
Although 1:2-dihydro-1-keto-2-thianaphthalene-3-carboxylic acid titrates normally with cold 0.1 N-sodium hydroxide to phenolphthalein as a monobasic acid, on heating it with an excess of alkali, followed by back-titration of the hot solution, it was found that two equivalents of alkali were taken up. This indicates that under these conditions the thiolactone ring opens, and this result is in agreement with the observations of Bamberger and Kitschelt (50) and of Zinke (54) that isocoumarin-3-carboxylic acid titrated against hot alkali took up two equivalents of alkali with lactone ring opening.



Decarboxylation of 1:2-Dihydro-1-keto-2-thianaphthalene-3-carboxylic acids.

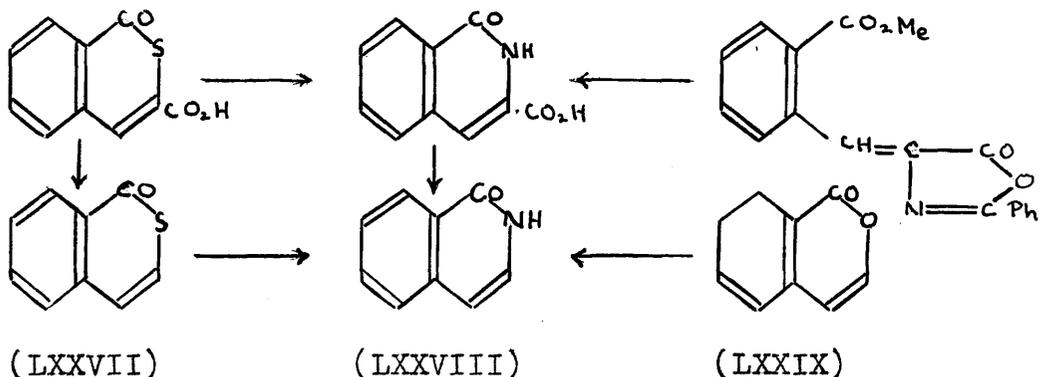
1:2-Dihydro-1-keto-7:8-dimethoxy-2-thianaphthalene-3-carboxylic acid was heated at 330° at atmospheric pressure for five minutes when decarboxylation took place, to give in very low yield a mixture of products from which 1:2-dihydro-1-keto-7:8-dimethoxy-2-thianaphthalene (LXXVI) could be separated by sublimation and chromatography.

It has been shown in the Introduction that 1:2-dihydro-4-keto-2-thianaphthalene (XXIX) has been prepared by Lesser and Mehrländer (41) by the internal condensation of benzylthiolacetic acid with aluminium chloride; reduction of the 4-ketothianaphthalene led to 1:2-dihydro-2-thianaphthalene (XXXVI). No reference, however, can be found in the literature to the preparation or properties of 1-keto-2-thianaphthalenes.



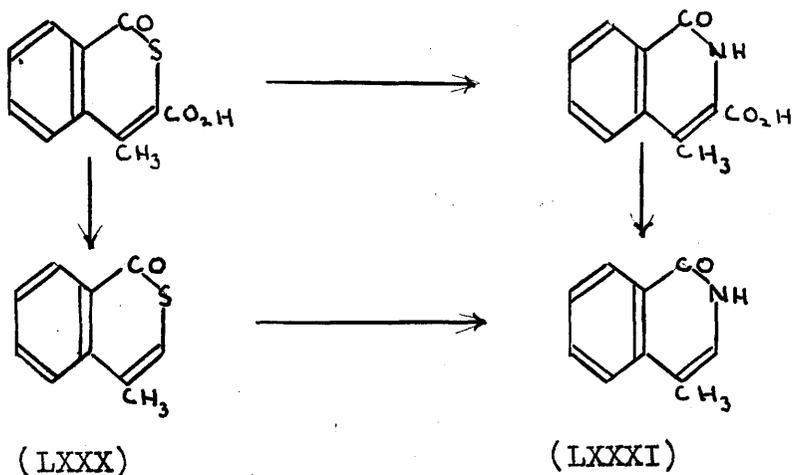
Decarboxylation of 1:2-dihydro-1-keto-2-thianaphthalene-3-carboxylic acid proceeded smoothly and 1:2-dihydro-1-keto-2-thianaphthalene (LXXVII) was obtained in 41% yield. 1:2-Dihydro-1-keto-2-thianaphthalene reacted with aqueous ammonia to give 1:2-dihydro-1-ketoisoquinoline (LXXVIII), which has been obtained by Bamberger and Frew (55) by similar treatment of isocoumarin (LXXIX), and by Bain, Perkin, and Robinson (45) by the decarboxylation of 1:2-dihydro-1-ketoisoquinoline-3-carboxylic acid prepared by the azlactone route. 1:2-Dihydro-1-ketoisoquinoline was also prepared by the decarboxylation of the isoquinoline acid obtained from 1:2-dihydro-1-keto-2-thianaphthalene-

3-carboxylic acid, and was shown to be identical with the product obtained by the direct ammonolysis of the decarboxylated thianaphthalene.



Unlike isocoumarin, 1:2-dihydro-1-keto-2-thianaphthalene does not reduce Fehling's solutions, indicating that the thiolactone ring is more stable than the lactone ring.

Similarly, 1:2-dihydro-1-keto-4-methyl-2-thianaphthalene-3-carboxylic acid readily decarboxylated to give 1:2-dihydro-1-keto-4-methyl-2-thianaphthalene (LXXX), which on treatment with aqueous ammonia gave



1:2-dihydro-1-keto-4-methylisoquinoline (LXXXI), identical with the product obtained by the decarboxylation of 1:2-dihydro-1-keto-4-methylisoquinoline-3-carboxylic acid.

Johnston, Kaslow, Langsjoen, and Shriner (56) reported that in pharmacological tests isocoumarin-3-carboxylic acid was found to be about one-half as effective as dicoumarol in retarding clotting of the blood, and caused a transient fall in the blood pressure of anaesthetized cats. Kamal, Robertson and Tittensor (57) also report that isocoumarins possess physiological properties. While these authors do not report any bacteriological properties for the isocoumarins, it was felt that an examination of their sulfur analogues, the 2-thianaphthalenes, for these properties was worthwhile. The results obtained were not encouraging, and are tabulated below (Table III).

Report on in vitro tests against M. tuberculosis.

(Obtained from Dr. J. Walker, National Institute of Medical Research. The work was carried out by Dr. A.T. Fuller and Dr. P.A. d'Arcy-Hart.)

The tests were carried out in Dubos basal medium plus 0.25% albumin. Inoculum 1/250 mg. of human strain H37Rv per 5 ml. medium. The compounds were dissolved in water at 1 mg./ml. with the aid, where necessary, of a little saturated sodium hydrogen carbonate, and

sterilized in a boiling water-bath for 10 minutes.

- (a) TB grew at 1 in 10,000 concentration.
- (b) ditto
- (c) ditto
- (d) Complete inhibition at 1 in 10,000, but grew at 1 in 20,000.

where (a) was 1:2-dihydro-1-keto-2-thianaphthalene-3-carboxylic acid

(b) was -4-methyl- ditto

(c) was -8-hydroxy-7-methoxy- ditto

and (d) was -7:8-dimethoxy- ditto

Table III

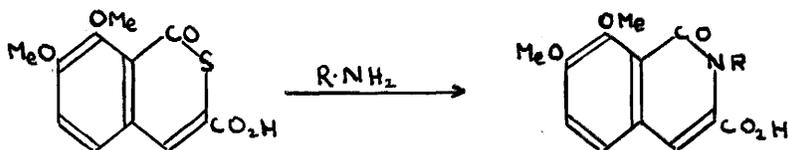
Inhib. conc. for	<u>Strep.haem.</u>	<u>Staph.aur.</u>	<u>B-coli</u>	<u>M.tub.</u> (avia)
(a)	100	50	50	50
(b)	100	50	50	50
(c)	50	50	50	50
(d)	50	50	50	50

Concentrations in mg./100 ml. which prevented visible growth in Hedley-Wright broth overnight at 37°.

Conversion of 1:2-Dihydro-1-keto-2-thianaphthalene-3-carboxylic acids to N-Substituted isoQuinoline-3-carboxylic acids.

1:2-Dihydro-1-keto-7:8-dimethoxy-2-thianaphthalene-3-carboxylic acid on treatment with aqueous ethanolic methylamine and aqueous ethanolic ethylamine was converted in almost quantitative yield into 1:2-dihydro-1-

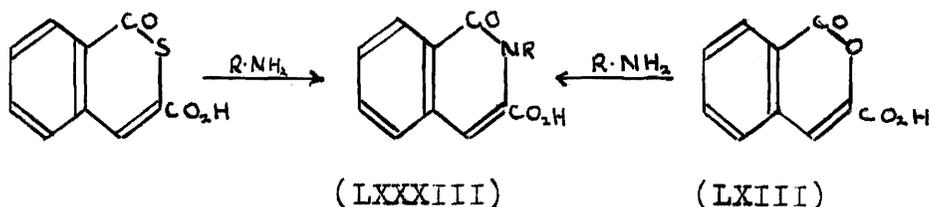
keto-2-methyl- (LXXXII; R = Me) and 2-ethyl-1:2-dihydro-1-keto-7:8-dimethoxyisoquinoline-3-carboxylic acid (LXXXII; R = Et), respectively. Attempts to decarboxylate 1:2-dihydro-1-keto-7:8-dimethoxyisoquinoline-3-carboxylic acid consistently yielded a neutral product, m.p. 233°, and which depressed the m.p. of the acid. Analysis of the product showed it was isomeric with the starting material; it also had the same m.p. as the product obtained by Bain, Perkin, and Robinson (45) from the decarboxylation of the acid, and which they suggested was 1:2-dihydro-1-keto-7:8-dimethoxyisoquinoline but which was destroyed before these authors had it analysed. No evidence as to the structure of this compound could be obtained.



(LXXXII)

In the same way, 1:2-dihydro-1-keto-2-thianaphthalene-3-carboxylic acid on heating with aqueous ethanolic methylamine and aqueous ethanolic ethylamine under sealed tube conditions, and on refluxing with aniline and benzylamine gave the corresponding N-methyl, N-ethyl, N-phenyl, and N-benzyl derivatives of 1:2-dihydro-1-ketoisoquinoline-3-carboxylic acid (LXXXIII; R = Me,

Et, Ph, and CH_2Ph respectively) in very good yield (80-90%), the first three of which have been similarly obtained from isocoumarin-3-carboxylic acid (LXIII) by Bamberger and Kitschelt (50).

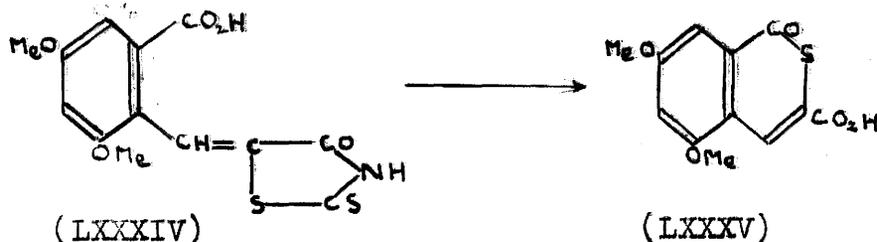


Insufficient 1:2-dihydro-1-keto-4-methyl-2-thianaphthalene-3-carboxylic acid was available to examine its conversion with primary amines into N-substituted-4-methylisoquinoline-3-carboxylic acids, but there is no reason to doubt that, in view of its reaction with ammonia, these would be formed with equal facility.

The results obtained in the case of 1:2-dihydro-1-keto- and of 1:2-dihydro-1-keto-7:8-dimethoxy-2-thianaphthalene-3-carboxylic acid on treatment with ammonia and primary amines indicate that the use of the readily available 2-thianaphthalenes in the synthesis of substituted isoquinolines is a useful alternative and general route to those methods now available.

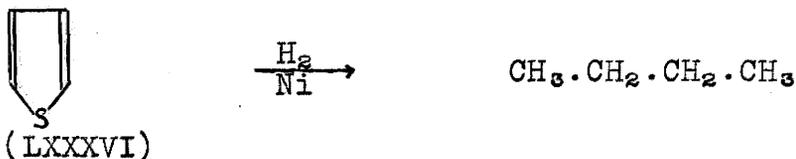
When the work so far described had been completed, the communication of Kamal, Robertson, and Tittensor (57) appeared describing the conversion of 5-(6'-carbo-methoxy-2':4'-dimethoxybenzylidene)-rhodanine (LXXXIV)

into 1:2-dihydro-1-keto-5:7-dimethoxy-2-thianaphthalene-3-carboxylic acid (LXXXV) by hydrolysis with dilute alkali.



Conversion of 1:2-Dihydro-1-keto-2-thianaphthalenes to Indan-1-ones.

Mozingo (59) has shown that an active form of Raney nickel, containing large amounts of occluded hydrogen can be prepared by digesting a 50% nickel aluminium alloy with aqueous sodium hydroxide at 50° for 45 minutes. Bougault, Cattelain, and Chabrier (58) discovered that this active grade of Raney nickel had simultaneous reducing and desulphurizing properties; these workers demonstrated this reaction with thio-carbonyls, thiols, disulphides and heterocyclic compounds. In the latter class of substances they showed that thiophene (LXXXVI) was converted into n-butane.



Mozingo and his co-workers (59,60) extended the reaction to include sulphides, sulphoxides, and sulphones.

Blicke and Sheets (61) have found that 1-thianaphthene-2-carboxylic acid (LXXXVII) in aqueous sodium carbonate solution is simultaneously reduced and desulphurized by Raney nickel to give β -phenylpropionic acid (LXXXVIII).

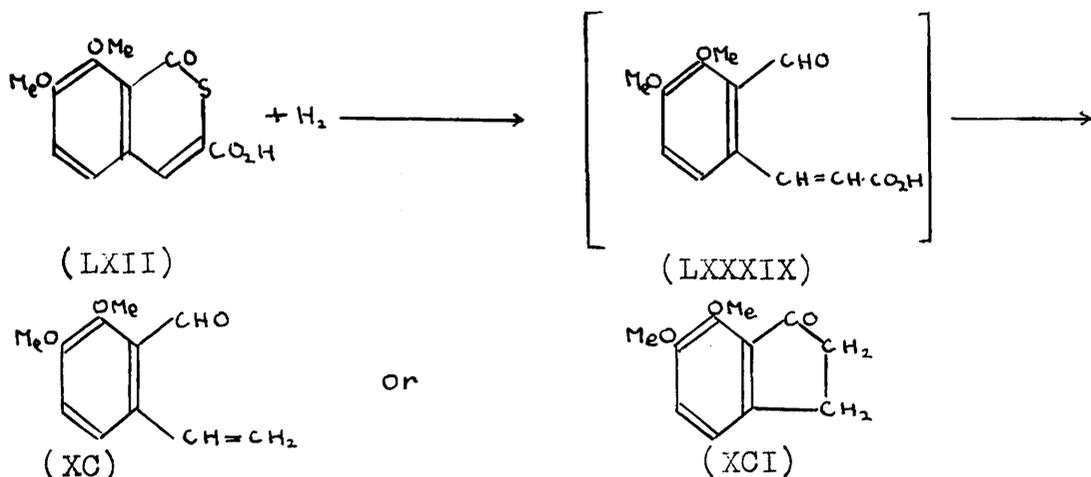


(LXXXVII)

(LXXXVIII)

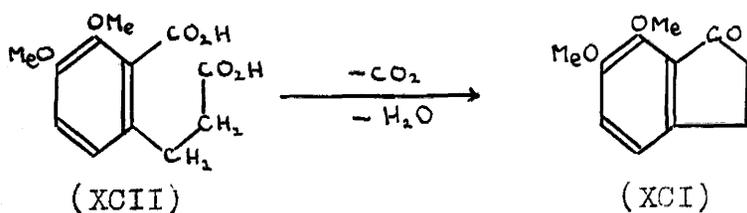
In view of these results it was therefore decided to investigate the action of Raney nickel on the 2-thianaphthalenes. 1:2-Dihydro-1-keto-7:8-dimethoxy-2-thianaphthalene-3-carboxylic acid was refluxed for five hours with a suspension ten times its weight of Raney nickel in ethanol. If desulphurization had taken place without secondary reactions occurring, apart from reduction, the product expected would be either 2-formyl-3:4-dimethoxycinnamic acid (LXXXIX) or β -(2-formyl-3:4-dimethoxyphenyl)-propionic acid. Filtration and concentration of the reaction mixture gave a neutral oil, which did not contain sulphur, and which readily formed a 2:4-dinitrophenylhydrazone with Brady's solution and a semicarbazone with semicarbazide acetate. As the oil could not be crystallised and insufficient was available for distillation it was characterised through its derivatives. Analyses of these derivatives showed

that the oil had the empirical formula $C_{11}H_{14}O_3$, and had been formed by the loss of carbon dioxide from the intermediate o-formylcinnamic acid (LXXXIX). Thus the product could be formulated as either 2-formyl-3:4-dimethoxystyrene (XC) or as the isomeric 6:7-dimethoxyindan-1-one (XCI). The latter compound was considered the more likely product, as it was difficult to envisage the o-formylstyrene not being reduced in situ to 2-formyl-3:4-dimethoxyethylbenzene under the reaction conditions.



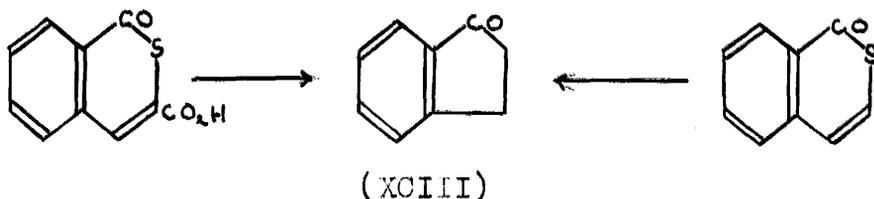
An examination of the literature showed that 6:7-dimethoxyindan-1-one was known and had been prepared by Schöpf, Jackh-Tettweiler, Meyer, Perry-Fehrenbach, and Winterhalter (62) by the simultaneous decarboxylation and internal condensation of β -(2-carboxy-3:4-dimethoxyphenyl)-propionic acid (XCII) on heating with acetic anhydride. 6:7-Dimethoxyindan-1-one was formed with considerable charring and decomposition, and could not be isolated by distillation as the above authors suggest.

Consequently, the reaction solution was treated with an aqueous ethanolic solution of semicarbazide acetate and the indanone isolated as the semicarbazone. The latter, after one crystallisation from aqueous ethanol, on refluxing with oxalic acid, liberated 6:7-dimethoxyindan-1-one as a slightly coloured crystalline solid, m.p.43°. This authentic specimen of 6:7-dimethoxyindan-1-one gave a 2:4-dinitrophenylhydrazone with Brady's reagent identical with that obtained from the product of Raney nickel on the substituted thianaphthalene acid; as this derivative melted with decomposition, the ultraviolet light absorption characteristics of the 2:4-dinitrophenylhydrazones were compared and found to be identical.

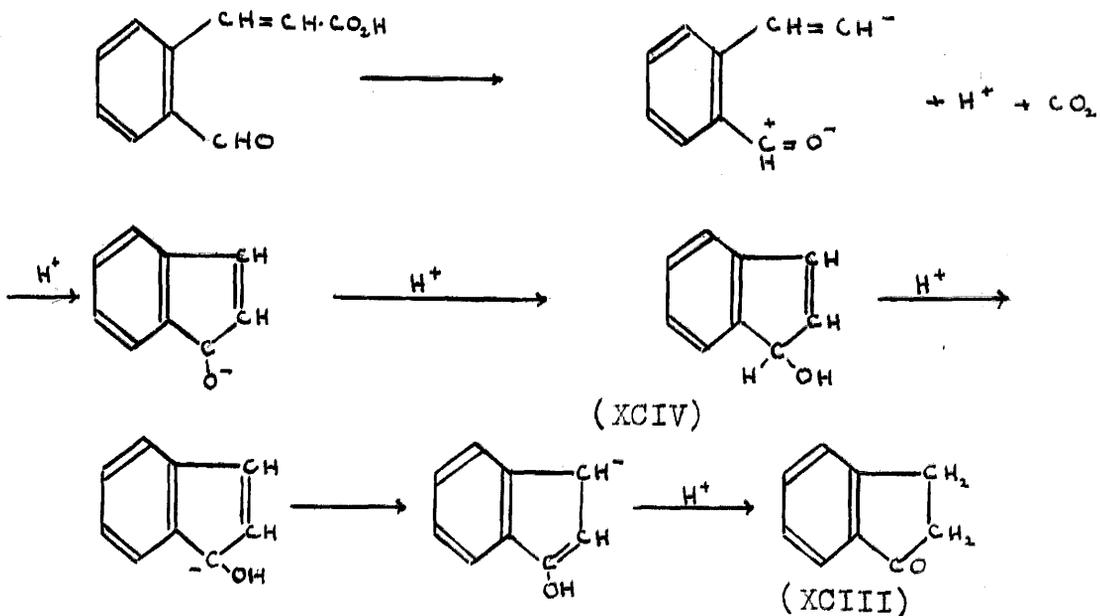


1:2-Dihydro-1-keto-2-thianaphthalene-3-carboxylic acid on similar treatment with Raney nickel gave indan-1-one (XCIII), which was isolated from the reaction mixture, after filtration and concentration, by steam distillation. Extraction of the aqueous distillate with ether, and evaporation of the ethereal solution gave indan-1-one as an oil. The oil formed a 2:4-dinitrophenylhydrazone and semicarbazone identical in m.p. and ultraviolet spectrum absorption with the same

derivatives prepared from an authentic specimen of indan-1-one. Indan-1-one was also obtained by a similar desulphurization of 1:2-dihydro-1-keto-2-thianaphthalene.

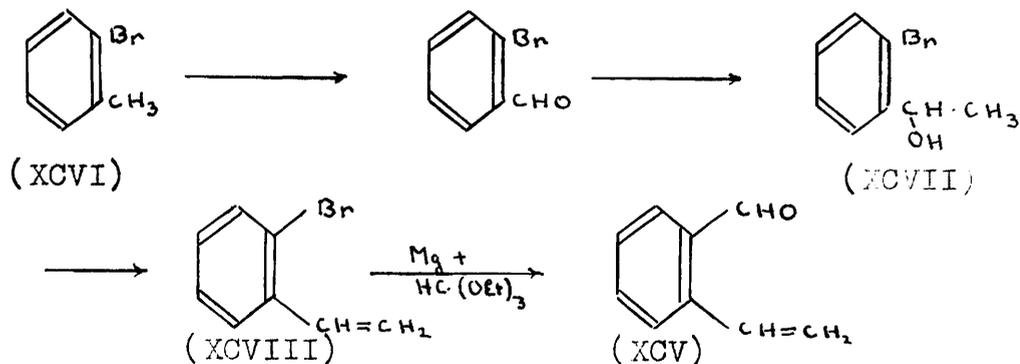


The mechanism of decarboxylation is the same as that advanced by Wiley and Hobson (63) in their paper on the attempted formation of *o*-formyl styrenes. These authors condensed together phthalaldehyde and malonic acid to obtain *o*-formylcinnamic acid (XCIV); they found that this acid decarboxylated on dissolving in quinoline at room temperature to give indan-1-one, and that the rate of decarboxylation was accelerated by the addition of copper powder. Wiley and Hobson account for the formation of indan-1-one by the tendency of the ion formed on decarboxylation of *o*-formylcinnamic acid, to combine, internally, with the carbonyl carbon rather than the proton; followed by subsequent addition of the proton to the carbonyl oxygen to give the carbinol (XCIV). The subsequent rearrangement of (XCIV) to indan-1-one is similar to the prototropic change of α -phenyl allyl alcohols to propiophenones which has been previously noted by Tiffeneau (64).

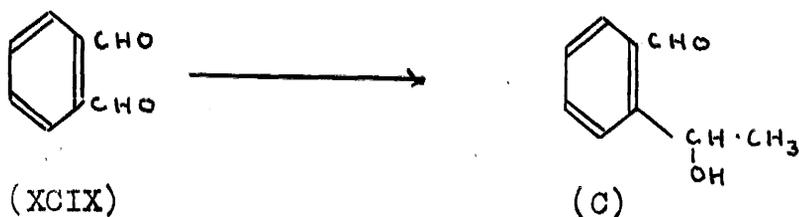


Two methods were examined for the attempted preparation of *o*-formylstyrene (XCV) by unambiguous routes. *o*-Bromobenzaldehyde was prepared by the Etard oxidation of *o*-bromotoluene (XCVI) according to the method of Reich and Chaskelis (65). *o*-Bromobenzaldehyde was condensed, under Grignard conditions, with methyl magnesium bromide, and the complex hydrolysed with saturated ammonium chloride to give *o*-bromophenylmethylcarbinol (XCVII) as a colourless oil, b.p.100-105°/0.1 mm. The latter on dehydration with sodium hydrogen sulphate at 200° and at 125 mm. gave in poor yield *o*-bromostyrene (XCVIII) as a colourless oil, b.p.61-63°/3 x 10⁻²mm. An attempt to form a Grignard complex of *o*-bromostyrene with magnesium and to react it with ethylorthoformate, by the entrainment method, to give on

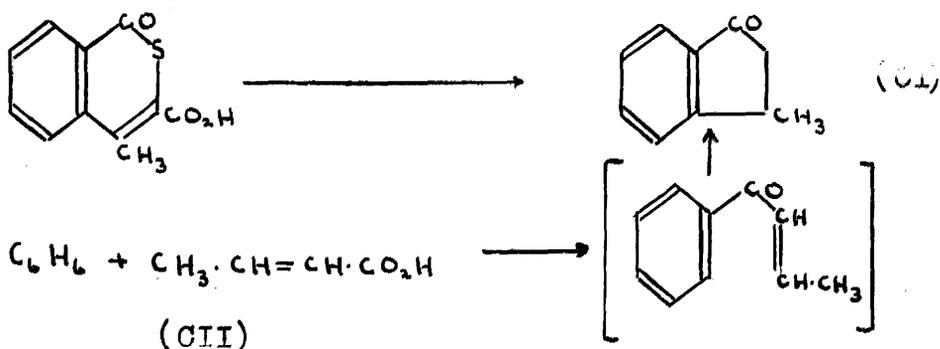
hydrolysis o-formylstyrene was unsuccessful and only unchanged starting material could be recovered from the reaction mixture.



As the failure in the latter synthesis was due to the lack of reactivity of the bromine atom, a fresh approach was made starting with o-phthalaldehyde (XCIX). One molecular proportion of methyl magnesium bromide was slowly added to a well stirred solution of o-phthalaldehyde in benzene so that reaction only took place at one of the formyl groups. If the phthalaldehyde solution had been added to the Grignard complex in the normal manner the product would have probably been the dimethyl carbinol. The product obtained from the reaction was, in fact, o-formylphenylmethylcarbinol (C) as a colourless oil, b.p. 86-88°/0.25 mm. o-Formylphenylmethyl carbinol on addition to sodium hydrogen sulphate at 200° decomposed with severe charring, and the only product that could be isolated from the reaction mixture was a very small quantity of unchanged starting material.



1:2-Dihydro-1-keto-4-methyl-2-thianaphthalene-3-carboxylic acid desulphurized smoothly on refluxing with a suspension of Raney nickel in ethanol, and 3-methylindan-1-one (CI) was formed in good yield. The product was isolated as an oil by steam distillation and characterised through its 2:4-dinitrophenylhydrazone and semicarbazone derivatives. The latter derivatives were found to be identical in m.p., and to have the same ultraviolet light absorption characteristics as specimens prepared from authentic 3-methylindan-1-one. The authentic indanone was prepared according to Koelsch, Hochmann, and Le Claire (66), from benzene and crotonic acid (CII) by an interesting application of the Friedel-Crafts reaction.



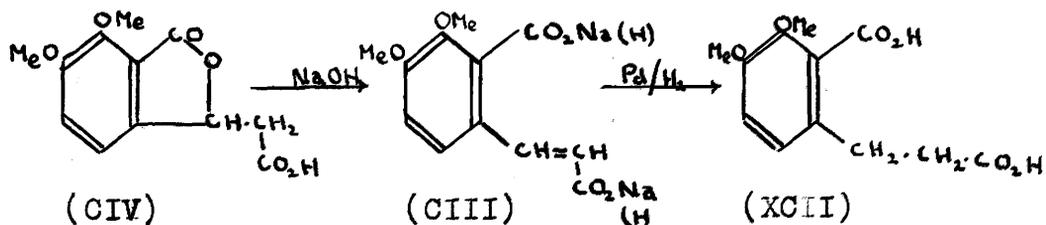
The method described above for the conversion of substituted 2-thianaphthalenes, on treatment with Raney nickel, into indan-1-ones is a general synthetic method

for the latter class of substances. It must be pointed out, however, that this method is far less efficient and more expensive in time and materials than the more normal routes described in the literature for the synthesis of indan-1-ones.

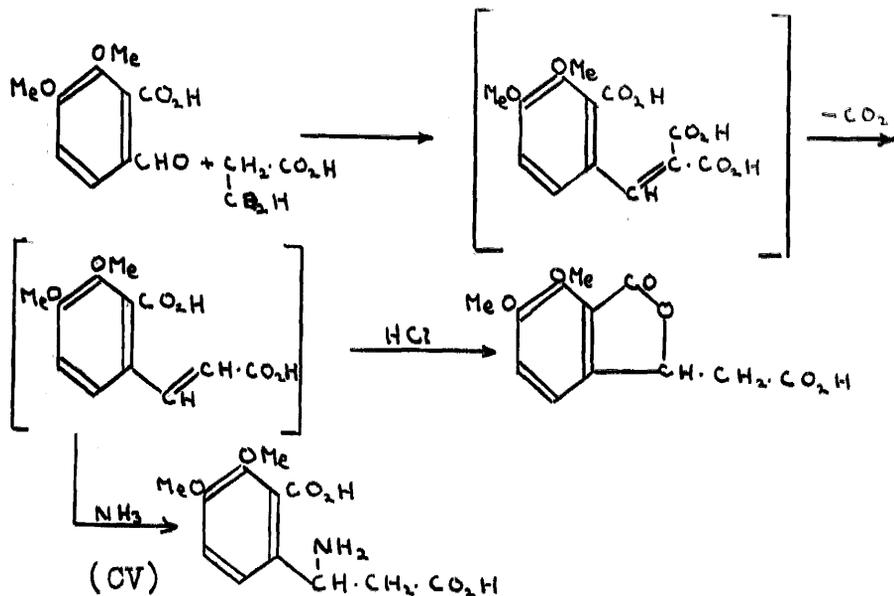
Condensation Products of Opianic Acid.

In the course of the preparation of authentic 6:7-dimethoxyindan-1-one several new intermediates were made, and owing to their interesting nature and chemistry, were studied concurrently with the synthesis of indan-1-ones.

Schöpf et al. (62) prepared 6:7-dimethoxyindan-1-one by the cyclisation of β -(2-carboxy-3:4-dimethoxyphenyl)-propionic acid (XCII), which they had obtained by the reduction of 2-carboxy-3:4-dimethoxycinnamic acid (CIII) with hydrogen in presence of a paladium catalyst. These authors prepared the intermediate cinnamic acid by vigorous hydrolysis of meconin acetic acid (CIV) to the disodium salt of (C) followed by careful acidification with cold dilute hydrochloric acid.

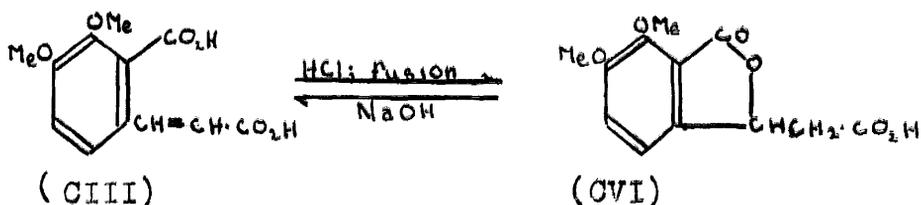


An attempt was made to prepare 2-carboxy-3:4-dimethoxycinnamic acid by the condensation of malonic acid with opianic acid by the Doebner modification of the Perkin reaction. On pouring the reaction solution into a mixture of concentrated hydrochloric acid and ice, the only product isolated was meconin acetic acid. It is, of course, quite probable that 2-carboxy-3:4-dimethoxycinnamic acid is formed transiently and lactonised under the reaction conditions; or more likely on pouring the reaction mixture into hydrochloric acid, when precipitation does not take place immediately. The product was compared and found to be identical with an authentic specimen of meconin acetic acid prepared according to the method of Rodinov and Fedorova (67). These authors condensed opianic acid with malonic acid in the presence of ethanolic ammonia, and isolated two products in equal yield. The first they showed was β -amino-(2-carboxy-3:4-dimethoxyphenyl)-propionic acid (CV) which was obtained as an acid insoluble product. The second was meconin acetic acid obtained by ethereal extraction of the filtrate. This behaviour indicates that lactonisation to meconin acetic acid occurs in the supersaturated acidic solution, as ring closure would not be expected to take place in the alkaline reaction medium.

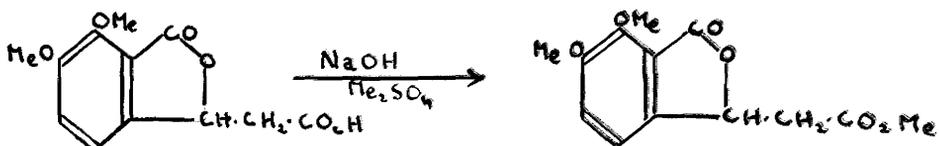


Schöpf et al.'s method for the hydrolysis of meconin acetic acid to the substituted cinnamic acid, by repeated evaporation to dryness with sodium hydroxide, was repeated and found to yield the required product, although the m.p. obtained was 8° lower than these authors reported. Schöpf et al. did not have their product analysed, and only showed it was different from meconin acetic acid by the depression in m.p. of a mixture. Repetition of this mixed melting-point determination showed there was no depression but merely an increase in the m.p. range. It was further found that 2-carboxy-3:4-dimethoxycinnamic acid on fusion was quantitatively converted into meconin acetic acid. Crystallisation of 2-carboxy-3:4-dimethoxycinnamic acid from 3N-hydrochloric acid also yielded meconin acetic acid, in agreement with the statement of Schöpf. Thus the ready interconversion of the substituted cinnamic acid

and the lactone means that in experiments where either of the compounds may be produced, the nature of the product must be found by molecular weight determination by titration with sodium hydroxide.



As Schöpf et al.'s method for the hydrolysis of meconin acetic acid is somewhat tedious in practice, a search was undertaken for alternative methods for the synthesis of 2-carboxy-3:4-dimethoxycinnamic acid. Meconin acetic acid was refluxed for two hours with two molecular proportions of sodium hydroxide, and the reaction solution taken to dryness under reduced pressure. The dried residue of sodium salts was refluxed with a methanolic solution of dimethylsulphate in the hope that methyl 2-carbomethoxy-3:4-dimethoxycinnamate would be obtained. The product isolated, however, on concentration of the reaction solution was a neutral ester $C_{13}H_{14}O_6$, m.p. 123.5-125°, and which was shown to be methyl meconin acetate (CVI) identical with a specimen prepared by the action of ethereal diazomethane on meconin acetic acid.

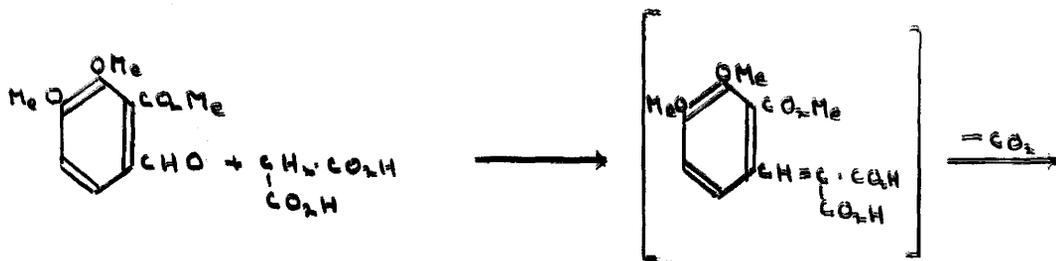


Methyl meconin acetate on refluxing with a molar proportion of sodium methoxide in methanol was smoothly converted into 2-carboxy-3:4-dimethoxycinnamic acid in almost quantitative yield (cf. Gabriel and Michael (47); Gabriel and Neumann (68)).



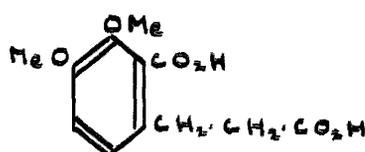
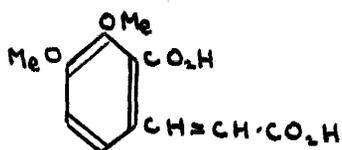
α -Methyl opianate condensed with malonic acid in the presence of piperidine and pyridine to give, on pouring the reaction solution into hydrochloric acid, 2-carbomethoxy-3:4-dimethoxycinnamic acid (CVII). In this case the ortho-carbomethoxy group blocks the possibility of cyclisation. The product can be reduced, in aqueous sodium hydrogen carbonate solution, by hydrogen at atmospheric pressure (in the presence of Adam's catalyst) to give β -(2-carbomethoxy-3:4-dimethoxyphenyl)-propionic acid (CVIII). The latter acid on alkaline hydrolysis gave the dicarboxylic acid, identical in physical properties with the acid obtained by Schöpf et al. from the reduction of 2-carboxy-3:4-dimethoxycinnamic acid.

2-Carbomethoxy-3:4-dimethoxycinnamic acid was converted by alkaline hydrolysis, followed by careful acidification of the cooled reaction solution, into the



(CVII)

(CVIII)

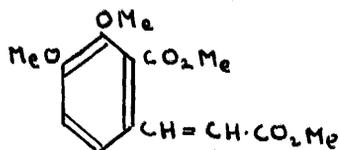


(CII)

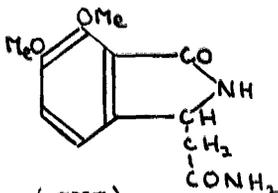
(XCII)

dicarboxylic acid. The monomethyl ester was readily esterified with dry methanol in the presence of concentrated sulphuric acid to give methyl 2-carbomethoxy-3:4-dimethoxycinnamate (CIX). The latter ester on treatment with methanolic ammonia at 100° gave a product, m.p. 218° , which analysed for $\text{C}_{12}\text{H}_{14}\text{O}_4\text{N}_2$ and which could have been either the diamide (CX) or the amide of 6:7-dimethoxyisoinindolinone-3-carboxylic acid (CXI), of the type prepared by Rowe, Haigh, and Peters (69). An examination of the ultraviolet light absorption spectra

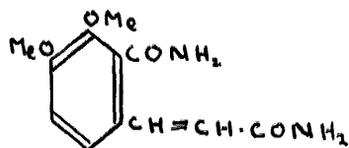
of the product showed that it closely approximated to that obtained from meconin acetic acid (CI) and showed wide divergences from the spectral curve of 2-carboxy-3:4-dimethoxycinnamic acid (C).



(CIX)



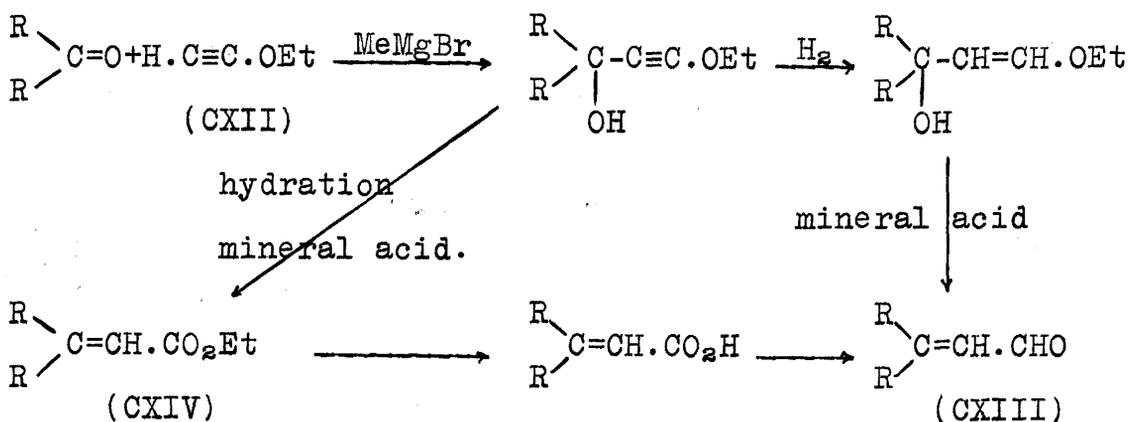
(CXI)



(CX)

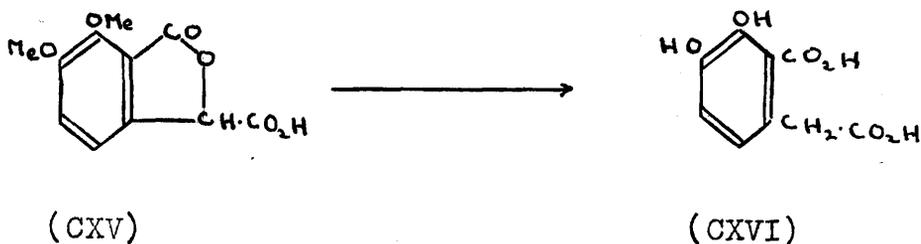
Unfortunately, the amide described above was destroyed in the fire in this Department before it had received more than a cursory examination. Hydrolysis with alkali had indicated that it was not a derivative of 2-carboxy-3:4-dimethoxycinnamic acid or of meconin acetic acid; consequently, the compound was more probably a derivative of isoindolinone than of cinnamic acid.

A further method for the lengthening of the aldehydic side chain in opianic acid, by the use of ethoxyacetylene (CXII) was examined. The use of this reagent for the preparation of α,β -unsaturated aldehydes (CXIII) was first noted by Van Dorp (70), and its extension to the synthesis of α,β -unsaturated ethyl esters (CXVI) was reported by Heilbron, Jones, Julia, and Weedon (71).



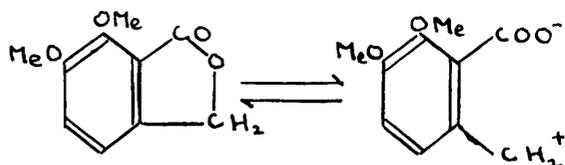
An ethereal solution of α -methyl opianate was added to a well cooled solution of the Grignard complex of ethoxyacetylene. After stirring for several hours the reaction mixture was poured into saturated ammonium chloride to hydrolyse the complex. The aqueous mixture on ethereal extraction only yielded unchanged α -methyl opianate, and not as was hoped ethyl 2-carbomethoxy-3:4-dimethoxycinnamate.

Schöpf et al. condensed opianic acid with sodium cyanide, and on subsequent hydrolysis with hydrochloric acid obtained meconin-3-carboxylic acid (CXV). The same authors found that the latter product, on heating with hydriodic acid and red phosphorus at 135°, was converted in 50% yield into 2-carboxy-3:4-dihydroxyphenylacetic acid (CXVI).



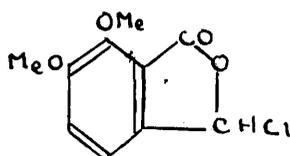
In an attempt to obtain 2-carboxy-3:4-dimethoxy-phenylacetic acid by a more direct route, α -methyl opianate was treated with anhydrous hydrogen cyanide in the presence of ammonia as a basic catalyst. A yellow oil was obtained as a product which could not be purified or identified.

Meconin was prepared by the reduction of opianic acid with sodium amalgam, according to the method of Liebermann (52), and treated with ethanol in the presence of hydrogen chloride. It was hoped that partial hydrolysis of the lactone ring would occur in solution and that recyclisation would be blocked by simultaneous esterification. A quantitative recovery of starting material was made, showing that there is no tautomerism in acid solution, i.e.



does not occur.

It was found that 3-chloromeconin (CXVII) on condensation with potassium or cuprous cyanide gave resinous intractable products which could not be identified.



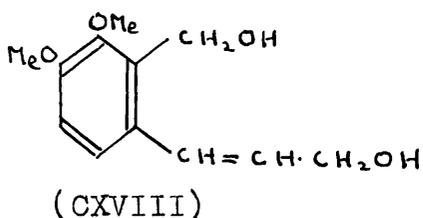
(CXVII)

Reduction of 1:2-Dihydro-1-keto-7:8-dimethoxy-2-thianaphthalene-3-carboxylic acid with Lithiumaluminium Hydride.

While the use of lithiumaluminium hydride as a specific reagent for the reduction of aldehydic, ketonic and carboxylic acid groupings, without reduction of unsaturated carbon centres, has been widely studied (72, 73), no record exists in the literature of its reaction with sulphur containing compounds. In view of the results obtained from the action of Raney nickel on 1:2-dihydro-1-keto-2-thianaphthalenes it was felt that lithiumaluminium hydride might well effect a similar desulphurisation.

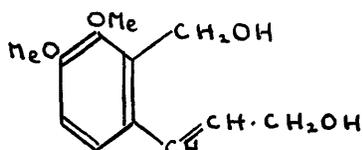
An ethereal solution of methyl 1:2-dihydro-1-keto-7:8-dimethoxy-2-thianaphthalene-3-carboxylic acid was slowly added to an excess of a suspension of lithium-aluminium hydride in ether. The mixture was refluxed for several hours, water added to destroy the excess of reagent, and acidified. The ethereal layer was separated and on removal of the solvent gave a yellow gum possessing a strong smell of hydrogen sulphide. The product was treated with methanolic sodium hydroxide in order to hydrolyse any unchanged ester to the acid. The neutral fraction gave a gum, which did not contain sulphur, and which could not be purified or identified. The acidic fraction gave a brown tar, which on treatment

with ethanol gave in very low yield a colourless crystalline material. The latter product was very soluble in chloroform, ether and ethyl acetate, and completely insoluble in ethanol and water. The compound separated from ethanolic chloroform as small prisms, m.p. 281-282°, and analysed for $C_{12}H_{16}O_4$. Although this analysis result was what was required for 2-hydroxy-methyl-3:4-dimethoxycinnamyl alcohol (CXVIII), the insolubility of the product in ethanol and its high m.p. were not in agreement with the expected properties of the above alcohol. No further products could be identified from the tar.

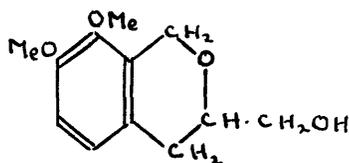


An attempt was made to prepare an authentic specimen of 2-hydroxymethyl-3:4-dimethoxycinnamyl alcohol by the application of lithiumaluminium hydride reduction to methyl 2-carbomethoxy-3:4-dimethoxycinnamate. The product obtained was a gum; and on hydrolytic treatment with methanolic sodium hydroxide was mainly recovered in the neutral fraction, still as a gum. Attempts to purify the gum or to obtain a solid 3:5-dinitrobenzoate from it were unsuccessful. It would thus appear that the solid product obtained from the thianaphthalene acid

was not the cinnamyl alcohol (CXVIII) but an isomer. Consideration of the mode of formation of the product shows that there is only one alternative formulation, 3:4-dihydro-3-hydroxymethyl-7:8-dimethoxy-2:1-benzopyran (CXIX). Unfortunately the quantity of the product obtained was so small (54 mg. from 2.2 g.) that sufficient material was not obtained to permit an examination of its structure to be undertaken. It can be claimed, however, that lithiumaluminium hydride does effect desulphurisation of the 2-thianaphthalenes; the gummy material obtained may well have been the expected cinnamyl alcohol.



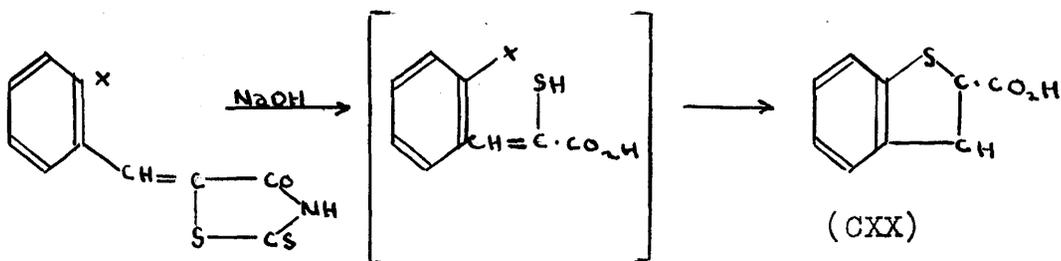
(CXVIII)



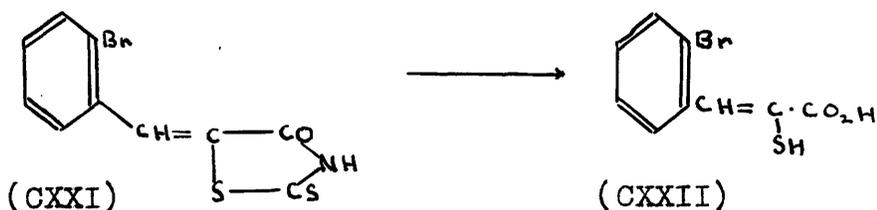
(CXIX)

Condensation of Rhodanine with o-Halogenobenzaldehydes.

In view of the success achieved by the internal condensation of o-carboxy- α -thiolcinnamic acids, it was considered possible that o-halogenobenzylidenerhodanines on hydrolysis would yield an intermediate that would cyclise by a similar route to give substituted benzthiophenes (CXX).

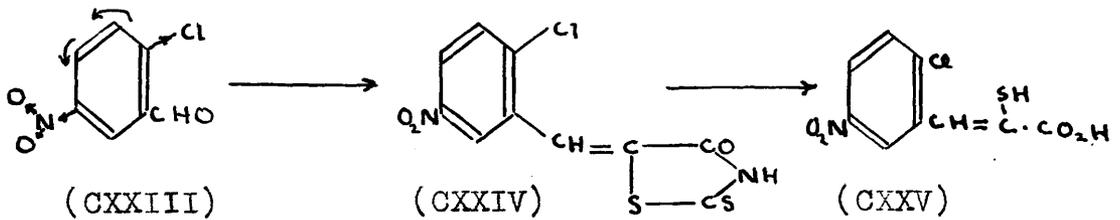


Consequently, o-bromobenzaldehyde was condensed with rhodanine to give o-bromobenzylidenerhodanine (CXXI). The latter on hydrolysis with aqueous sodium hydroxide gave a product which could only be purified with difficulty; it was obtained, however, as a colourless sublimate which still contained bromine, showing that cyclisation had not occurred. Although the product was destroyed in the fire in this Department before its examination was completed, it can confidently be formulated as o-carboxy- α -thiolcinnamic acid (CXXII).



In view of the above result, it was considered that activation of the halogeno atom with an ortho or para nitro group might enable cyclisation to take place. 2-Chloro-5-nitrobenzaldehyde (CXXIII) was prepared by the direct nitration of o-chlorobenzaldehyde. The nitroaldehyde condensed with rhodanine to give 5-(2'-chloro-5'-nitrobenzylidene)-rhodanine (CXXIV), which separated from the cooled reaction solution as well defined red needles. The rhodanine on hydrolysis with dilute caustic alkali, under varying conditions, gave

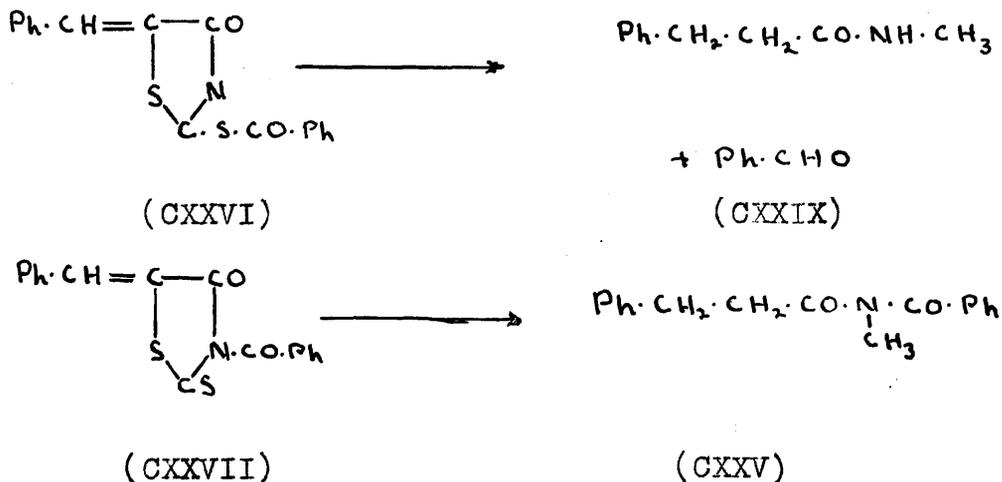
an intractable brown resin as product which could not be identified. 5-(2'-Chloro-5'-nitrobenzylidene)-rhodanine was not affected on refluxing with an aqueous suspension of barium hydroxide. With caustic alkali, hydrolysis probably proceeds in the first instance to 2-chloro-5-nitro- α -thiolcinnamic acid (CXXV) which immediately decomposes under the reaction conditions. This line of investigation was discontinued because of the lack of encouraging results.



Action of Raney nickel on 5-Benzylidenerhodanines.

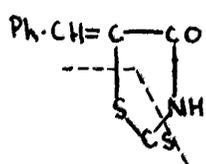
Gränacher (13) showed that 5-benzylidenerhodanine on treatment with benzoyl chloride gave a monobenzoyl derivative which Gränacher stated was the S-benzoyl derivative (CXXVI). It has been shown earlier in this Thesis that the principal acidic centre in 5-benzylidenerhodanine is the imino group. Thus one would have expected that the benzoyl derivative would be 3-benzoyl-5-benzylidenerhodanine (CXXVII). Desulphurisation of the rhodanine can obviously show whether the compound is a S- or a N-substituted rhodanine; since N-benzoylbenzylidenerhodanine would be expected to give N-benzoyl-N-

methylhydrocinnamamide (CXXVIII)(reduction of the intermediate cinnamic acid occurring under the reaction conditions), and S-benzoyl-5-benzylidenerhodanine to give a mixture of benzaldehyde and N-methylhydrocinnamamide (CXXIX).



The action of Raney nickel on 5-benzylidenerhodanine and on 5-benzylidene-3-methylrhodanine was investigated first as model cases. 5-Benzylidenerhodanine was refluxed with a suspension of Raney nickel in ethanol. The reaction solution gave a mixture of products, from which N-methylhydrocinnamamide and hydrocinnamamide (CXXX) were separated, together with an unidentified product, m.p.189-191°, which analysed for C₁₅H₁₆O₂N. Thus the desulphurisation has been followed by a remarkable split of a carbon-nitrogen link; this split was found to occur to the same extent in several different reactions, the two amides always being obtained

in approximately equal amounts.



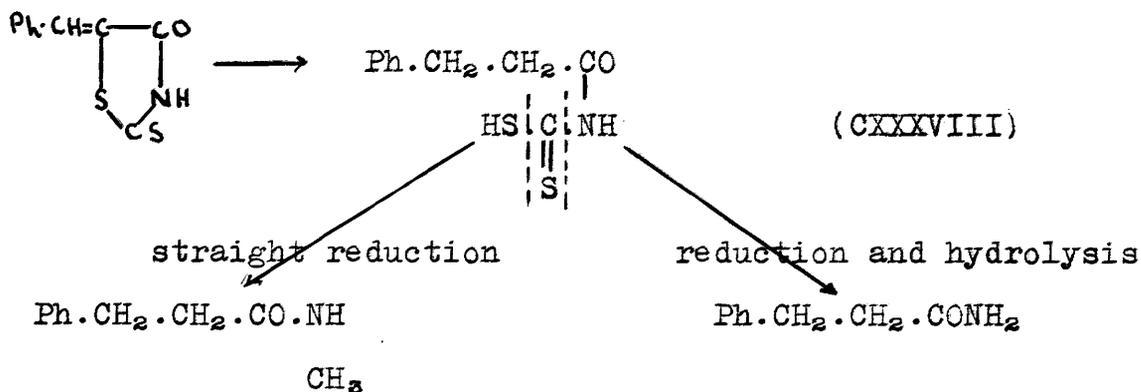
(a) m.p.189-191°

(b) Ph.CH₂.CH₂.CONH.CH₃

(c) Ph.CH₂.CH₂.CONH₂

(CXXX)

The isolation of N-methylhydrocinnamamide and of hydrocinnamamide shows that the reaction can proceed in two ways. It can be postulated that initial reduction gives the intermediate (CXXXVIII) which can either be reduced straightway to N-methylhydrocinnamamide, or alternatively hydrolysed under the reaction conditions to give hydrocinnamamide.



In the same way 5-benzylidene-3-methylrhodanine on treatment with Raney nickel gave a mixture of N-dimethylhydrocinnamamide and N-methylhydrocinnamamide. In this case, however, the dimethylhydrocinnamamide was the major reaction product.

The 5-benzylidenerhodanine benzoate desulphurised to give only one product. No trace of benzaldehyde

could be found in the reaction solution, indicating that the starting material was not the S-benzoyl derivative. The product obtained behaved as a mixture. It could not be separated by crystallisation, sublimation, or chromatography into two components. It melted over a considerable range, and consistent analyses could not be obtained for it. The remarkable feature of the analyses results was that they showed the product to contain over 10% of nitrogen, and to have a very low C value. These results cannot be explained on the basis of any normal reaction mechanism. The product on hydrolysis did not yield a pure acid, but a mixture in very low yield. Neither the acid nor the starting material were identified.

EXPERIMENTAL

EXPERIMENTAL.

All melting points are uncorrected.

Opianic acid.— (cf. Wegscheider, Monatsh., 1882, 3, 350).

Narcotine (50 g.) was dissolved in dilute sulphuric acid (750 c.c. water; 42.5 c.c. concentrated sulphuric acid) and the mixture heated to boiling. Manganese dioxide (30 g. of technical grade) was rapidly added portionwise. When the vigorous reaction had subsided the hot reaction mixture was filtered. The filtrate on cooling yielded discoloured crystals of opianic acid (20 g.; 79%), which separated from water (charcoal) as small colourless needles, m.p. 143-146°.

It was found that if precipitated manganese dioxide was used instead of technical grade quality, that due to the small particle size and consequently large surface area, oxidation proceeded too vigorously, and large amounts of a black tar were obtained with very low yields of opianic acid. It was also found that opianic anhydride is much more readily formed than is indicated in the literature; while Liebermann (Ber., 1886, 19, 2286) state that the anhydride is only formed on heating opianic acid for 16 hours at 160° in a stream of air, it was found in fact that drying in an oven at 100° for 2 hours gave a quantitative yield of the anhydride, m.p. 222-224°, which could be converted back into the acid on refluxing

with aqueous sodium hydroxide followed by acidification.

α -Methyl opianate.— (a) (According to Wegscheider, Monatsh., 1882, 3, 358.) Silver opianate (6.4 g.) (prepared from sodium opianate and silver fluoride in 43% yield), methyl iodide (10 c.c.) and methanol were shaken together for 2 hours; a further quantity of methyl iodide (10 c.c.) was added and shaking continued for a further 2 hours. The reaction mixture was filtered to remove precipitated silver iodide. The filtrate on concentration yielded a crystalline solid (4.2 g.) as plates, m.p. 100-102°. The product was found to be pseudomethyl opianate, and did not depress the m.p. of an authentic specimen of the pseudo ester prepared according to Ciamician and Silber, Ber., 1903, 36, 4271. None of the required α -methyl ester was isolated from the reaction mixture.

Found: C, 58.7; H, 5.5.

Calc. for $C_{11}H_{12}O_5$: C, 58.9; H, 5.4%.

(b) (cf. Bain, Perkin and Robinson, J., 1914, 2398). A hot concentrated aqueous solution of silver nitrate (20 g.) was added quickly with stirring to a hot solution of potassium carbonate (7.0 g.) and opianic acid (21.0 g.) in water (50 c.c.). Silver opianate quickly crystallised from the hot solution, and when cold the crystals were collected and washed with a little ethanol and ether. The silver salt was treated during 30 minutes with methyl

iodide (30 g.) in boiling ether (100 c.c.). The reaction mixture was filtered, and the residue of silver iodide well washed with ether. The combined filtrate and washings were concentrated under diminished pressure when α -methyl opianate (14.5 g.) was obtained as prisms, m.p. 75-80°.

Phthalaldehydic acid.— Phthalide (prepared from phthalimide according to Org. Synth., Coll. Vol. II, 526) was brominated either by direct passage of a stream of bromine through molten phthalide (ibid., 23, 74) or by the action of N-bromosuccinimide in chloroform (Hirshberg, Lavie, and Bergmann, J., 1951, 1033) to give 2-bromophthalide. Hydrolysis with water by the method described in Org. Synth. (loc. cit.) gave phthalaldehydic acid in 47% yield, m.p. 95-96°.

α -Methyl phthalaldehydate.— (cf. Graebe and Trümpy, Ber., 1898, 31, 375; Racine, Ann., 1887, 239, 84). Phthalaldehydic acid (30 g.) was added in small portions to a solution of potassium carbonate (14 g.) in water (100 c.c.); the resulting solution was heated to boiling when a hot concentrated aqueous solution of silver nitrate (40 g.) was added with stirring. The precipitated silver salt of phthalaldehydic acid was collected and washed with a little ethanol and ether, and treated during 30 minutes with methyl iodide (27 c.c.) in boiling

ether (200 c.c.). The precipitated silver iodide was well washed with ether, and the combined washings and filtrate on removal of the solvent gave α -methyl phthalaldehyde as a colourless oil (18 g.), b.p. 220-222°.

2-Carboxyacetophenone.— (cf. Gabriel and Michael, Ber., 1877, 10, 1554). Phthalic anhydride (30 g.), freshly fused potassium acetate (20 g.) and acetic anhydride (40 c.c.) were heated together under reflux. The temperature was first raised rapidly to 100°, and then more slowly to 150-160° and maintained at this temperature for 10 minutes. After the reaction solution had been cooled, the addition of hot water (100 c.c.) precipitated phthalylacetic acid (15 g.) as a pale yellow solid; m.p. 243-246° (decomp.). The latter acid (5 g.) on treatment with water (25 c.c.) at 200° for 4 hours gave a mixture of a tar and a clear aqueous solution. The aqueous phase was decanted from the tar and reduced in bulk under diminished pressure. 2-Carboxyacetophenone (1.8 g.) was precipitated; it separated from water as needles, m.p. 114-115°.

Rhodanine.— Rhodanine was prepared according to the method given in Org. Synth., 27, 73. The latter method gave rhodanine in good yield, whereas the method of Julian and Sturgis (J. Amer. Chem. Soc., 1935, 57, 1126)

invariably yielded carboxymethyl trithiocarbonate, as did the modification of their method proposed by Campbell and McKail (J., 1948, 1251).

5-(2'-Carbomethoxy-3'-4'-dimethoxybenzylidene)-rhodanine.—

α -Methyl opianate (10.0 g.) and rhodanine (6.0 g.) were dissolved in hot glacial acetic acid (30 c.c.) and powdered fused sodium acetate (12.0 g.) added. After heating under reflux for 30 minutes dissolution was complete and the hot reaction mixture was poured into cold water (500 c.c.). The precipitated solid was collected and crystallised from ethanol, when 5-(2'-carbomethoxy-3':4'-dimethoxybenzylidene)-rhodanine separated as yellow prisms, m.p. 191-193°.

Found: C, 49.7; H, 4.2; N, 3.7; S, 18.4.

$C_{14}H_{13}O_5NS_2$ requires: C, 49.5; H, 3.9; N, 4.1; S, 18.9%

Opianic acid and rhodanine.— Opianic acid (10.0 g.), rhodanine (6.0 g.) fused sodium acetate (12.0 g.) and glacial acetic acid (30 c.c.) were heated together under reflux for 30 minutes, and the hot reaction mixture poured into cold water (500 c.c.). A yellow solid (16.0 g.) separated which was insoluble in ethanol and the usual organic solvents. Crystallisation from water gave yellow needles of a sodium salt, decomposing without melting at ca. 220.

Found: C, 39.55; H, 4.5; N, 5.5; Na, 7.7.

$C_{13}H_{10}O_5NS_2Na \cdot 4H_2O$ requires: C, 39.45; H, 4.5; N, 3.5; Na, 5.8%.

Molecular weight determination by titration with 0.1N sodium hydroxide to phenolphthalein end-point gave a value of 420. 5-(2'-carboxy-3':4'-dimethoxybenzylidene)-rhodanine requires 162.5. The sodium salt on crystallisation from aqueous ethanolic hydrochloric acid gave a dicarboxylic acid as small prisms, m.p. 237-240° (decomp.). Equiv. 167. Light absorption in water: Maxima at 2700 ($\epsilon = 9400$) and at 2860Å ($\epsilon = 9800$); light absorption in 0.1N sodium hydroxide: Maxima at 3740 ($\epsilon = 17,800$) and an inflection at 2580Å ($\epsilon = 8100$). (cf. light absorption of 1:2-dihydro-1-keto-7:8-dimethoxy-2-thianaphthalene-3-carboxylic acid in 0.1N sodium hydroxide: Maxima at 3290Å ($\epsilon = 15,000$)).

5-(2'-Carbomethoxybenzylidene)-rhodanine. — α -Methyl phthalaldehyde (10 g.), rhodanine (6.0 g.), fused sodium acetate (12.0 g.) and glacial acetic acid (30 c.c.) were heated together for 30 minutes under reflux. On pouring the hot reaction mixture into water (500 c.c.) 5-(2'-carbomethoxybenzylidene)-rhodanine (4.5 g.; 60%) separated as a flocculent yellow precipitate. The product on crystallisation from ethanol was obtained as pale yellow needles, m.p. 215-216°.

Found: C,51.6; H,3.5; N,5.0; S,22.3.

$C_{12}H_9O_3NS_2$ requires: C,51.6; H,3.2; N,5.0; S,23.0%.

Light absorption in ethanol: Maxima at 2610 ($\epsilon = 8800$), 2780 ($\epsilon = 7600$) and at $3610\overset{\circ}{\text{Å}}$ ($\epsilon = 27,000$).

5-(2-Carboxybenzylidene)-rhodanine.— Phthalaldehydic acid (10.0 g.), rhodanine (6.0 g.), fused sodium acetate (12.0 g.) and glacial acetic acid (30 c.c.) were heated together under reflux during 30 minutes. When the hot reaction mixture was poured into cold water (500 c.c.) 5-(2'-carboxybenzylidene)-rhodanine was obtained in 74% yield. The latter compound separated from ethanol as yellow needles, m.p.265-266°.

Found: C,49.7; H,3.0. Equiv.134.

$C_{11}H_7O_3NS_2$ requires: C,49.8; H,2.7%. Equiv.132.5.

Light absorption in ethanol: Maxima at 2590 ($\epsilon = 7900$), 2830 ($\epsilon = 8000$) and at $3600\overset{\circ}{\text{Å}}$ ($\epsilon = 25,200$).

5-(2'-Carboxy- α -methylbenzylidene)-rhodanine.— 2-Carboxyacetophenone (1.8 g.) dissolved in glacial acetic acid (10 c.c.) was refluxed for one hour with rhodanine (1.35 g.) and fused sodium acetate (2.5 g.). The reaction solution was poured into water (300 c.c.) and the emulsion which formed, on standing overnight at 0°, deposited a brown tarry solid (2.4 g.). The product was twice crystallised from aqueous methanol (charcoal) to give 5-(2'-carboxy- α -methylbenzylidene)-rhodanine as

yellow needles, m.p.192-194°.

Found: C,52.0; H,3.7%. Equiv.141.5.

$C_{12}H_9O_2NS_2$ requires: C,51.6; H,3.2%. Equiv.139.5.

Light absorption in ethanol: Maxima at 2270 ($\epsilon = 8400$), 2560 ($\epsilon = 8000$), 2980 ($\epsilon = 11,400$) and at 3460Å ($\epsilon = 3300$).

5- α -Methylbenzylidenerhodanine. — 5- α -Methylbenzylidenerhodanine was prepared by the above method from acetophenone (2.4 g.), rhodanine (2.7 g.), fused sodium acetate (3.0 g.) and glacial acetic acid (10 c.c.) in 25% yield; it separated from methanol as yellow needles, m.p.166-167°. (Brown, Bradsher, McCallum and Potter, J.Org.Chem., 1950, 15, 174, give m.p.165-166° for 5- α -methylbenzylidinerhodanine prepared by the condensation of acetophenone with rhodanine in the presence of ammonium chloride in aqueous ammonia.)

Found: C,56.2; H,3.9; N,6.0%. Equiv.233.

Calc. for $C_{11}H_9ONS_2$: C,56.1; H,3.9; N,6.0%. Equiv.235.

Light absorption in ethanol: Maxima at 2780 ($\epsilon = 9300$) and at 3530Å ($\epsilon = 28,500$).

5-Benzylidenerhodanine. — (cf. Gränacher, Gerö, Ofner, Klopfenstein and Schlatter, Helv.Chim.Acta, 1923, 6, 458). Benzaldehyde (5 c.c.), rhodanine (5 g.), glacial acetic acid (20 c.c.) and fused sodium acetate (4 g.) were heated together under reflux during 30 minutes. On

pouring into water 5-benzylidenerhodanine separated, and on crystallisation from ethanol was obtained as yellow needles, m.p.199°.

Found: equiv.224.

Calc. for $C_{10}H_7ONS_2$: equiv.221.

Light absorption in ethanol: Maxima at 2720 ($\epsilon = 10,000$) and at 3740A ($\epsilon = 44,000$).

3-Methylrhodanine.— (cf. Andreasch and Zipser, Monatsh., 1904, 25, 167). Methyl isothiocyanate (7.3 g.; Org. Synth., 21, 81) and mercaptoacetic acid (11.0 g.) were heated together under reflux with ethanol (20 c.c.) and water (10 c.c.) for $2\frac{1}{2}$ hours. Water (10 c.c.) was then added and on cooling 3-methylrhodanine (15.5 g.) separated as almost colourless rods, m.p.72-72.5°. (Andreasch and Zipser, loc.cit., record m.p.72°).

5-Benzylidene-3-methylrhodanine.— (a) Benzaldehyde (3.0 g.), 3-methylrhodanine (3.8 g.), fused sodium acetate (5.0 g.) were heated together under reflux in glacial acetic acid (15 c.c.) during 15 minutes. The hot solution from which solid had separated was poured into cold water and the yellow product collected (4.5 g.; 61%); 5-benzylidene-3-methylrhodanine separated from methanol as light yellow needles, m.p.169-170°. (Andreasch and Zipser, loc.cit., give m.p.169°; preparation by the method of these authors (without the use of sodium

acetate) gives ca. 5% yield). Light absorption in ethanol: Maxima at 2720 ($\epsilon = 11,200$) and at 3750Å ($\epsilon = 38,000$).

(b) 5-Benzylidenerhodanine (0.5 g.) suspended in methanol (10 c.c.) was treated with a large excess of an ethereal solution of diazomethane (50 c.c. prepared from N-nitrosomethylurea (5.0 g.) and 15 c.c. of 50% aqueous potassium hydroxide). Dissolution was rapidly effected with evolution of nitrogen followed by the separation of crystals. The solution was concentrated and the yellow solid (210 mg.) m.p.162-164° which separated collected. Crystallisation from methanol gave 5-benzylidene-3-methylrhodanine as pale yellow needles, m.p.169-170° alone and in admixture with a specimen from preparation (a).

Found: C,56.2; H,4.2.

Calc. for $C_{11}H_9ONS_2$: C,56.1; H,3.9%.

5-(2'-Carbomethoxybenzylidene)-3-methylrhodanine.—

(a) α -Methyl phthalaldehyde (5.0 g.), 3-methylrhodanine (3.0 g.) and fused sodium acetate (6 g.) were heated together under reflux in glacial acetic acid (20 c.c.) for 1 hour. The hot solution was poured into water and the solid which separated, m.p.200-211° (6.0 g.) collected. Crystallisation from ethanol gave 5-(2'-carbomethoxybenzylidene)-3-methylrhodanine as pale yellow

needles, m.p.175-177°.

Found: C,53.4; H,3.4.

$C_{13}H_{11}O_3NS_2$ requires: C,53.3; H,3.75%.

Light absorption in ethanol: Maxima at 2620 ($\epsilon = 8000$), 2780 ($\epsilon = 7500$) and at $3610\overset{\circ}{\text{Å}}$ ($\epsilon = 26,900$).

(b) 5-(2'-carboxybenzylidene)-rhodanine (1.0 g.) was suspended in methanol and an excess of an ethereal solution of diazomethane (60 c.c.; prepared from N-nitrosomethylurea (4.0 g.)) was added. An immediate evolution of nitrogen occurred, but no solid material separated. When the reaction had apparently ceased, the solution was taken to dryness under reduced pressure, and a residue (1.0 g.) was obtained as an evil smelling yellow gum. The latter product was dissolved in 50% benzene/light petroleum (b.p.60-80°) and adsorbed on a column (1 x 12 cm.) of alumina (Grade II). The column was washed with the same solvent (500 c.c.) and 100 c.c. fractions collected. Removal of the solvent from the eluates only gave a yellow gum which would not crystallise.

(c) 5-(2'-Carbomethoxybenzylidene)-rhodanine (1.0 g.) was treated with an ethereal solution of diazomethane (60 c.c.; prepared from 4 g. N-nitrosomethylurea). A yellow gum was again obtained on removal of the solvent and absorption on a column (1 x 12 cm.) of alumina (Grade II) in benzene/light petroleum (b.p.60-80°) did not resolve the product. Further attempts to obtain

a solid product were also unsuccessful.

Condensation of 3-methylrhodanine with α -methyl opianate.—

α -Methyl opianate (3.3 g.), 3-methylrhodanine (2.0 g.) and fused sodium acetate (4.0 g.) were refluxed together under glacial acetic acid (15 c.c.) during 30 minutes. The hot reaction solution was poured into water and the yellow product (4.5 g.), m.p.163-230° collected. Only part of the reaction product was soluble in ethanol, and after crystallisation, had m.p.199-200°. Analysis showed the product was 5-(2'-carboxy-3':4'-dimethoxy-benzylidene)-3-methylrhodanine and not the expected 5-(2'-carbomethoxy-3':4'-dimethoxybenzylidene)-3-methylrhodanine.

Found: C,49.6; H,3.8%. Equiv.168.

$C_{14}H_{15}O_5NS_2$ requires: C,49.6; H,3.8%. Equiv.170.

$C_{15}H_{15}O_5NS_2$ requires: C,51.1; H,4.2%. Equiv.350.

The whole product from the condensation of α -methyl opianate and 3-methylrhodanine was continuously extracted with dry chloroform in a Soxhlet apparatus. The yellow chloroform solution obtained after two days extraction yielded, on removal of the solvent, a yellow solid, m.p.168-180°. The latter product on crystallisation from aqueous ethanol gave 5-(2'-carboxy-3':4'-dimethoxybenzylidene)-3-methylrhodanine as the only isolable product, m.p.199-200°, alone and in admixture with a

specimen obtained by direct crystallisation as described above.

Found: C,49.7; H,3.8%.

The residue left in the Soxhlet thinble was found to be a sodium salt, which on crystallisation from ethanol/dilute hydrochloric acid gave 5-(2'-carboxy-3':4'-dimethoxybenzylidene)-3-methylrhodanine, m.p.199-200°, alone and in admixture with a specimen obtained by chloroform extraction.

5-(2'-Carbomethoxy-3':4'-dimethoxybenzylidene)-2-amino-4-ketothiazolidine.— (cf. Libermann, Himbert and Hengl, Bull.Soc.Chim.,1948,17,1120). α -Methyl opianate (10.0 g.), ψ -thiohydantoin (5.5 g.) and fused sodium acetate (10.0 g.) were heated under reflux in glacial acetic acid (25 c.c.) for 2 hours. The hot reaction solution was poured into cold water (1000 c.c.) and the bright yellow solid which separated, m.p.206-215°, collected (2.5 g.). The reaction product could only be crystallised with difficulty from chloroform/light petroleum as prisms, m.p.273-274°, which did not analyse well for the required 5-(2'-carbomethoxy-3':4'-dimethoxybenzylidene)-2-amino-4-ketothiazolidine.

Found: C,51.4; H,4.9.

$C_{14}H_{14}O_5N_2S$ requires: C,52.3; H,4.35%.

The thiazolidene was very soluble in all the usual solvents

except water and light petroleum.

1:2-Dihydro-1-keto-7:8-dimethoxy-2-thianaphthalene-3-carboxylic acid.— (a) 5-(2'-Carbomethoxy-3':4'-dimethoxy-benzylidene)-rhodanine (3.0 g.) was heated with aqueous sodium hydroxide (20 c.c.; 15%) on the water-bath for 30 minutes. The reaction solution was cooled and poured into an excess of dilute hydrochloric acid and the precipitated solid collected. The latter separated from ethanol as small needles; 1:2-dihydro-1-keto-7:8-dimethoxy-2-thianaphthalene-3-carboxylic acid had m.p. 257-258°.

Found: C, 54.3; H, 4.0; S, 12.3%. Equiv. 264.

$C_{12}H_{10}O_5S$ requires: C, 54.1; H, 3.8; S, 12.0%. Equiv. 266.

$C_{13}H_{14}O_5S$ requires: C, 52.3; H, 4.7; S, 10.7%.

Light absorption in ethanol: Maxima at 2460 ($\epsilon = 29,500$), 3320 ($\epsilon = 14,600$), 3700 ($\epsilon = 11,300$) and at 3880Å ($\epsilon = 10,000$).

1:2-Dihydro-1-keto-7:8-dimethoxy-2-thianaphthalene-3-carboxylic acid was also obtained from the condensation product of opianic acid and rhodanine by the same alkaline treatment recorded above, followed by acidification;

Found: C, 54.3; H, 3.7%

or more simply by dissolving the acid in dilute sodium hydroxide in the cold and pouring into an excess of dilute

hydrochloric acid.

Found: C,54.0; H,3.4%. Equiv.264.

(b) Alkaline hydrolysis of 5-(2'-carbomethoxy-3':4'-dimethoxybenzylidene)-2-amino-4-ketothiazolidine followed by acidification also yielded 1:2-dihydro-1-keto-7:8-dimethoxy-2-thianaphthalene-3-carboxylic acid, m.p.257-258°, alone and in admixture with a specimen obtained from preparation (a).

Found: C,53.8; H,3.9%. Equiv.264.

Methyl 1:2-dihydro-1-keto-7:8-dimethoxy-2-thianaphthalene-3-carboxylate. — 1:2-Dihydro-1-keto-7:8-dimethoxy-2-thianaphthalene-3-carboxylic acid (0.5 g.) was suspended in dry methanol (10 c.c.) and an ethereal solution (30 c.c.) of diazomethane (prepared from 2 g. N-nitroso-methylurea) added. There was an immediate vigorous evolution of nitrogen followed by the separation of a crystalline solid, m.p.145-149° (0.4 g.). Crystallisation from ethanol gave methyl 1:2-dihydro-1-keto-7:8-dimethoxy-2-thianaphthalene-3-carboxylate as pale yellow laths, m.p.152-153°.

Found: C,55.5; H,4.4.

$C_{13}H_{12}O_5$ requires: C,55.7; H,4.3%.

1:2-Dihydro-8-hydroxy-1-keto-7-methoxy-2-thianaphthalene-3-carboxylic acid. — 1:2-Dihydro-1-keto-7:8-dimethoxy-2-thianaphthalene-3-carboxylic acid (0.5 g.) was heated

under reflux with constant boiling hydrobromic acid (20 c.c.) during 3 hours. The cooled reaction mixture was filtered and the greenish-yellow product crystallised from ethanol as very small needles, m.p.304-305°.

Found: C,52.6; H,3.5.

$C_{11}H_8O_5S$ requires: C,52.4; H,3.2%.

An ethanolic solution of 1:2-dihydro-8-hydroxy-1-keto-7-methoxy-2-thianaphthalene-3-carboxylic acid gave a dark olive-green colour with aqueous ferric chloride.

1:2-Dihydro-1-keto-2-thianaphthalene-3-carboxylic acid.—
5-(2'-Carbomethoxybenzylidene)-rhodanine (2.1 g.) was heated with aqueous sodium hydroxide (20 c.c.; 15%) on the water-bath during 1 hour. The cooled reaction solution on pouring into an excess of dilute hydrochloric acid gave 1:2-dihydro-1-keto-2-thianaphthalene-3-carboxylic acid (82%) which separated from aqueous ethanol as almost colourless prisms, m.p.261-263°.

Found: C,58.6; H,2.8%. Equiv.205.

$C_{10}H_8O_3S$ requires: C,58.2; H,2.9%. Equiv.206.

1:2-Dihydro-1-keto-2-thianaphthalene-3-carboxylic acid (80%) was also obtained from 5-(2'-carboxybenzylidene)-rhodanine by the same method. The product again separated from aqueous ethanol as prisms, m.p.261-263°, alone and in admixture with a specimen from the first preparation.

Found: C,58.5; H,3.1%. Equiv.204.

Light absorption in ethanol: Maxima at 2220 ($\epsilon = 29,000$), 2750 ($\epsilon = 5000$), 3000 ($\epsilon = 7100$), 3120 ($\epsilon = 7800$) and at 3470Å ($\epsilon = 7600$); an inflection was also observed at 2450Å ($\epsilon = 18,500$).

Methyl 1:2-dihydro-1-keto-2-thianaphthalene-3-carboxylate.—

An ethereal solution of diazomethane (30 c.c.; prepared from 2 g. N-nitrosomethylurea) was added to a solution of 1:2-dihydro-1-keto-2-thianaphthalene-3-carboxylic acid (0.5 g.) in dry methanol (10 c.c.). Evolution of nitrogen occurred immediately with separation of the methyl ester. Methyl 1:2-dihydro-1-keto-2-thianaphthalene-3-carboxylate was obtained as fine colourless needles, m.p.138-139°.

Found: C,59.9; H,3.6.

$C_{11}H_8O_3S$ requires: C,60.0; H,3.7%.

1:2-Dihydro-1-keto-4-methyl-2-thianaphthalene-3-carboxylic acid.— 5-(2'-Carboxy- α -methylbenzylidene)-rhodanine (350 mg.) was dissolved in aqueous potassium hydroxide (5 c.c.; 20%) and heated on the water-bath for 1 hour. The hot solution was cooled and poured into an excess of dilute hydrochloric acid. The precipitated acid was collected and crystallised from ethyl acetate/light petroleum (b.p.60-80°) to give 1:2-dihydro-1-keto-4-methyl-2-thianaphthalene-3-carboxylic acid (200 mg.)

as fine colourless needles, m.p.243-245°.

Found: C,60.1; H,3.7%. Equiv.217.

$C_{11}H_8O_3S$ requires: C,60.0; H,3.7%. Equiv.220.

Light absorption in ethanol: Maxima at 2480 ($\epsilon = 22,400$), 3000 ($\epsilon = 6300$) and at $3610\overset{\circ}{\text{Å}}$ ($\epsilon = 4800$).

Methyl 1:2-dihydro-1-keto-4-methyl-2-thianaphthalene-3-carboxylate. — 1:2-Dihydro-1-keto-4-methyl-2-thianaphthalene-3-carboxylic acid (0.5 g.) on treatment with an excess of an ethereal solution of diazomethane gave the methyl ester which separated from methanol as fine felted needles, m.p.152-154°.

Found: C,61.7; H,4.3.

$C_{12}H_{10}O_3S$ requires: C,61.5; H,4.3%.

1:2-Dihydro-1-keto-7:8-dimethoxy-2-thianaphthalene. — 1:2-Dihydro-1-keto-7:8-dimethoxy-2-thianaphthalene-3-carboxylic acid (0.65 g.) was heated to 330° for 5 minutes at atmospheric pressure in a sublimation unit. On cooling both the sublimate and the residue were extracted with chloroform and the combined extracts washed once with 2N potassium hydroxide and once with water and then dried over anhydrous sodium sulphate. The residue obtained on removal of the solvent was sublimed at 180°/0.1 mm. to give a yellow gummy sublimate (65 mg.). The sublimate was dissolved in dry

benzene (10 c.c.) and adsorbed on a column of alumina (Brockmann, Grade II; 1 x 7 cm.). The column was washed with benzene/ether (1:1; 50 c.c.) and the eluate evaporated to give an almost colourless solid A (20 mg.). Further elution with the same solvent (50 c.c.) and evaporation of the eluate gave a second solid B (15 mg.). Further elution of the column with ether gave a negligible residue.

Solid A, m.p.85-90°, was sublimed at 100°/0.5 mm. and the sublimate crystallised from light petroleum (b.p.60-80°) from which 1:2-dihydro-1-keto-7:8-dimethoxy-2-thianaphthalene separated as small needles, m.p.92-94°.

Found: C,59.3; H,4.6.

C₁₁H₁₀O₃S required: C,59.4; H,4.5%.

Light absorption in ethanol: Maxima at 2440 ($\epsilon = 20,000$), 2900 ($\epsilon = 4400$), and at 3800Å ($\epsilon = 2200$).

Solid B, m.p.148-150°, separated from light petroleum (b.p.80-100°) as fine needles, m.p.152°.

Found: C,54.6; H,4.2%.

A mixture of the solid B and 1:2-dihydro-1-keto-7:8-dimethoxy-2-thianaphthalene could be separated by sublimation at 100°/0.5 mm. when only the latter sublimed.

1:2-Dihydro-1-keto-2-thianaphthalene. — 1:2-Dihydro-1-keto-2-thianaphthalene-3-carboxylic acid (500 mg.) was heated to 330° for 10 minutes at atmospheric pressure

in a sublimation apparatus. Sublimation was then carried out at 150°/0.5 mm. The sublimate was dissolved in ether and washed with 2N sodium hydroxide and water; and the ethereal solution dried over sodium sulphate. The alkaline washings on acidification yielded a small quantity of unchanged acid (100 mg.). The ethereal solution was evaporated to dryness and the residue sublimed at 100°/0.5 mm. to give a yellow sublimate (130 mg.; 41%), m.p.77-78°. Two crystallisations from light petroleum (b.p.60-80°) gave 1:2-dihydro-1-keto-2-thianaphthalene as colourless needles, m.p.78-79°.

Found: C,66.6; H,3.7.

C₉H₈OS requires: C,66.6; H,3.7%.

Light absorption in ethanol: Maxima at 2130 ($\epsilon = 26,300$), 2430 ($\epsilon = 26,000$), 2650 ($\epsilon = 5400$), 2850 ($\epsilon = 5000$) and at 3450Å ($\epsilon = 4300$).

1:2-Dihydro-1-keto-2-thianaphthalene is insoluble in water but soluble in all the common organic solvents with exception of light petroleum. It dissolves on warming in 2N potassium hydroxide to give a colourless solution and does not reduce Fehling's solution on prolonged boiling.

1:2-Dihydro-1-keto-4-methyl-2-thianaphthalene. — 1:2-Dihydro-1-keto-4-methyl-2-thianaphthalene-3-carboxylic acid (150 mg.) was heated to 310-315° for 10 minutes at

atmospheric pressure in a sublimation apparatus. Sublimation was then carried out at $100^{\circ}/0.5$ mm. The sublimate was dissolved in ether and washed once with 2N sodium hydroxide and once with water and dried (sodium sulphate). The residue obtained on removal of the ether was sublimed at $100^{\circ}/0.5$ mm. The pale yellow sublimate (80 mg.) had m.p. $71-74^{\circ}$; it was dissolved in light petroleum (b.p. $60-80^{\circ}$) and adsorbed on a column of alumina (1 x 7 cm.; Grade II). The column was washed with the same solvent (50 c.c.); evaporation of the combined eluates gave a negligible residue. Elution with benzene gave a crystalline material, m.p. $75-77^{\circ}$ (60 mg.), which still retained a slight yellow colour. The colour was not removed by crystallisation from light petroleum (b.p. $60-80^{\circ}$) from which the material separated as fine needles. A colourless product was obtained by two sublimations at $80^{\circ}/0.5$ mm. subliming only the first two thirds of the material. In this way 1:2-dihydro-1-keto-4-methyl-2-thianaphthalene was obtained as colourless needles, m.p. $75-77^{\circ}$.

Found: C, 68.4; H, 4.6.

$C_{10}H_8OS$ requires: C, 68.1; H, 4.6%.

The yellow material gave consistently high C values. Light absorption in ethanol: Maxima at 2170 ($\epsilon = 29,000$), 2470 ($\epsilon = 25,000$), 2680 ($\epsilon = 5500$), 2870 ($\epsilon = 5000$), 2990 ($\epsilon = 5000$) and at $3510\overset{\circ}{\text{Å}}$ ($\epsilon = 4500$).

1:2-Dihydro-1-keto-7:8-dimethoxyisoquinoline-3-carboxylic acid. — 1:2-Dihydro-1-keto-7:8-dimethoxy-2-thianaphthalene-3-carboxylic acid (0.5 g.) was heated at 130° for 2½ hours with ethanolic ammonia (saturated at 0°) (20 c.c.) in a sealed tube. On cooling the solid ammonium salt (0.45 g.) which had separated as large, lustrous yellow needles was collected and dissolved in water (1 c.c.). The solution was made acid to Congo red with dilute hydrochloric acid when 1:2-dihydro-1-keto-7:8-dimethoxy-isoquinoline-3-carboxylic acid was precipitated (0.4 g.; 80%). The acid separated from ethanol as fine needles, m.p. 256-257°, alone or in admixture with an authentic specimen prepared after Bain, Perkin and Robinson, (J., 1914, 2392; see below).

Found: C, 58.1; H, 4.3; N, 5.7.

Calc. for C₁₂H₁₁O₅N: C, 57.8; H, 4.4; N, 5.6%.

Light absorption in ethanol: Maxima at 2210 ($\epsilon = 26,000$), 3120 ($\epsilon = 16,500$), 3400 ($\epsilon = 11,300$) and at 3450Å ($\epsilon = 11,300$).

5-(2'-Carbomethoxy-3':4'-dimethoxybenzylidene)-2-phenyl-oxazol-4-one. — (cf. Bain, Perkin and Robinson, loc. cit.). α -Methyl opianate (11.0 g.), hippuric acid (10.0 g.) and fused sodium acetate (6.0 g.) were heated together with acetic anhydride (25 c.c.) on a steam-bath for 3 hours. The red solution obtained was poured into water and when

all the acetic anhydride had decomposed the yellow precipitate was collected. Crystallisation from ethanol gave 5-(2'-carbomethoxy-3':4'-dimethoxybenzylidene)-2-phenyloxazolone as golden yellow needles, m.p.133-134° (loc.cit. give m.p.134°). Light absorption in ethanol: Maxima at 2630 ($\epsilon = 15,800$) and at 3900 ($\epsilon = 38,100$); an inflection was observed at 2770Å⁰ ($\epsilon = 11,500$).

1:2-Dihydro-1-keto-7:8-dimethoxyisoquinoline-3-carboxylic acid.— (cf. Bain, Perkin and Robinson, loc.cit.).

5-(2'-Carbomethoxy-3':4'-dimethoxybenzylidene)-2-phenyloxazol-4-one (5 g.) was heated on a boiling water-bath with aqueous sodium hydroxide (100 c.c.; 10%) during 30 minutes. The reaction solution was made acid to Congo red with dilute hydrochloric acid; the precipitated acid collected and well washed with hot water to remove benzoic acid. 1:2-Dihydro-1-keto-7:8-dimethoxyisoquinoline-3-carboxylic acid separated as small colourless needles from ethanol, m.p.257-258° (loc.cit. give m.p. 261°).

1:2-Dihydro-1-ketoisoquinoline-3-carboxylic acid.—

1:2-Dihydro-1-keto-2-thianaphthalene-3-carboxylic acid (0.5 g.) was heated for 2 hours at 130° in an autoclave with concentrated aqueous ammonia (25 c.c.; s.g.0.88).

The reaction solution was reduced in bulk (5 c.c.) under diminished pressure and acidified with dilute hydrochloric acid. The precipitated 1:2-dihydro-1-ketoisoquinoline-3-carboxylic acid separated from ethanol as fine needles, m.p. 326-328°, alone or in admixture with a specimen prepared by the alkaline hydrolysis of 5-(2'-carbomethoxybenzylidene)-2-phenyloxazol-4-one obtained by the condensation of α -methylphthalaldehyde and hippuric acid by the method described above. (Bain, Perkin and Robinson, loc.cit.). (These authors and Bamberger and Kitchelt, loc.cit. give m.p. 320°).

Found: C, 63.6; H, 3.3.

Calc. for $C_{10}H_7O_3N$: C, 63.5; H, 3.7%.

Light absorption in ethanol: Maxima at 2240 ($\epsilon = 18,600$), 2480 ($\epsilon = 8800$), 3010 ($\epsilon = 12,500$), 3220 ($\epsilon = 8800$) and at 3360Å ($\epsilon = 5600$).

1:2-Dihydro-1-keto-4-methylisoquinoline-3-carboxylic acid. — 1:2-Dihydro-1-keto-4-methyl-2-thianaphthalene-3-carboxylic acid (0.5 g.) was heated with concentrated aqueous ammonia (20 c.c.; s.g. 0.88) at 130° for 2 hours. The reaction mixture was cooled and the volume reduced in bulk (5 c.c.) under lowered pressure. Acidification (Congo red) with dilute hydrochloric acid precipitated 1:2-dihydro-1-keto-4-methylisoquinoline-3-carboxylic acid (65%) which separated from ethanol as small

colourless needles, m.p. 335-336°.

Found: C, 65.5; H, 4.7.

$C_{11}H_9O_3N$ requires: C, 65.0; H, 4.5%.

Light absorption in ethanol: Maxima at 2120 ($\epsilon = 20,500$), 2270 ($\epsilon = 14,500$), 2540 ($\epsilon = 5900$) and at 3070 ($\epsilon = 12,200$); inflection at $3250\overset{\circ}{\text{Å}}$ ($\epsilon = 8200$).

1:2-Dihydro-1-keto-7:8-dimethoxy-2-methylisoquinoline-3-carboxylic acid. — 1:2-Dihydro-1-keto-7:8-dimethoxy-2-thianaphthalene-3-carboxylic acid (0.5 g.) was heated at 130° with aqueous methylamine (20 c.c.; 40%) and ethanol (20 c.c.) for 2 hours. The reaction solution was concentrated under reduced pressure and acidified (Congo red) with dilute hydrochloric acid. The precipitated acid was crystallised from water to give 1:2-dihydro-1-keto-7:8-dimethoxy-2-methylisoquinoline-3-carboxylic acid monohydrate as well defined colourless needles, m.p. 198-199°.

Found: C, 55.1; H, 5.5.

$C_{13}H_{13}O_5N \cdot H_2O$ requires: C, 55.5; H, 5.4%.

Light absorption in ethanol: Maxima at 2230 ($\epsilon = 39,000$), 3050 ($\epsilon = 12,400$) and at 3460 ($\epsilon = 8500$).

1:2-Dihydro-1-keto-2-methylisoquinoline-3-carboxylic acid. — 1:2-Dihydro-1-keto-2-thianaphthalene-3-carboxylic acid (0.5 g.) was heated with aqueous methylamine (20 c.c.) and ethanol (20 c.c.) at 130° for 2 hours. The reaction

mixture was cooled, reduced in bulk and acidified (Congo red) with dilute hydrochloric acid. The precipitated solid was collected and on crystallisation from water 1:2-dihydro-1-keto-2-methylisoquinoline-3-carboxylic acid (80%) separated as fine colourless needles, m.p. 238-240° (Bamberger and Frew, *loc.cit.* give m.p.238°).

Found: C,65.2; H,4.1.

Calc. for $C_{11}H_9O_3N$: C,65.0; H,4.5%.

Light absorption in ethanol: Maxima at 2240 ($\epsilon = 32,700$) and at 2950 ($\epsilon = 10,000$); inflection at 3280Å ($\epsilon = 8200$).

2-Ethyl-1:2-dihydro-1-keto-7:8-dimethoxyisoquinoline-3-carboxylic acid. — 1:2-Dihydro-1-keto-7:8-dimethoxy-2-thianaphthalene-3-carboxylic acid (0.5 g.) was heated at 130° with ethanol (20 c.c.) and aqueous ethylamine (20 c.c.; 33%) for 2 hours. The reaction solution was cooled and the excess of ethylamine removed by distillation under reduced pressure. The residue was made acid to Congo red with dilute hydrochloric acid and the precipitated solid (0.32 g.; 70%) collected. Crystallisation from water gave 2-ethyl-1-keto-7:8-dimethoxyisoquinoline-3-carboxylic acid monohydrate as pale yellow needles, m.p.128-130°.

Found: C,57.4; H,5.4.

$C_{14}H_{15}O_5N.H_2O$ requires: C,56.9; H,5.6%.

On drying a specimen of the monohydrate at 70°/0.1 mm.

it became gummy and the m.p. rose to ca.160°. Light absorption in ethanol: Maxima at 2200 ($\epsilon = 33,200$), 3020 ($\epsilon = 11,500$) and at 3500Å ($\epsilon = 7700$).

2-Ethyl-1:2-dihydro-1-ketisoquinoline-3-carboxylic acid.—

1:2-Dihydro-1-keto-2-thianaphthalene-3-carboxylic acid (0.5 g.) was heated at 130° for 2 hours with ethanol (20 c.c.) and aqueous ethylamine (20 c.c.; 33%). The reaction solution was cooled and reduced in bulk under diminished pressure. The mixture was then acidified with dilute hydrochloric acid, and the precipitated acid collected. Crystallisation from water gave 2-ethyl-1:2-dihydro-1-ketisoquinoline-3-carboxylic acid as small prisms, m.p.200-201°. (Bamberger and Frew, loc.cit. give m.p.202°).

Found: C,66.6; H,5.0.

Calc. for $C_{12}H_{11}O_2N$: C,66.3; H,5.1%.

Light absorption in ethanol: Maxima at 2220 ($\epsilon = 18,800$) and at 2980 ($\epsilon = 8600$); inflection at 3270Å ($\epsilon = 6300$).

1:2-Dihydro-1-keto-2-phenylisoquinoline-3-carboxylic acid.— 1:2-Dihydro-1-keto-2-thianaphthalene-3-carboxylic acid (0.4 g.) was heated under reflux with aniline (5 c.c.) for 2 hours. The excess of aniline was partially removed under reduced pressure and the residual solution made acid to Congo red with dilute hydrochloric acid, and the precipitated acid (85%) collected. Crystallisation

from aqueous ethanol gave 1:2-dihydro-1-keto-2-phenyl-isoquinoline-3-carboxylic acid as small prisms, m.p. 272-273° (cf. Bamberger and Frew, loc.cit., whose preparation from isocoumarin-3-carboxylic acid had m.p. 265°).

Found: C,72.6; H,3.9.

Calc. for $C_{16}H_{11}O_3N$: C,72.4; H,4.2%

2-Benzyl-1:2-dihydro-1-ketoisoquinoline-3-carboxylic acid. — 1:2-Dihydro-1-keto-2-thianaphthalene-3-carboxylic acid (0.4 g.) was heated under reflux with benzylamine (5 c.c.) for 30 minutes. The cooled reaction mixture was poured into an excess of dilute hydrochloric acid and the precipitate (0.45 g.) collected. 2-Benzyl-1:2-dihydro-1-ketoisoquinoline-3-carboxylic acid separated from ethanol as small laths, m.p. 223-224°.

Found: C,73.1; H,4.7.

$C_{17}H_{13}O_3N$ requires: C,73.1; H,4.7%.

Light absorption in ethanol: Maxima at 2060 ($\epsilon = 39,000$), 3010 ($\epsilon = 11,500$) and at 3260 ($\epsilon = 6500$); inflection at 2230A ($\epsilon = 26,000$).

Attempted decarboxylation of 1:2-dihydro-1-keto-7:8-dimethoxyisoquinoline-3-carboxylic acid. — 1:2-Dihydro-1-keto-7:8-dimethoxyisoquinoline-3-carboxylic acid (200 mg.) was heated at 280° until effervescence ceased (ca. 10 minutes). The residue was allowed to cool and

then sublimed at $150^{\circ}/5.3 \times 10^{-3}$ mm. The white sublimate obtained, m.p. $225-228^{\circ}$, was dissolved in ether and washed with dilute sodium hydroxide and then twice with water. The ether solution was dried over sodium sulphate and yielded on subsequent removal of the ether a colourless residue (50 mg.). The latter product on sublimation at $150/10^{-3}$ mm. gave a neutral material as a sublimate, which separated from ethanol as small colourless needles, m.p. $233-234^{\circ}$.

Found: C, 58.1; H, 4.3.

$C_{11}H_{11}O_3N$ requires: C, 64.5; H, 5.4.

Calc. for $C_{12}H_{11}O_5N$: C, 58.1; H, 4.3%.

Bain, Perkin and Robinson, loc. cit., report 1:2-dihydro-1-keto-7:8-dimethoxyisoquinoline as having m.p. 233° ; they did not have their product analysed.

1:2-Dihydro-1-ketoisoquinoline. — (a) 1:2-Dihydro-1-keto-2-thiaphthalene (100 mg.) was heated with methanolic ammonia (15 c.c.; saturated at 0°) at 130° for 2 hours. The reaction mixture was evaporated to dryness and the residue crystallised from aqueous ethanol from which 1:2-dihydro-1-ketoisoquinoline (75 mg.) separated as small needles, m.p. 209° (Bamberger and Kitchelt, loc. cit. give m.p. 208°).

Found: C, 75.0; H, 4.5.

Calc. for C_9H_7ON : C, 74.5; H, 4.85%.

Light absorption in ethanol: Maxima at 2800 ($\epsilon = 9300$) and at 3240Å ($\epsilon = 4900$); cf. Ewing and Steel, J. Amer. Chem. Soc., 1946, 68, 2181, give maxima at 2800 ($\epsilon = 8000$) and at 3250Å ($\epsilon = 4500$).

(b) 1:2-Dihydro-1-ketoisoquinoline-3-carboxylic acid (200 mg.) (prepared from either 1:2-dihydro-1-keto-2-thianaphthalene-3-carboxylic acid or from 5-(2'-carbo-methoxybenzylidene)-2-phenyloxazol-4-one) was heated to 350° until effervescence ceased. The residue was sublimed at 150/10⁻⁵mm. The sublimate was dissolved in ether and washed once with 2N sodium hydroxide, once with water and dried over sodium sulphate. Removal of the ether and sublimation gave 1:2-dihydro-1-ketoisoquinoline which separated from aqueous ethanol as needles, m.p. 209-210°, alone and undepressed by a specimen from preparation (a).

Found: C, 74.65; H, 4.5%.

1:2-Dihydro-1-keto-4-methylisoquinoline. — (a) 1:2-Dihydro-1-keto-4-methyl-2-thianaphthalene (100 mg.) was heated with methanolic ammonia (15 c.c.; saturated at 0°) at 130° for 2 hours. The reaction mixture was evaporated to dryness and the residue crystallised from water, from which 1:2-dihydro-1-keto-4-methylisoquinoline separated as fine needles, m.p. 173-174°.

Found: C,75.7; H,5.5.

$C_{10}H_9ON$ requires: C,75.45; H,5.7%.

Light absorption in ethanol: Maxima at 2250 ($\epsilon = 16,200$), 2850 ($\epsilon = 8900$) and at 3310\AA ($\epsilon = 5400$).

(b) 1:2-Dihydro-1-keto-4-methylisoquinoline-3-carboxylic acid (10 mg.) was heated to $340-350^\circ$ until effervescence ceased and the residue sublimed at $120^\circ/10^{-5}\text{mm}$. The sublimate (2 mg.) crystallised from water as fine needles, m.p. $172-173^\circ$, alone or in admixture with a specimen from preparation (a).

Meconin acetic acid.— (a) (cf. Rodinov and Fedorova, J. Amer. Chem. Soc., 1930, 52, 370). Opianic acid (20 g.) and malonic acid (10 g.) were heated together under reflux with ethanolic ammonia (40 c.c.; 10%) for 2 hours on a boiling water-bath. The solvent was removed under reduced pressure and the condensation product dissolved in aqueous sodium hydroxide (20 c.c.; 10%), and the solution filtered to remove a small amount of tar. The filtrate was acidified to Congo red with dilute hydrochloric acid and extracted 3 times with ether (250 c.c.). Removal of the ether gave meconin acetic acid (11.0 g.; 45%) which separated from water as small plates, m.p. $166-167^\circ$.

(b) Opianic acid (10.0 g.), malonic acid (10.0 g.), pyridine (30 c.c.) and piperidine (2 c.c.) were refluxed

together on the water-bath for 2 hours. The reaction mixture was cooled and poured, with vigorous stirring into a mixture of chopped ice (150 g.) and concentrated hydrochloric acid (100 c.c.). A colourless solid (5.8 g.) m.p.163-165° separated immediately; the product separated from water as laths, m.p.166-167°, and did not depress the melting point of a specimen of meconin acetic acid obtained from preparation (a).

Found: C,57.0; H,5.1.

Calc. for $C_{12}H_{12}O_6$: C,57.2; H,4.8%.

Light absorption in ethanol: Maxima at 2120 ($\epsilon = 25,000$) and at 3050Å ($\epsilon = 4200$).

Treatment of meconin acetic acid with sodium hydroxide and dimethyl sulphate.— Meconin acetic acid (7.0 g.; 0.03 mole) was refluxed for 2 hours with aqueous sodium hydroxide (50 c.c.; 5%; 0.06 mole). The reaction solution was taken to dryness under reduced pressure and the white residue of sodium salts crushed and dried in vacuo over phosphorus pentoxide. The dried residue was refluxed for 2 hours with dimethyl sulphate (20 c.c.) and methanol (30 c.c.). On cooling the reaction solution set to a gel like mass which on vigorous stirring separated into a mixture which could be filtered. The residue (3.0 g.) m.p.54-132° was dissolved in hot ethanol and a small amount of an inorganic residue

(sodium sulphate) removed by filtration; the filtrate on concentration and cooling yielded unchanged meconin acetic acid, m.p.166-167°, alone or in admixture with a specimen of starting material.

The filtrate obtained from the gel, on dilution with water, gave a colourless solid (3.5 g.), m.p.79-104°. The latter material separated from ethanol as hexagonal plates, m.p.123.5-125.5° and analysed well for methyl meconin acetate.

Found: C,58.7; H,5.7.

$C_{13}H_{14}O_6$ requires: C,58.7; H,5.3%.

Methyl meconin acetate.— An ethereal solution of diazomethane (30 c.c.; from 2 g. N-nitrosomethylurea) was added, all at once, to a suspension of meconin acetic acid (1.26 g., in methanol (15 c.c.)). When evolution of nitrogen had ceased the reaction solution was reduced in bulk, and on cooling a solid product separated (1.1 g.). Crystallisation from ethanol gave methyl meconin acetate as plates, m.p.123.5-125°, alone or in admixture with a specimen prepared by the action of dimethyl sulphate on sodium meconin acetate.

Found: C,58.3; H,5.3.

Calc. for $C_{13}H_{14}O_6$: C,58.7; H,5.3%.

Treatment of methyl meconin acetate with sodium methoxide and methanol.— Methyl meconin acetate (1.33 g.) was

heated under reflux on a water-bath with a solution of sodium methoxide (from 0.12 g. sodium) in methanol (50 c.c.) for 1 hour. The solvent was removed under reduced pressure and the residue dissolved in water (20 c.c.). The aqueous solution was extracted with ether (3 x 30 c.c.) and the ethereal solution dried over sodium sulphate. Removal of the ether gave a negligible amount of a yellow gum. The aqueous phase on acidification with dilute hydrochloric acid yielded a discoloured yellow solid (0.75 g.), m.p. 159-161°, which separated from water as colourless needles, m.p. 165-166°. The product depressed the m.p. of meconin acetic acid by 10; equivalent weight determinations by titration against 0.01 N-sodium hydroxide (phenolphthalein) showed the product to be 2-carboxy-3:4-dimethoxycinnamic acid.

Found: C, 56.8; H, 4.7%. Equiv. 127.

Calc. for $C_{12}H_{12}O_6$: C, 57.2; H, 4.8%. Equiv. 125.

Treatment of α -methyl opianate with hydrogen cyanide.—
 α -Methyl opianate (4.0 g.) was dissolved in the minimum volume of methanol at 0° required for complete solution. The solution was cooled by immersion in an ice-bath and liquid hydrogen cyanide (50 c.c.) was added, followed by the addition of 4 drops of concentrated aqueous ammonia (s.g. 0.88). The mixture was allowed to stand

at room temperature for 48 hours, and the excess of hydrogen cyanide and the methanol were removed by distillation under reduced pressure. A yellow oil was obtained as a residue which could be neither crystallised nor distilled. In view of the intractable nature of the product the investigation of this reaction was abandoned.

Treatment of α -methyl opianate with ethoxyacetylene.—

Ethyl magnesium bromide was prepared by adding an ethereal solution (5 c.c.) of ethyl bromide (2.2 g.) to a well stirred suspension of Grignard magnesium (0.48 g.) in ether (5 c.c.). The solution was well cooled and ethoxyacetylene (1.4 g.) in ether (25 c.c.) added over 10 minutes with stirring. α -Methyl opianate (4.48 g.) in ether was added during 15 minutes; the solution was vigorously stirred for 2 hours at 0° and the temperature then allowed to rise slowly to room temperature and stirring continued for a further hour. The reaction mixture was poured into a saturated solution of ammonium chloride and the ethereal layer separated. The latter was washed twice with saturated ammonium chloride and once with water and dried over sodium sulphate. Removal of the ether under reduced pressure gave a crystalline residue (3.2 g.) m.p. 75-77° alone or in admixture with a specimen of α -methyl opianate. No other product could

be isolated.

Meconin.— (cf. Liebermann, Ber., 1896, 19, 2290). Opianic acid (4.2 g.) was dissolved in hot water and sodium amalgam (60 g.; 4%) was added. The mixture was heated on the water-bath with mechanical stirring for 6 hours. The mixture was filtered and the filtrate on cooling and extraction with ether gave meconin (3.6 g.). The product on crystallisation from water was obtained as colourless needles, m.p. 99-102°. (Liebermann, loc.cit. gives m.p. 102°).

Attempted hydrolysis of meconin.— Meconin (3.0 g.) was dissolved in dry ethanol (50 c.c.) under reflux. A stream of dry hydrogen chloride was passed for 3 hours and the reaction solution taken to dryness under reduced pressure. The residue (3.0 g.) m.p. 77-78° was found to be unchanged starting material.

3-Chloromeconin.— (cf. Meyer, Monatsh., 1901, 22, 783). Opianic acid (9.0 g.) and phosphorus trichloride (50 c.c.) were allowed to stand together at room temperature for 24 hours. The excess of phosphorus trichloride was removed by distillation under reduced pressure and the residue of 3-chloromeconin (9.2 g.) after one crystallisation from light petroleum (b.p. 60-80°) was obtained as colourless needles, m.p. 94°.

3-Chloromeconin and potassium cyanide.— 3-Chloromeconin (5.0 g.) and potassium cyanide (4.0 g.) were refluxed together in water (100 c.c.) for 3 hours. The reaction mixture was made acid to Congo red with dilute hydrochloric acid when a dark brown solid (1.0 g.) m.p.219° (decomp.) separated. The brown coloured filtrate was extracted with ether (both the ethereal and aqueous phases were strongly fluorescent in ultra-violet light: green and blue respectively). The ether extract after drying over sodium sulphate and removal of the ether gave a small quantity of a gum (50 mg.) which slowly crystallised on standing to give unchanged starting material, m.p.94°. The brown solid which was obtained as the main reaction product, and which appeared to be resinous in character, could not be purified; because of its intractable nature it was not investigated further.

3-Chloromeconin and cuprous cyanide.— 3-Chloromeconin (4.3 g.) was refluxed with a suspension of cuprous cyanide (4.0 g.) in dry pyridine (50 c.c.) for 4 hours. The reaction mixture was filtered, and the filtrate taken to dryness under reduced pressure. A black glass was obtained as a residue which was incapable of purification. Attempts to decolourise it by boiling with ethanol and activated animal charcoal were unsuccessful

as was an attempt to purify by sublimation. The examination of the product had to be abandoned because of its intractable nature.

2-Carbomethoxy-3:4-dimethoxycinnamic acid.— α -Methyl opianate (10.0 g.), malonic acid (10.0 g.) and piperidine (2 c.c.) were heated together under pyridine (50 c.c.) on the water-bath during 2 hours. The pale yellow reaction mixture was well cooled and poured into a mixture of ice (150 g.) and concentrated hydrochloric acid (100 c.c.) with vigorous stirring. A colourless solid (10.0 g.) rapidly separated and was removed by filtration. Crystallisation from ethanol gave 2-carbomethoxy-3:4-dimethoxycinnamic acid as colourless rectangular prisms, m.p.161-162°.

Found: C,59.05; H,5.7%. Equiv.264.

$C_{13}H_{14}O_6$ requires: C,58.8; H,5.3%. Equiv.266.

2-Carboxy-3:4-dimethoxycinnamic acid.— (a) 2-Carbomethoxy-3:4-dimethoxycinnamic acid (0.5 g.) was dissolved in aqueous potassium hydroxide solution (10 c.c.; 2N) and heated on the water-bath for 1 hour. The reaction solution was cooled in an ice-salt bath and made acid to Congo red with dilute hydrochloric acid, and the precipitated solid (0.35 g.) collected, m.p.157-160°. 2-Carboxy-3:4-dimethoxycinnamic acid separated from

water as small fine needles, m.p.171-172°.

Found: C,56.6; H,4.9%. Equiv.130.

Calc. for $C_{12}H_{12}O_8$: C,57.2; H,4.8%. Equiv.125.

(b) (cf. Schöpf et al., Ann.,1940,544,77). A solution of meconin acetic acid (4.5 g.) in aqueous potassium hydroxide (23 c.c.; 50%) was evaporated to dryness on the steam-bath. The residue was redissolved in water (23 c.c.) and the solution again taken to dryness. Water (50 c.c.) was then added and the solution, cooled in an ice-salt bath, acidified with dilute hydrochloric acid (2N) to Congo red. The precipitated 2-carboxy-3:4-dimethoxycinnamic acid separated from water as fine needles, m.p.171-172° (loc.cit. give m.p.178-180°); a mixture with meconin acetic acid had m.p.158-172°.

Found: C,57.2; H,4.9%. Equiv.125.

Light absorption in ethanol: Maxima at 2350 ($\epsilon = 15,000$) and at 3000 $\overset{\circ}{\text{A}}$ ($\epsilon = 18,900$).

Methyl 2-carbomethoxy-3:4-dimethoxycinnamate.— 2-

Carbomethoxy-3:4-dimethoxycinnamic acid (2 g.) was dissolved in dry methanol (100 c.c.) and concentrated sulphuric acid (2 c.c.) added; the solution was heated on the water-bath under reflux for 2 hours. The solution was concentrated under reduced pressure to 30 c.c., and the residue poured into water (400 c.c.). The resulting emulsion on standing at room-temperature for several

hours deposited small needles. The mixture was extracted with ether (3 x 100 c.c.) and the ethereal solution washed with saturated sodium hydrogen carbonate (100 c.c.) and with water (100 c.c.) and dried over sodium sulphate. Removal of the ether gave a yellow oil (1.8 g.) which solidified on treatment with methanol and water. Methyl 2-carbomethoxy-3:4-dimethoxycinnamate separated as well defined needles, m.p.64-66°.

Found: C,59.95; H,5.8.

$C_{14}H_{16}O_6$ requires: C,60.0; H,5.7%.

Effect of heat on 2-carboxy-3:4-dimethoxycinnamic acid.—

2-Carboxy-3:4-dimethoxycinnamic acid (100 mg.) was heated to just above its m.p. and maintained at that temperature (ca. 170°) for 30 seconds, and then allowed to cool. The resultant solid was crystallised from water, when meconin acetic acid separated as colourless laths, m.p.166-167°.

Found: C,57.3; H,5.0%. Equiv.265.

Calc. for $C_{12}H_{12}O_6$: C,57.2; H,4.8%. Equiv.252.

Action of hydrochloric acid on 2-carboxy-3:4-dimethoxy-cinnamic acid.—

2-Carboxy-3:4-dimethoxycinnamic acid (100 mg.) was dissolved in hot dilute hydrochloric acid (6 c.c.; 3N). On cooling meconin acetic acid separated as colourless laths, m.p.166-167°.

Found: C,57.35; H,4.85%. Equiv.248.

Calc. for $C_{12}H_{12}O_6$: C,57.2 ; H,4.8%. Equiv.252.

β -(2-Carbomethoxy-3:4-dimethoxyphenyl)-propionic acid.—

2-Carbomethoxy-3:4-dimethoxycinnamic acid (1.33 g.) was dissolved in water (100 c.c.) containing sodium hydrogen carbonate (0.42 g.), and the solution shaken with platinum (from 100 mg. of Adam's platinum oxide) in an atmosphere of hydrogen at 18° and 1 atmosphere pressure. When no further absorption of hydrogen took place (uptake 136 c.c.; calc. 132 c.c.) the catalyst was removed by filtration and the solution made acid to Congo red with dilute hydrochloric acid. The solution was extracted with ether (3 x 40 c.c.) and the combined ether extracts dried over sodium sulphate. Removal of the ether gave an oil as a residue which slowly solidified on storage.

β -(2-Carbomethoxy-3:4-dimethoxyphenyl)-propionic acid (0.71 g.) separated from light petroleum (b.p.40-60°) as small needles, m.p.88-89°.

Found: C,58.5; H,6.2%. Equiv.264.

$C_{13}H_{16}O_6$ requires: C,58.3; H,6.0%. Equiv.268.

β -(Carboxy-3:4-dimethoxyphenyl)-propionic acid.— β -(2-Carbomethoxy-3:4-dimethoxyphenyl)-propionic acid

(300 mg.) was dissolved in aqueous potassium hydroxide (5 c.c.; 2N) and the solution heated on the water bath for 1 hour. The reaction solution was acidified (Congo red) with dilute hydrochloric acid and extracted with ether (3 x 10 c.c.), and the ethereal solution

dried over sodium sulphate. Evaporation of the ether gave a yellow oil which was dissolved in benzene (5 c.c.) and the solvent boiled off. Crystallisation of the residue from benzene-light petroleum (b.p.40-60°) gave β -2-carboxy-3:4-dimethoxyphenyl)-propionic acid (260 mg.) as small prismatic needles, m.p.125-126° (Schöpf et al., loc.cit., give m.p.125-127° for the anhydrous acid prepared by catalytic hydrogenation of 2-carboxy-3:4-dimethoxycinnamic acid).

Found: C,56.5; H,5.7%. Equiv.125.

Calc. for $C_{12}H_{14}O_6$: C,56.7; H,5.6%. Equiv.127.

Action of methanolic-ammonia on methyl 2-carbomethoxy-3:4-dimethoxycinnamate.— Methyl 2-carbomethoxy-3:4-dimethoxycinnamate (1.0 g.) was dissolved in methanol (30 c.c.) saturated with ammonia gas at 0°. The solution was heated at 100-105° in an autoclave for 16 hours. After cooling the brown reaction solution was concentrated under reduced pressure when a brown residue (0.91 g.) m.p.210° was obtained. The product separated from methanol (charcoal) as small, colourless rods, m.p.215-217°. The material was finally crystallised from water when it was obtained as rods having m.p.218°.

Found: C,58.0; H,5.4; N,10.8.

$C_{12}H_{14}O_4N$ requires: C,57.6; H,5.6; N,11.2%.

Light absorption in ethanol: Maxima at 2120 ($\epsilon = 33,900$),

2280 ($\epsilon = 21,800$) and at $2960\overset{\circ}{\text{Å}}$ ($\epsilon = 5680$).

Raney-nickel.— The grade of Raney-nickel used in the following desulphurisations was that known as W.6 and was first prepared by Adkins and Billica (J.Amer.Chem. Soc., 1948, 70, 695) and later incorporated in Org.Synth., 29, 25).

6:7-Dimethoxyindan-1-one.— (a) 1:2-Dihydro-1-keto-7:8-dimethoxy-2-thianaphthalene-3-carboxylic acid (5.0 g.) was refluxed for 5 hours with suspension of Raney-nickel (50 g.) in ethanol (100 c.c.). The residue of nickel sludge was removed by filtration and well washed with ethanol. The combined filtrate and washings were taken to dryness under reduced pressure when an oily brown residue (3.5 g.) was obtained. The oil was dissolved in a little ethanol (5 c.c.) and the solution diluted with ether (100 c.c.). The ethereal solution was washed once with aqueous sodium hydroxide (20 c.c.; 5%) and twice with water and dried over sodium sulphate. Acidification of the alkaline wash liquors with dilute hydrochloric acid precipitated a small quantity (0.74 g.) of a pale yellow material, m.p. 249-252°; on crystallisation from ethanol it had m.p. 257-258° or in admixture with a specimen of starting material.

The ethereal extract on removal of the solvent yielded a pale yellow oil which could not be crystallised,

and which possessed no acidic properties. The oil (0.5 g.) on treatment with aqueous ethanolic semicarbazide acetate gave 6:7-dimethoxyindan-1-one semicarbazone (0.32 g.) m.p.178-188°. The product separated from aqueous ethanol as small needles, m.p.217-219° (decomp.).

Found: C,57.5; H,6.0.

Calc. for $C_{12}H_{15}O_3N_3$: C,57.8; H,6.0.

Calc. for $C_{12}H_{15}O_3H_3 \cdot H_2O$: C,54.9; H,6.4%.

Light absorption in ethanol: Maxima at 2210 ($\epsilon = 25,600$) and at 2810 ($\epsilon = 19,800$); inflection at 3100 $\overset{\circ}{\text{Å}}$ ($\epsilon = 9300$). It was undepressed in m.p. when mixed with a specimen of the authentic semicarbazone m.p.217-219° (decomp.). (Schopf et al., loc.cit. give m.p.217-219° (decomp.) for the monohydrate from ethanol, but quote no analysis results).

Addition of Brady's reagent to the crude 6:7-dimethoxyindan-1-one precipitated the 2:4-dinitrophenylhydrazone. The latter product was dissolved in benzene and adsorbed on a column of alumina (1 x 7 cm.; Brockmann Grade II). The column was washed with the same solvent (50 c.c. fractions). Removal of the solvent from the combined eluates gave almost pure 6:7-dimethoxyindan-1-one 2:4-dinitrophenylhydrazone. The product separated from benzene-light petroleum (b.p.60-80°) as small reddish-orange prisms, m.p.246-248° (decomp.), undepressed

on mixture with an authentic specimen of 6:7-dimethoxyindan-1-one 2:4-dinitrophenylhydrazone, m.p.246-248° (decomp.).

Found: C,55.3; H,4.2.

$C_{17}H_{16}O_6N_4$ requires: C,54.9; H,4.2.

$C_{18}H_{16}O_8N_4$ requires: C,52.0; H,3.85%.

Light absorption in chloroform: Maxima at 2490 ($\epsilon = 13,900$) and at $3900\overset{\circ}{\text{Å}}$ ($\epsilon = 29,100$).

(b) (cf. Schöpf et al., loc.cit.). β -(2-Carboxy-3:4-dimethoxyphenyl)-propionic acid (10.0 g.) was heated for 3 hours with acetic anhydride (100 c.c.) under reflux. The excess of acetic acid and acetic anhydride was removed by distillation under reduced pressure when a residue of unchanged acid and of product was obtained. With the apparatus still evacuated the oil bath temperature was raised to 200° when ring closure took place with evolution of carbon dioxide to give 6:7-dimethoxyindan-1-one. The author was unable to isolate the product by distillation (Schöpf gives b.p.186-190°/20 mm.) due to the considerable decomposition which took place at this temperature and to the relatively small quantity of material being used. Consequently, the black tarry product was dissolved in a small volume of ethanol (20 c.c.) and shaken with a concentrated aqueous solution of semicarbazide hydrochloride and sodium acetate.

The precipitated semicarbazone was collected and crystallised once from aqueous ethanol, and decomposed by refluxing with aqueous oxalic acid. The ketonic product was not isolated by steam distillation; the reaction solution was extracted with ether (3 x 20 c.c.) and the ethereal solution washed once with dilute sodium hydroxide, twice with water and dried over sodium sulphate. Evaporation of the ether gave 6:7-dimethoxyindan-1-one as a slightly discoloured solid, m.p.43-45° (Schöpf gives m.p.40-43°). The semicarbazone prepared from the product separated from aqueous ethanol as needles, m.p.217-219°. Light absorption in ethanol: Maxima at 2200 ($\epsilon = 19,000$) and at 2800 ($\epsilon = 25,000$); inflection at $3100\overset{\circ}{\text{Å}}$ ($\epsilon = 9000$).

6:7-Dimethoxyindan-1-one on treatment with Brady's reagent gave a bright red 2:4-dinitrophenylhydrazone. The latter was dissolved in benzene and adsorbed on a column of alumina (1 x 7 cm.; Grade II) and the 2:4-dinitrophenylhydrazone washed through with the same solvent. The combined eluates, on removal of the benzene, gave the required product as an orange-red solid, m.p.242-244° (decomp.). 6:7-Dimethoxyindan-1-one 2:4-dinitrophenylhydrazone separated from benzene-light petroleum (b.p.60-80°) as small prisms, m.p.246-248° (decomp.).

Found: C,55.4; H,4.2%.

Light absorption in chloroform: Maxima at 2470 ($\epsilon = 14,600$) and at $3910\overset{\circ}{\text{Å}}$ ($\epsilon = 29,000$).

Indan-1-one. — (a) 1:2-Dihydro-1-keto-2-thianaphthalene-3-carboxylic acid (2.7 g.) was heated under reflux for 5 hours with a suspension of Raney nickel (30 g.) in ethanol (100 c.c.). The residue of nickel was filtered off and well washed with ethanol. The combined filtrate and washings were taken to dryness under reduced pressure when an oily residue was obtained. Water (50 c.c.) was added to the reaction product and the mixture steam distilled. An oil separated from the distillate and was extracted with ether (3 x 20 c.c.). The ethereal solution was dried over sodium sulphate; evaporation of the solvent gave indan-1-one (1.3 g.) as an oil which could not be induced to solidify. The product was, consequently, characterised through its semicarbazone and 2:4-dinitrophenylhydrazone derivatives. The crude indan-1-one (0.5 g.) was converted into the semicarbazone (0.68 g.) by treatment with aqueous ethanolic semicarbazide acetate, and which separated from ethanol as small prisms, m.p. 237° (decomp.).

Found: C,63.8; H,5.4.

Calc. for $C_{10}H_{11}ON_3$: C,63.5; H,5.8%.

Light absorption in ethanol: Maxima at 2080 ($\epsilon = 17,000$),

2690 ($\epsilon = 16,300$), 2780 ($\epsilon = 16,200$), 2990 ($\epsilon = 14,600$) and at 3090 ($\epsilon = 12,900$); inflection at $2200\overset{\circ}{\text{Å}}$ ($\epsilon = 12,000$). The semicarbazone was not depressed in m.p. on mixture with an authentic specimen, m.p. 237° (decomp.) of indan-1-one semicarbazone (from a specimen of indan-1-one, m.p. $39-40^{\circ}$, prepared after Org. Synth., Coll. Vol. II, p. 336, in the stated yield; Revis and Kipping, J., 1871, 238, give m.p. 239° (decomp.); v. Auwers and Auffenberg, Ber., 1919, 52, 92, give m.p. 233° (decomp.)). Light absorption in ethanol: Maxima at 2070 ($\epsilon = 16,100$), 2700 ($\epsilon = 16,500$), 2970 ($\epsilon = 14,200$), 2800 ($\epsilon = 16,600$) and at 3080 ($\epsilon = 12,900$); inflection at $2200\overset{\circ}{\text{Å}}$ ($\epsilon = 12,700$).

A specimen of the crude indan-1-one (0.5 g.) was treated with an excess of Brady's reagent and the precipitated 2:4-dinitrophenylhydrazone (1.02 g.) collected. The product was dissolved in benzene (50 c.c.) and passed down a short column of alumina (1 x 7 cm. Grade II) to remove traces of unreacted reagent. Removal of the benzene from the eluate gave indan-1-one 2:4-dinitrophenylhydrazone which separated from ethyl acetate as bright red rods, m.p. $258-260^{\circ}$ (decomp.).

Found: C, 58.3; H, 3.7.

Calc. for $C_{15}H_{12}O_4N_4$: C, 57.8; H, 3.85%.

Light absorption in chloroform: Maxima at 2500 ($\epsilon = 13,500$) and at $3900\overset{\circ}{\text{Å}}$ ($\epsilon = 31,000$). The derivative

showed no m.p. depression on mixing with an authentic specimen of indan-1-one 2:4-dinitrophenylhydrazine (purified as above) m.p.258-260° (decomp.). (Allen, J.Amer.Chem.Soc.,1930,52,2955, give m.p.258°; Seka and Kellerman, Ber.,1942,75B,1730 give m.p.265°). Light absorption in ethanol: Maxima at 2500 ($\epsilon = 15,000$) and at 3890Å ($\epsilon = 30,800$).

(b) 1:2-Dihydro-1-keto-2-thianaphthalene (1.4 g.) was refluxed for 5 hours with a suspension of Raney nickel (14 g.) in ethanol (100 c.c.). The nickel sludge was removed by filtration and well washed with ethanol. Removal of the solvent from the washings and filtrate gave an oily residue (0.95 g.). Water (50 c.c.) was added and the mixture steam distilled. An oil, which solidified on cooling the distillate in ice, separated in the receiving flask. The solid (0.11 g.) was filtered off and sucked dry; it had m.p.35-38°. Sublimation of the solid at 60°/10⁻³mm. gave a colourless sublimate, m.p.38-40°, alone or in admixture with authentic indan-1-one, m.p.39-40°. The filtrate obtained after removal of the solid indan-1-one was extracted with ether, (3 x 25 c.c.), and the combined extracts dried over sodium sulphate. Evaporation of the ether gave a further quantity of indan-1-one (0.42 g.).

The crude product (0.25 g.) was converted into the semicarbazone (0.34 g.); indan-1-one semicarbazone separated from ethanol as small prisms, m.p. 237° (decomp.) alone or mixed with authentic indan-1-one semicarbazone.

Found: C, 63.4; H, 5.8%.

Light absorption in ethanol: Maxima at 2100 ($\epsilon = 17,000$), 2690 ($\epsilon = 17,100$), 2780 ($\epsilon = 17,200$), 2980 ($\epsilon = 14,500$) and 3080 ($\epsilon = 13,000$); inflection at 2200Å ($\epsilon = 13,000$).

A specimen of the crude indan-1-one (0.2 g.) on treatment with Brady's reagent gave the 2:4-dinitrophenylhydrazone (0.41 g.), which separated from ethyl acetate as bright red rods, m.p. 258-260°, alone and in admixture with an authentic specimen of indan-1-one 2:4-dinitrophenylhydrazone.

Found: C, 58.3; H, 3.7%

Light absorption in chloroform: Maxima at 2500 ($\epsilon = 14,400$) and at 3880Å ($\epsilon = 31,900$).

3-Methylindan-1-one. — (a) 1:2-Dihydro-1-keto-4-methyl-2-thianaphthalene-3-carboxylic acid (0.5 g.) was refluxed for 5 hours with a suspension of Raney nickel (5 g.) in ethanol (50 c.c.). The mixture was filtered and the sludge well washed with ethanol. The combined filtrate and washings were concentrated under reduced pressure to 5 c.c.; water (50 c.c.) was added and the mixture extracted with ether (4 x 20 c.c.). The ethereal solution

was washed once with aqueous sodium hydroxide (20 c.c.; 5%), once with water (20 c.c.) and dried (sodium sulphate). Removal of the ether gave a colourless oil as a residue (0.28 g.).

The crude product (0.14 g.) on treatment with an ethanolic aqueous solution of semicarbazide acetate gave 3-methylindan-1-one semicarbazone, which separated from ethanol as prisms, m.p. 231° (decomp.).

Found: C, 65.4; H, 6.1.

Calc. for $C_{11}H_{13}ON_3$: C, 65.0; H, 6.4%.

Light absorption in ethanol: Maxima at 2100 ($\epsilon = 16,500$), 2590 ($\epsilon = 17,700$), 2790 ($\epsilon = 18,400$), 2980 ($\epsilon = 15,300$) and at 3080Å ($\epsilon = 13,950$). The product was undepressed by a specimen of the semicarbazone, m.p. 231° (decomp.) prepared from authentic 3-methylindan-1-one from preparation (b). (v. Braun and Kirschbaum, Ber., 1913, 46, 3044, give same value for m.p.). The crude 3-methylindan-1-one (0.14 g.) on treatment with Brady's reagent gave a 2:4-dinitrophenylhydrazone (0.26 g.) which separated from ethyl acetate as lustrous red rods, m.p. 239-240° (decomp.).

Found: C, 59.3; H, 3.9.

Calc. for $C_{16}H_{14}O_4N_4$: C, 59.3; H, 4.3%.

Light absorption in chloroform: Maxima at 2500 ($\epsilon = 12,000$) and at 3890Å ($\epsilon = 31,200$). It showed no m.p. depression

when mixed with an authentic specimen, m.p.239-240° (decomp.) (Marvel, Dee and Cooke, J.Amer.Chem.Soc., 1940,62,3499, give m.p.239-241°).

(b) (cf. Koelsch, Hochmann and Le Claire, J.Amer.Chem.Soc.,1943,65,59). A solution of crotonic acid (23 g.) in benzene (170 c.c.) was slowly added to finely crushed anhydrous aluminium chloride (106 g.). When the initial reaction had somewhat subsided the mixture was heated, under reflux, for 5 hours on the steam bath. The cooled reaction solution was added from a dropping-funnel to a mixture of concentrated hydrochloric acid (100 c.c.) and ice (600 g.). The mixture was well stirred and allowed to stand at room temperature for 2 hours to complete hydrolysis. The organic layer was separated and filtered to remove small quantities of tar; it was washed once with dilute hydrochloric acid, twice with water, once with aqueous sodium hydroxide (5%) and finally twice with water and dried over calcium chloride. The dried solution was distilled under reduced pressure when 3-methylindan-1-one was obtained as a colourless oil (18 g.) b.p.108-111°/0.5 mm. The semicarbazone which separated from ethanol as small prisms had m.p.231° (decomp.). Light absorption in ethanol: Maxima at 2130 ($\epsilon = 15,100$), 2690 ($\epsilon = 18,100$), 2790 ($\epsilon = 18,600$), 2980 ($\epsilon = 15,900$) and at 3080^oA ($\epsilon = 14,600$). The 2:4-dinitrophenylhydrazone separated from ethyl acetate as prismatic rods, m.p.239-

240° (decomp.); it had light absorption in chloroform: Maxima at 2500 ($\epsilon = 11,000$) and at 3900Å ($\epsilon = 31,000$).

2-Bromobenzaldehyde.— (a) (cf. Adams and Vollweiller, J. Amer. Chem. Soc., 1918, 40, 1737). Bromine (18 g.) was added dropwise to 2-bromotoluene, maintained at 90° and irradiated with ultraviolet light. The oil bath temperature was then raised to 140° and a further quantity of bromine (80 g.) slowly added; the total time of addition was approximately 4 hours. The reaction product was refluxed for 8 hours with a mixture of calcium carbonate (600 g.) and water (1500 c.c.) and the hydrolysis mixture steam distilled. The distillate was extracted with ether (3 x 120 c.c.) and the ethereal solution dried over sodium sulphate. The yellow oil, obtained as a residue on evaporation of the ether, was shaken with an excess of an aqueous solution of sodium metabisulphite and the solid material which separated removed by filtration. (This residue was a severe lachramator and visicant, but was unfortunately destroyed in the fire in this department before an examination of its chemical nature could be undertaken.) The filtrate was made alkaline with sodium carbonate and steam distilled. An oil separated from the distillate and was extracted with ether. The ethereal solution was dried over sodium sulphate and on removal of the ether yielded

o-bromobenzaldehyde (30 g.). The product was distilled under reduced pressure when it had b.p.130-135°/0.5 mm.

(b) (cf. Reich and Chaskelis, Bull.Soc.Chim.,1916,19, 287). Chromic anhydride (60 g.) was added portionwise to a well stirred, cooled mixture of glacial acetic acid (180 c.c.), acetic anhydride (520 g.), concentrated sulphuric acid (90 g.) and o-bromotoluene (70 g.) at such a rate that the temperature was maintained between 5 and 10°. Stirring was continued for a further 2 hours after the addition of the chromic anhydride had been completed and the mixture then poured into ice water. The aqueous mixture was allowed to stand overnight at room temperature and then extracted with ether (5 x 200 c.c.). The ethereal solution was washed with sodium carbonate until the wash liquors remained alkaline, twice with water and dried over sodium sulphate. Removal of the ether gave a yellow oil which on distillation under reduced pressure gave o-bromotoluene (41 g.) b.p.65-70°/0.5 mm. as the first fraction and o-bromobenzaldehyde (24 g.) b.p.132°/0.5 mm. This method (b) was far quicker and more pleasant to operate than method (a).

o-Bromophenylmethylcarbinol.— Magnesium methyl iodide was made in the usual manner from magnesium (2.4 g.), methyl iodide (14.2 g.) and ether (100 c.c.). o-Bromobenzaldehyde (18.5 g.; 0.1 mole) dissolved in ether

(50 c.c.) was added dropwise to the mechanically stirred Grignard reagent, and the mixture warmed under gentle reflux for 2 hours. Water (10 c.c.) was added to destroy any unreacted magnesium methyl iodide, followed by the addition of saturated ammonium chloride (100 c.c.). The ethereal layer was separated and washed twice with saturated ammonium chloride, once with water and dried (sodium sulphate). Evaporation of the solvent gave a yellow viscous oil as a residue; the latter product on distillation under reduced pressure gave o-bromophenylmethylcarbinol as a viscous oil (11.1 g.) b.p.100-105°/0.1 mm.

o-Bromostyrene.— A mixture of o-bromophenylmethylcarbinol (11.1 g.) and picric acid (0.002 g.) was slowly added from a dropping-funnel to a mixture of sodium hydrogen sulphate (2.0 g.) and picric acid (0.005 g.) contained in a 25 c.c. 3-necked round-bottomed flask maintained at 200-220° by means of an oil-bath. The flask was fitted with a short fractionating column (4") surrounded by a vacuum jacket, and packed with glass heliscies. The column led to a small cold finger condenser and receiver. The system was partially evacuated (125 mm.); when all the o-bromophenylmethylcarbinol had been added the pressure was reduced to 20 mm., and distillation continued until no further product condensed

in the receiver. Distillation of the product under reduced pressure gave o-bromostyrene (4.0 g.) b.p. 61-63°/3 x 10⁻² mm. in poor yield.

Attempted preparation of o-formylstyrene from o-bromostyrene.— A solution of ethyl iodide (3.4 g.) in ether (50 c.c.) was added dropwise to a mixture of o-bromostyrene (4.0 g.), magnesium (1.05 g.), a crystal of iodine and ether (50 c.c.). The mixture was heated under reflux for 3 hours, and a solution of ethyl orthoformate (6.5 g.) in ether (50 c.c.) rapidly added over 5 minutes, and the mixture refluxed for a further 5 hours. The ether was removed by distillation on the steam bath; when almost all the solvent had been removed the residue was rapidly cooled by immersion in an ice-salt bath and allowed to stand overnight. Ice (50 g.) and cold dilute hydrochloric acid (125 c.c.; 5N) were added and the residual ether evaporated. The mixture was refluxed on the steam-bath for 30 minutes, and steam distilled until no more oil separated from the distillate. The distillate was extracted with ether (3 x 50 c.c.) and the ethereal solution dried over sodium sulphate. The dried solution was evaporated on the water bath to remove the ether and propionic aldehyde. A residue of a yellow oil (2.0 g.) was obtained and distilled at 60-65°/3 x 10⁻² mm. The product, which did

not possess any ketonic properties, was unchanged o-bromostyrene. No evidence of the formation of o-formylstyrene could be found.

o-Phthalaldehyde.— (cf. Thiele and Günther, Ann., 1906, 347, 107). (a) Bromine (70 c.c.) was slowly added to o-xylene (700 g.), irradiated by means of an ultraviolet lamp. The temperature was slowly raised, by means of an oil bath, to 120° at the end of the addition. The temperature was then raised to 160° and a further quantity of bromine (70 c.c.) added. The temperature was maintained at 160° for 2 hours and the warm reaction mixture poured into an evaporating basin. The liquid rapidly set to a light brown cake, which on crystallisation from chloroform gave tetrabromo-o-xylene as almost colourless needles (150 g.) m.p. 114°.

(b) The tetrabromo compound (60 g.), crystalline potassium oxalate (54 g.), water (375 c.c.) and ethanol (350 c.c.) were refluxed together for 40 hours, to give a clear yellow solution. The bulk of the ethanol was distilled off; the distillate was redistilled to a residue of 20 c.c., which was added to the original distilland. Sodium phosphate (110 g.) was added and the mixture steam distilled (1.5 l. of distillate was collected). The distillate was saturated with sodium chloride and extracted with ethyl acetate (10 x 75 c.c.),

and the combined extracts dried for 2 hours over anhydrous magnesium sulphate. The solvent was removed under reduced pressure and the residue heated at 100° under vacuum to remove the last traces of ethyl acetate. Light petroleum (b.p.60-80°) was added and the two phase mixture cooled and shaken when o-phthalaldehyde (15 g.) separated as needles, m.p.53-55°, which were dried in vacuo (phosphorus pentoxide).

o-Formylphenylmethylcarbinol.— A Grignard reagent was made in the usual manner from methyl bromide (12.5 g.), magnesium (2.6 g.) and ether (50 c.c.). When the formation of the complex was complete it was rapidly transferred to a dropping-funnel and added dropwise to a mechanically stirred solution of o-phthalaldehyde (15.0 g.) in dry ether (50 c.c.). The mixture was heated under reflux for 2 hours and then decomposed with an excess of dilute hydrochloric acid; destruction of the Grignard complex with saturated ammonium chloride resulted in the precipitation of a dark olive green solid and a black solution, although this did not appear to greatly influence the yield of product. The acidic solution was extracted with ether (3 x 30 c.c.) and the ethereal solution dried over magnesium sulphate. Removal of the ether gave o-formylphenylmethylcarbinol as an almost colourless oil, b.p.86-88°/0.25 mm.

Found: C,71.6; H,6.4.

$C_8H_{10}O_2$ requires: C,72.0; H,6.7%.

The oil with semicarbazone acetate gave o-formylphenylmethylcarbinol semicarbazone which separated from ethanol as prisms, m.p.217-219°.

Found: C,57.75;H,5.75;N,20.7.

$C_{10}H_{13}O_2N_3$ requires: C,58.0; H,6.3; N,20.3%.

The 2:4-dinitrophenylhydrazone separated from ethyl acetate-light petroleum (b.p.60-80°) as orange prisms, m.p.199°.

Attempted dehydration of o-formylphenylmethylcarbinol.—

A mixture of o-formylphenylmethylcarbinol (4.0 g.) and picric acid (0.002 g.) was slowly added from a dropping-funnel to a mixture of sodium hydrogen sulphate (1.0 g.) and picric acid (0.005 g.) maintained at 200° by means of an oil bath. The apparatus and method used have already been described under the preparation of o-bromostyrene (p.119). The distillation was carried out 125 mm. and a small quantity (0.3 g.) of a yellow oil collected in the receiver. Considerable decomposition took place with charring when o-formylphenylmethylcarbinol was added to the hot dehydrating agent. The oil collected was found to be ketonic, and gave with Brady's reagent an orange 2:4-dinitrophenylhydrazone, m.p.199°, alone and in admixture with a specimen prepared

from starting material. No evidence of dehydration having occurred could be found.

Action of lithium aluminium hydride on methyl 1:2-dihydro-1-keto-7:8-dimethoxy-2-thianaphthalene-3-carboxylate.—

Methyl 1:2-dihydro-1-keto-7:8-dimethoxy-2-thianaphthalene-3-carboxylate (2.2 g.) was placed in the Soxhlet thimble of a continuous ether extraction apparatus. The flask contained a suspension of finely ground lithium aluminium hydride (1.8 g.; 75% ether soluble) in ether (250 c.c.). The mixture was heated under reflux and with continuous mechanical stirring for 4 hours, by which time all the methyl ester from the Soxhlet thimble had been added to the contents of the flask. The reaction mixture was heated under reflux for a further 3 hours with continued stirring. Water was added cautiously to the well cooled reaction mixture to destroy any excess of unreacted lithium aluminium hydride. The mixture was acidified to Congo red with dilute sulphuric acid, a transient red colour being obtained, and the ethereal layer separated. The aqueous phase was extracted with ether (3 x 70 c.c.) and the combined ethereal solutions dried over sodium sulphate. Evaporation of the ether yielded a yellow gum (1.88 g.), possessing a strong smell of hydrogen sulphide. The product was dissolved in a little methanol (10 c.c.), filtered and heated with methanolic

potassium hydroxide (1 g. in 25 c.c. methanol) under reflux for 30 minutes in order to hydrolyse any unchanged ester to the acid. The reaction mixture was diluted with water (5 c.c.) and the methanol removed under reduced pressure. Water (30 c.c.) was added to the residue which was then extracted with ether (3 x 30 c.c.). Evaporation of the solvent from the dried (sodium sulphate) ethereal solutions gave a residue of a yellow gum A (0.26 g.).

The alkaline aqueous residue was acidified to Congo red with dilute hydrochloric acid; the acidified solution was bright red at first, but the colour gradually faded on standing. The solution was extracted with ether (3 x 30 c.c.) and the combined ether extracts dried over sodium sulphate. Evaporation of the ether gave a residue B (0.96 g.) as a dark brown tar. The latter product on treatment with ethanol (10 c.c.) gave a colourless solid (54 mg.), m.p. 271-273°. This material, which was completely insoluble in water and ethanol and was very soluble in chloroform, ether and ethyl acetate, separated from chloroform-ethanol as small prisms, m.p. 281-282°, and which analysed well for 2-hydroxymethyl-3:4-dimethoxycinnamyl alcohol.

Found: C, 64.3; H, 6.6

$C_{12}H_{16}O_4$ requires: C, 64.3; H, 7.1%.

Light absorption in chloroform: Maximum at 2800^oA
($\epsilon = 2430$). Neither the gum A nor the tar B could be induced to yield any further crystalline material.

Action of lithium aluminium hydride on methyl 2-carbomethoxy-3:4-dimethoxycinnamate.— Methyl 2-carbomethoxy-3:4-dimethoxycinnamate (8.0 g.) dissolved in dry ether (100 c.c.) was added over 2 hours to a well stirred suspension of lithium aluminium hydride (4.0 g.) in dry ether (200 c.c.). The mixture was heated under reflux for 5 hours with mechanical stirring; cooled, and the excess of lithium aluminium hydride destroyed by the addition of water (50 c.c.). The reaction solution was acidified to Congo red with dilute sulphuric acid. The ethereal layer was separated and the aqueous phase extracted with ether (4 x 50 c.c.). The combined ether solutions were dried over sodium sulphate, and on removal of the ether gave a pale yellow viscous oil (3.7 g.). The latter material could not be induced to deposit any crystalline products. The gum (1.0 g.) was dissolved in methanol (10 c.c.) and refluxed for 1 hour with methanolic potassium hydroxide (50 c.c.; 4%). The reaction mixture was diluted with water (50 c.c.) and the methanol removed by distillation under reduced pressure. The alkaline solution was extracted with ether (3 x 30 c.c.); the dried (sodium sulphate) ethereal

solution on evaporation of the solvent gave a gum which could not be crystallised. The aqueous phase was acidified with dilute hydrochloric acid and re-extracted with ether (3 x 30 c.c.). Removal of the ether from the dried extract again gave a gum as a residue (0.20 g.), which could not be induced to yield a solid product.

5-(2'-Bromobenzylidene)-rhodanine.— o-Bromobenzaldehyde (5.4 g.), rhodanine (4.0 g.) and fused sodium acetate (4.0 g.) were refluxed together in glacial acetic acid (30 c.c.) for 30 minutes. The dark brown reaction solution was poured into cold water (500 c.c.) and the resulting emulsion stored overnight at 0°, when the yellow solid (6.8 g.), m.p.151-160°, which had separated was collected. 5-(2'-Bromobenzylidene)-rhodanine separated from methanol as large, lustrous yellow needles, m.p.183-184°.

Found: C,40.2; H,2.7.

C₁₀H₈ONBrS₂ requires: C,40.0; H,3.0%.

2-Bromo- α -thiolcinnamic acid.— 5-(2'-Bromobenzylidene)-rhodanine (5.0 g.) was suspended in aqueous potassium hydroxide (50 c.c.; 20%) and heated on the water bath for 1 hour. The reaction solution was cooled and poured into an excess of dilute hydrochloric acid and the colourless precipitated acid collected (2.2 g.).

Considerable difficulty was experienced in finding a suitable solvent for the crystallisation of the product; it separated from aqueous ethanol or benzene-light petroleum (b.p.60-80°) as an oil. The material, however, sublimed at 100°/10⁻³ mm. to give 2-bromo- α -thiolcinnamic acid, m.p.123-137°. The sublimate was found to contain bromine, on qualitative analysis, and thus the product must be the thiolcinnamic acid and not benzthiophene. The product was unfortunately destroyed before its examination had been completed; the preparation was not repeated as it was felt that there was no chance of the desired product being formed.

2-Chloro-5-nitrobenzaldehyde.— (cf. Erdmann, Ann., 1893, 272, 153). o-Chlorobenzaldehyde (70 g.) was dissolved in concentrated sulphuric acid (160 c.c.) and the cooled, mechanically stirred, solution treated at 10-16° with a mixture of fuming nitric acid (s.g. 1.52; 44 g.) and concentrated sulphuric acid (80 c.c.), added dropwise. Stirring was continued for 30 minutes and the mixture poured onto ice; the precipitated nitroaldehyde was filtered off and well washed with water, saturated sodium carbonate and water again, and dried in vacuo over phosphorus pentoxide. 2-Chloro-5-nitrobenzaldehyde separated from chloroform-light petroleum (b.p.60-80°) as dense clusters of needles, m.p.77-79°. The product

gave with Brady's reagent a 2:4-dinitrophenylhydrazone which has not previously been described. It separated from nitrobenzene-light petroleum (b.p.100-120°) as small orange prisms, m.p.284-285° (decomp.).

Found: C,42.7; H,2.4.

$C_{13}H_8O_6N_5Cl$ requires: C,42.6; H,2.2%.

5-(2'-Chloro-5-nitrobenzylidene)-rhodanine.— 2-Chloro-5-nitrobenzaldehyde (9.3 g.), rhodanine (6.7 g.) fused sodium acetate (4.2 g.) and glacial acetic acid (30 c.c.) were refluxed together on the water bath during 30 minutes. On cooling the reaction solution deposited a red crystalline material (7.2 g.), m.p.248-249° (decomp.). The product was collected and washed with a little ethanol and ether; 5-(2'-chloro-5'-nitrobenzylidene)-rhodanine separated from ethanol as orange-red needles, m.p.250-251° (decomp.).

Found: C,39.2; H,1.7.

$C_{10}H_5O_3N_2S_2Cl$ requires: C,39.9; H,1.7%

Light absorption in ethanol: Maxima at 2620 ($\epsilon = 15,300$) and at 3620 $\overset{\circ}{\text{A}}$ ($\epsilon = 27,200$).

Hydrolysis of 5-(2'-chloro-5'-nitrobenzylidene)-rhodanine.— 5-(2'-Chloro-5'-nitrobenzylidene)-rhodanine (2.0 g.) was heated on the water bath with aqueous sodium hydroxide (20 c.c.; 20%) for 30 minutes. On pouring into an excess of dilute hydrochloric acid a dark brown solid separated.

The product which appeared to be resinous in character, was soluble in ethanol and insoluble in water, and could not be crystallised; on heating it decomposed without melting, and did not sublime at $200^{\circ}/10^{-5}\text{mm}$. Hydrolysis of the substituted rhodanine (2.0 g.) under less vigorous conditions with dilute sodium hydroxide (20 c.c.; 10%) on the water bath for 20 minutes, gave a product having similar characteristics to that previously described. 5-(2'-Chloro-5'-nitrobenzylidene)-rhodanine was recovered unchanged after refluxing for 2 hours with a suspension of barium hydroxide (8.0 g.) in water (50 c.c.).

Action of Raney nickel on 5-benzylidenerhodanine.— 5-Benzylidenerhodanine (3.0 g.) was refluxed for 5 hours with a suspension of Raney nickel (45 g.) in ethanol (100 c.c.). The mixture was filtered and the residue well washed with ethanol. The combined filtrate and washings were reduced in bulk (5 c.c.) and poured into water, and the precipitated solid, A, (105 mg.) collected. A separated from aqueous ethanol as small colourless needles, m.p. $189-191^{\circ}$.

Found: C, 74.9; H, 6.9; N, 5.9.

(Calc. for $\text{C}_{15}\text{H}_{16}\text{O}_2\text{N}$: C, 74.3; H, 6.6; N, 5.8%.)

Light absorption in ethanol: Maxima at 2100 and at
2600A

The filtrate was extracted with ether (3 x 60 c.c.); evaporation of the ether from the combined dried (sodium sulphate) extracts gave a residue (1.10 g.) which was a gum. The residue was dissolved in benzene (50 c.c.) and adsorbed on a column of alumina (Brockmann Grade II; 1 x 12.5 cm.); the column was eluted with the same solvent (50 c.c. fractions). Fractions I and II on evaporation of the solvent gave 160 mg. and 400 mg., respectively, of a yellow oil, B. Fractions III-VI gave gradually decreasing quantities (80, 70, 30, and 40 mg. respectively) of an oily solid. The column was then washed with methanolic benzene (2%) and fraction VII on evaporation to dryness gave an oil (390 mg.), C, which solidified on cooling.

The product from fractions I and II was combined and sublimed at 50-60°/7.7 x 10⁻²mm. to give a colourless oily sublimate (500 mg.) m.p.36-37°. Two further sublimations at 60°/10⁻²mm. gave N-methylhydrocinnamamide as colourless prismatic needles, m.p.56°. (Traverne, Rec.Trav.Chim.,1897,16,39 gives m.p.59-60° from ether).

Found: C,73.9; H,8.2; N,9.0.

Calc. for C₁₀H₁₃ON: C,73.6; H,8.0; N,8.6%.

B (400 mg.) was dissolved in methanol (5 c.c.) and heated for 2 hours on the steam bath with methanolic sodium hydroxide (20 c.c.; 10%). Water (10 c.c.) was added and the methanol removed under reduced pressure.

The residue was diluted with water (30 c.c.), and extracted with ether (3 x 30 c.c.). Evaporation of the ether from the dried extracts (sodium sulphate) gave unchanged N-methylhydrocinnamamide (140 mg.) as a yellow oil, which on sublimation was obtained as a colourless solid, m.p.56°, alone or in admixture with a specimen of starting material. The alkaline residue was acidified to Congo red with dilute hydrochloric acid, and extracted with ether (3 x 30 c.c.). The dried (sodium sulphate) ethereal solution on evaporation gave a yellow oil (120 mg.) as a residue, which solidified on storage for 2 weeks at 0°. The crude acid had m.p.37-38°; and on sublimation at 90°/10⁻³mm. hydrocinnamic acid, m.p.47°, alone or in admixture with a specimen of authentic hydrocinnamic acid, m.p.48°. (Erlenmeyer, Ann.,1866,137,330, gives m.p.47°; Wellgerodt and Merk, J.prakt.Chem.,1909,[2],80,196, give m.p.48°).

Found: C,72.4; H,7.1.

Calc. for C₉H₁₀O₂: C,72.0; H,6.7%.

C was crystallised from benzene-light petroleum (b.p.60-80°) when hydrocinnamamide separated as small needles, m.p.97-98°, alone or in admixture with an authentic specimen, m.p.101°, prepared from hydrocinnamic acid, thionyl chloride and aqueous ammonia. (Hofmann, Ber.,1885,18,2740, gives m.p.105° from water; Traverne, loc.cit.,p.255 gives m.p.103°).

Found: C,72.8; H,7.4; N,9.1.

Calc. for $C_9H_{11}ON$: C,72.5; H,7.4; N,9.4%.

The product (270 mg.) was hydrolysed with methanolic sodium hydroxide (25 c.c.; 4%) in the usual manner. The reaction solution was worked up as described above. A neutral fraction (120 mg.) was obtained which separated from benzene-light petroleum (b.p.60-80°) as needles, m.p.97°, undepressed by mixing with a specimen of starting material. The acid fraction yielded an oil (90 mg.) which on sublimation at 90°/10⁻⁵mm. gave hydro-cinnamic acid, m.p.45°, alone or in admixture with an authentic specimen of the acid.

Found: C,72.6; H,7.0.

Calc. for $C_9H_{11}O_2$: C,72.0; H,6.7%.

Action of Raney nickel on 5-benzylidene-3-methylrhodanine. —

5-Benzylidene-3-methylrhodanine (1.5 g.) was refluxed for 5 hours with a suspension of Raney nickel (23 g.) in ethanol (100 c.c.). The nickel residue was removed by filtration, washed with ethanol, and the combined filtrate and washings taken to dryness under reduced pressure. The residue (0.56 g.) was dissolved in benzene (50 c.c.) and adsorbed on a column of alumina (Grade II; 1 x 12 cm.). The column was washed with the same solvent (7 x 50 c.c.) and then with 5% methanolic benzene (50 c.c.). Fractions I, II and III contained

220, 160 and 35 mg., respectively, of an oil, A; fraction VIII yielded an oil, B, (120 mg.).

A was distilled at $90^{\circ}/10^{-3}$ mm. N-dimethylhydrocinnamamide was obtained as a colourless oil, b.p. $85-90^{\circ}/10^{-3}$ mm.

Found: C, 74.2; H, 8.3; N, 7.7.

Calc. for $C_{11}H_{13}ON$: C, 74.6; H, 8.5; N, 7.9%.

A (195 mg.) was hydrolysed with methanolic sodium hydroxide (25 c.c.; 8%) during 2 hours. Ether extraction (3 x 20 c.c.) of the alkaline solution yielded unchanged N-dimethylhydrocinnamamide (120 mg.). The solution was made acid to Congo red with dilute hydrochloric acid, and extracted with ether (3 x 20 c.c.). The dried (sodium sulphate) ethereal solution on evaporation of the solvent gave an oil (50 mg.), which after 3 sublimations gave hydrocinnamic acid (5 mg.) as a colourless solid, m.p. 44° , alone or in admixture with an authentic specimen having m.p. 48° .

B on sublimation at $90^{\circ}/10^{-2}$ mm. gave N-methylhydrocinnamamide as a colourless sublimate, m.p. 56° .

Found: C, 73.8; H, 8.4; N, 8.9.

Calc. for $C_{10}H_{13}ON$: C, 73.6; H, 8.0; N, 8.6%.

The product (70 mg.) on hydrolysis with methanolic sodium hydroxide (10 c.c.; 8%) gave unchanged starting material (40 mg.) in the neutral fraction, and hydrocinnamic acid (15 mg.) as an oil in the acid fraction.

The hydrocinnamic acid had, after sublimation, m.p.40° undepressed in admixture with an authentic specimen.

5-Benzylidene-3-benzoylrhodanine.— (cf. Gränacher, Helv.Chim.Acta,1920,3,152). 5-Benzylidenerhodanine (2.2 g.) was dissolved in ethanol (40 c.c.) and an aqueous solution of sodium hydroxide (8 c.c.; 5%) added. The solution was cooled in an ice-salt bath and benzoyl chloride (1.4 g.) added with shaking. The reaction solution was allowed to stand at room temperature for 1 hour when the mixture had solidified. The product was collected and crystallised from ethanol as prismatic needles, m.p.159-160° (loc.cit. give m.p.151-152°).

5-Benzylidene-3-benzoylrhodanine was insoluble in warm dilute aqueous sodium hydroxide; it showed light absorption in ethanol: Maxima at 2510 ($\epsilon = 18,200$) and at 3800Å ($\epsilon = 36,000$).

Raney nickel on 5-benzylidene-3-benzoylrhodanine.—

5-Benzylidene-3-benzoylrhodanine (0.9 g.) was refluxed with a suspension of Raney nickel (14 g.) in ethanol (100 c.c.) for 4 hours. The residue of nickel was filtered off and well washed with ethanol. Evaporation of the combined filtrate and washings to dryness under reduced pressure gave a gum as residue (0.44 g.). The product was dissolved in benzene (50 c.c.) and adsorbed on a column of alumina (Grade II; 1 x 10 cm.); the

column was washed with the same solvent 50 c.c. fractions being collected. Fractions I and II contained 30 and 20 mg., respectively, of a sweet smelling oil which was not examined. Further elution of the column with benzene (300 c.c.) yielded only negligible amounts of residue. The column was washed with 10% methanolic benzene (50 c.c.) and evaporation of the eluate to dryness gave a colourless solid as residue (230 mg.). Elution with methanol (250 c.c.) did not yield any further product in the combined eluates.

The product separated from benzene-light petroleum (b.p.60-80°) as needles, m.p.90-94°. Sublimation at 90°/10⁻³mm. gave a sublimate m.p.99-123°.

Found: C,68.7; H,7.3; N,10.6%.

The product (85 mg.) was hydrolysed with aqueous methanolic sodium hydroxide (10 c.c.; 10%) in the usual manner. A neutral fraction was obtained (55 mg.) which on sublimation at 90°/10⁻³mm. had m.p.99-123° alone or in admixture with a specimen of starting material. The acid fraction (15 mg.) on sublimation at 90°/10⁻³mm. gave a sublimate having m.p.77-106°. Insufficient material was obtained for an examination of this acid to be possible.

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PART II

THE USE OF ALIPHATIC DIAZO COMPOUNDS

in

ORGANIC SYNTHESIS

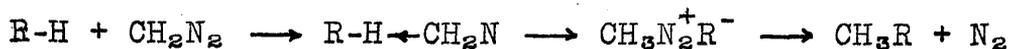
SUMMARY. Part II.

The condensation of diazoacetophenone and ethyl diazoacetate with amides and thioamides has been studied. It was found that these diazo compounds did not react with formamide, acetamide, benzamide, or p-nitrobenzamide; no reaction occurred between diazoacetophenone and urea or acetamidine hydrochloride. Diazoacetophenone condensed with S-benzylthiuronium hydrochloride to give benzylphenacyl sulphide.

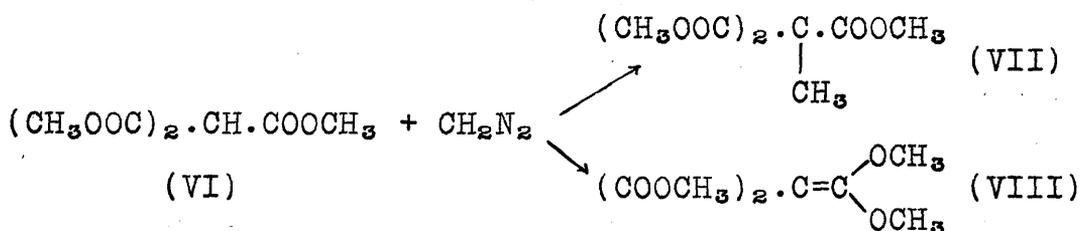
Diazoacetophenone and ethyl diazoacetate reacted with thiourea and with thioamides to give disubstituted thiazole derivatives. Ethyl diazoacetate condensed with imidazole to give the ethyl ester of 4-imidazole-acetic acid.

INTRODUCTION

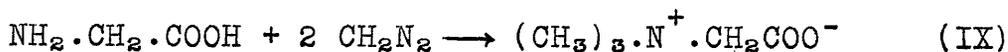
properties. Reaction of diazomethane with a compound (R-H) possessing a sufficiently acidic hydrogen atom, proceeds according to the following scheme (the diazomethane reacting as in formula (V)).



Diazomethane can react with compounds possessing keto-enol tautomerism in one of two ways. If the enol form is more acidic than the keto form, the enol ether is formed exclusively as the equilibrium shifts in its favour. If, however, the keto and enol forms possess similar acidities a mixture of products is obtained. Thus Arndt and Martius (4) showed that trimethyl methane-tricarboxylate (VI) yielded a mixture of trimethyl ethane-1:1:1-tricarboxylate (VII) and dimethyl ketene-dimethylacetal dicarboxylate (VIII).

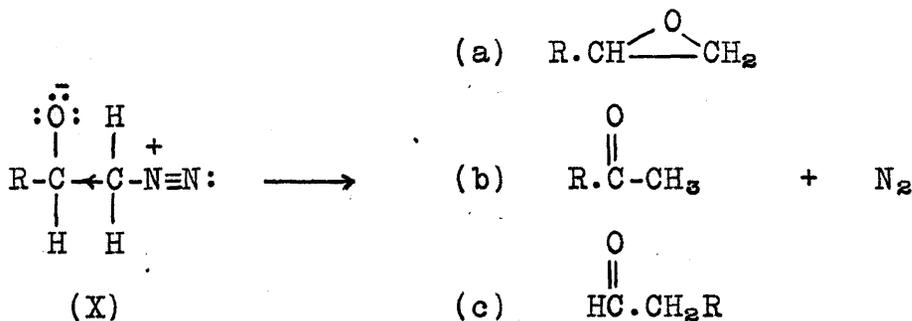


It has been shown by Biltz and Paetzold (5) that methylation and many addition reactions of diazomethane are catalytically accelerated by water or alcohol. Thus glycine does not react with diazomethane in dry ether, but on the addition of a little water or methanol a vigorous reaction takes place with the formation of betaine (IX).



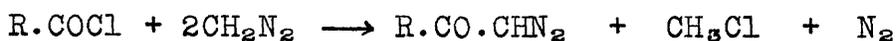
Diazomethane also reacts with the ammonium of amine salts of organic acids to yield the corresponding methyl esters (6), the amine being liberated.

In 1905 Meyer (7) discovered that diazomethane also reacts with aldehydes with the evolution of nitrogen. Schlotterbeck (8) showed that benzaldehyde and heptaldehyde yielded the corresponding methyl ketones. Arndt and Eistert (9) investigated this reaction systematically, and they found that the diazomethane entered into the carbonyl group of the aldehyde to give an addition product which can be designated as a diazonium betaine (X). The latter on slight warming loses nitrogen, and the rest of the molecule stabilises itself in one of three ways; it can form (a) the corresponding ethylene oxide, (b) the corresponding methyl ketone by anionic migration of the aldehydic hydrogen atom, or (c) the homologue of the starting aldehyde through anionic migration of the R-group.



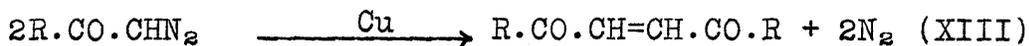
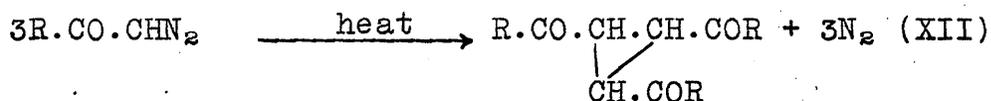
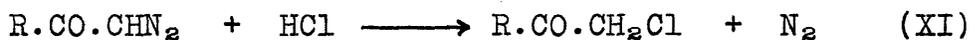
The three reactions proceed always side by side, the predominating reaction being dependent on the nature of the R-group. Ketones react with diazomethane in a similar manner (10,11,12).

Arndt, Eistert and other workers (13-16) showed that diazomethane readily reacts with acid halides to give diazo ketones.



While diazo ketones had been known earlier (17,18) they had been obtained through complex and troublesome reactions, and consequently had only limited preparative value. However, since they have become readily available, from acid chlorides and diazomethane, they have enjoyed considerable use as intermediates in organic synthesis.

Diazo ketones are quite stable towards alkalis, but are decomposed by concentrated halogen acids to give halomethyl ketones (XI)(17). Thermal decomposition of diazo ketones leads to cyclo propane derivatives (XII); while in the presence of copper compounds symmetrical diacylethylenes are formed (19).

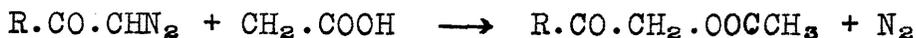


Dilute mineral acids, such as sulphuric acid, hydrolyse diazo ketones to hydroxymethyl ketones (XIV).

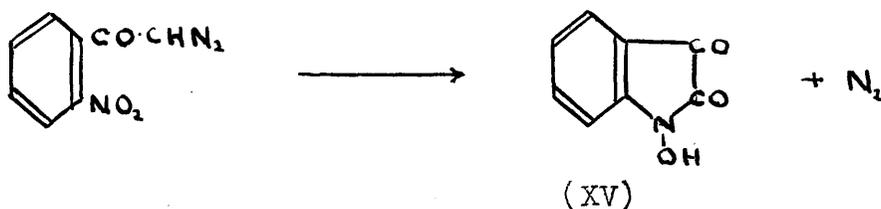


This latter reaction has been widely used in organic synthesis for the conversion of a carboxylic acid to a hydroxymethyl ketone. It has been used by Steiger and Reichstein (20) in the synthesis of compounds in the corticosterone series, and by Winterfeld and von Cosel (21) in the synthesis of lupinine.

Organic acids rapidly react with diazo ketones to form the corresponding esters of the hydroxymethyl ketones (22-24). Thus with glacial acetic acid, the acetate of the hydroxymethyl ketone is formed.

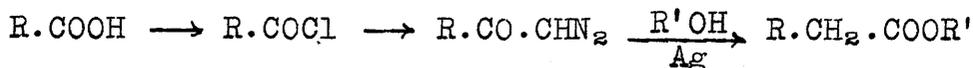


Ortho-substituted aromatic diazo ketones undergo ring closure on treatment with acids. Thus N-hydroxyisatin (XV) is obtained in good yield from diazo-o-nitroacetophenone (25).



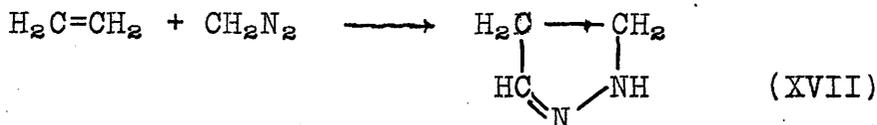
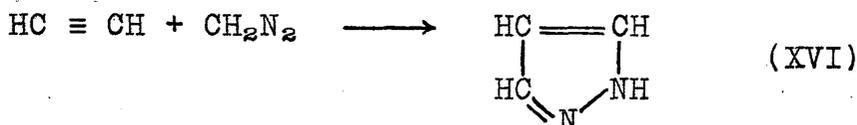
Finally, brief mention must be made of the Arndt-Eistert reaction (26). These authors showed that on hydrolysis of a diazo ketone in the presence of alcohol

and a metallic catalyst, decomposition occurred with the liberation of nitrogen, followed by the rearrangement of the residual molecule to yield derivatives of the homologous acid.



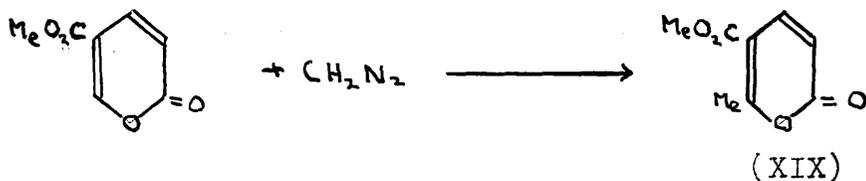
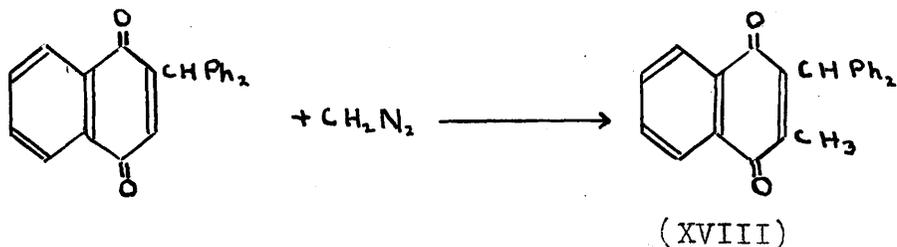
The Arndt-Eistert reaction has been of considerable value in the synthesis of natural products because of the relatively mild reaction conditions.

Diazomethane adds to acetylene and ethylene with the formation of pyrazole (XVI) (27,28) and pyrazoline (XVII)(29) respectively.

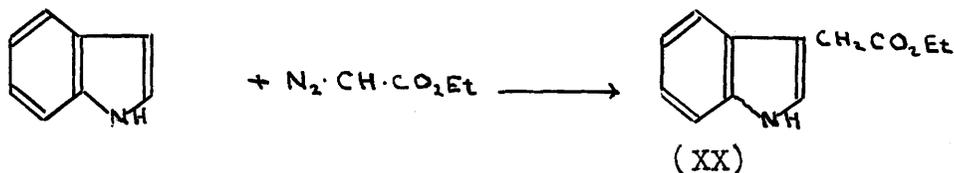


Substituted ethylenes also add diazomethane with the formation of pyrazolines. Various other products can be formed, however, depending on the nature of the substitution. Thus Fieser and Hartwell (30) have shown that diazomethane in the case of a naphthoquinone derivative gives a methyl substituted product (XVIII). α -Pyrone derivatives, containing a negative substituent in the 5-position, undergoes similar nuclear methylation

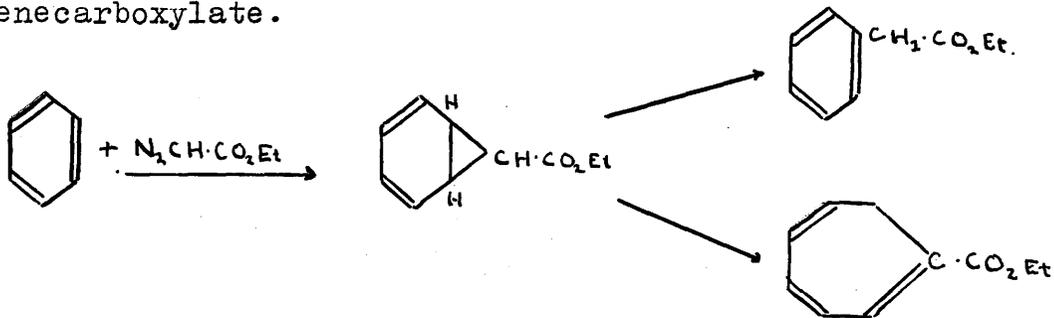
in the 6-position (XIX) on treatment with diazomethane (31).



Indole reacts in a similar manner with ethyl diazoacetate to give ethyl 3-indoleacetate (32)(XX).



Buchner (28a) and his co-workers have shown that ethyl diazoacetate reacts with benzene to yield ethyl norcaradienecarboxylate, which rearranges on heating to give a mixture of ethyl phenylacetate and ethyl cycloheptatrienecarboxylate.



THEORETICAL

THEORETICAL.

The reaction of diazomethane with acidic compounds, has been principally studied with compounds which possess ionic hydrogen atoms, e.g. carboxylic acids, phenols and enols. It was considered possible, from the electronic reaction mechanism of diazomethane, that diazomethane and its derivatives could react with a much wider range of compounds, provided that the latter possessed a positively charged centre. Thus it was hoped that any compound which could exhibit mesomeric-tautomerism, and consequently possessed a potential positive centre, would react with aliphatic diazo compounds to yield products of value as synthetic intermediates.

In this investigation two diazo compounds were used; ψ -diazacetophenone (XXI), prepared by the action of diazomethane on benzoyl chloride; and ethyl diazoacetate (XXII) prepared by the diazotisation of glycine ethyl ester.



Condensation of Diazacetophenone and Ethyl Diazoacetate with Amides.— The amides are known to possess weakly acidic properties (33,34). Thus they are capable of forming metallic salts having the structure R.C(ONa):NH . It can therefore be assumed that the amides under suitable conditions can react in one of two tautomeric forms

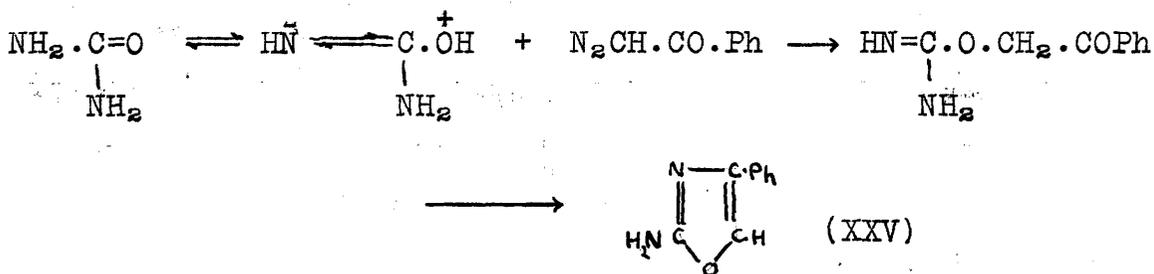
(XXIII or XXIV).



The hydrogen of the hydroxyl behaves as a weak acid in formula (XXIV).

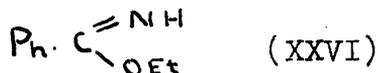
It was thus hoped that the amides would react with aliphatic diazo compounds. Two sets of reaction conditions were employed: molecular proportions of the amides and the diazo compounds were either heated together at 130° in the absence of a solvent, or refluxed together in ethanol or dioxan. The amides examined were formamide, acetamide, benzamide, and p-nitrobenzamide, and it was attempted to react them with diazoacetophenone in solution. Unfortunately in every case, the amide was quantitatively recovered unchanged indicating that the potential acidity was too low for reaction to take place.

It was considered possible, however, that urea might show greater reactivity, and condense with diazomethane to give an intermediate which could cyclise to yield 2-amino-4-phenyloxazole (XXV) by the following mechanism.

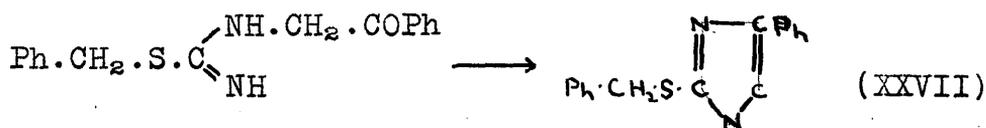
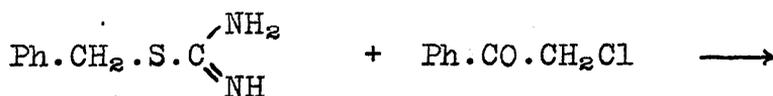
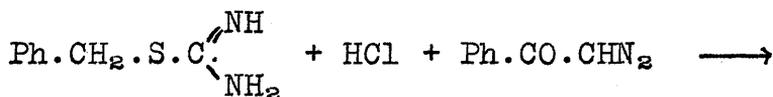


However, no reaction took place between urea and diazoacetophenone or ethyl diazoacetate under varying conditions. Under the heading of diazo compounds with amides may be mentioned the reaction with benzimido methyl ether, benzylthiuronium hydrochloride, and acetamidine hydrochloride.

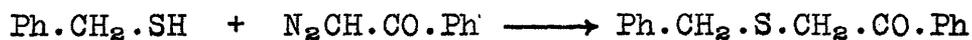
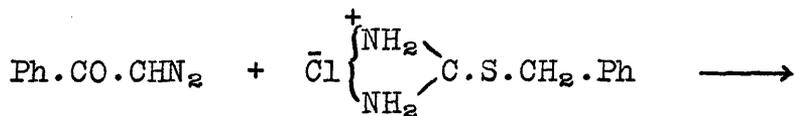
In the case of benzimido methyl ether (XXVI) no reaction took place, and the imido ether was recovered in quantitative yield.



In the case of benzythiuronium hydrochloride reaction with diazoacetophenone did occur in the absence of a solvent. It was expected that reaction would proceed by the initial formation of the free benzyl thiuronium base and ω -chloroacetophenone, which would then condense together under the reaction conditions. The reaction product could then be expected to cyclise to give 4-phenylimidazole-2-thiobenzyl ether (XXVII) by the following mechanism.



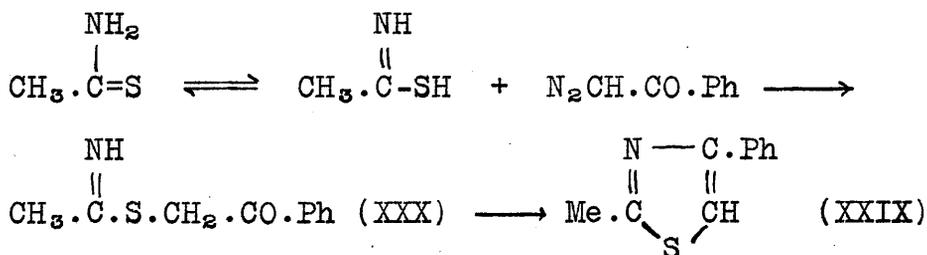
The product isolated from the reaction was found to contain no nitrogen; it had m.p. 89°, and analysed for C₁₅H₁₄OS. It was identified as benzylphenacyl sulphide, identical with the same compound prepared by Wahl (35) by the condensation of benzyl mercaptan with ω-bromoacetophenone. The product was characterised by the formation of its 2:4-dinitrophenylhydrazone and its sulphone derivatives. The reaction mechanism must therefore consist in the formation of the free benzyl thiuronium base, which is unstable under the reaction conditions, and decomposes to give benzyl mercaptan. The latter thiol reacts either with the ω-chloroacetophenone produced as a by-product in the first stage, or with a further molecule of diazoacetophenone, to give benzylphenacyl sulphide. It is considered that reaction with a second molecule of diazo ketone is more likely as ω-chloroacetophenone is always produced in the reaction mixture in appreciable yield, and about 50% of unchanged hydrochloride was recovered.



(XXVIII)

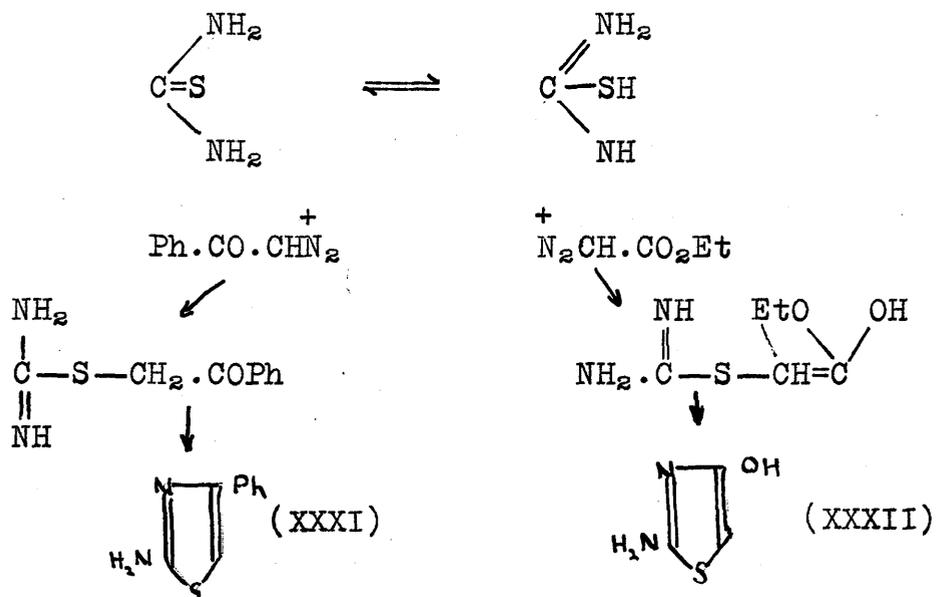
Consequently, in view of the above reaction it was hoped that a similar reaction would occur between acetamide hydrochloride and diazoacetophenone. In this case, however, reaction did not occur and the acetamide hydrochloride was recovered unchanged. This behaviour can be explained by the strong basicity of the amino group in acetamide hydrochloride; e.g. the free base is not liberated by strong ethanolic ammonia.

Condensation of Diazoacetophenone and Ethyl Diazoacetate with Thioamides.—The reaction of diazo compounds with the more acidic thioamides was then investigated. It was found that, on heating a dry intimate mixture of diazoacetophenone and thioacetamide at 130° until reaction had ceased, 2-methyl-4-phenylthiazole (XXIX) was obtained in good yield. The diazo ketone adds directly onto the sulphur atom of the thioamide to give a product (XXX) which cyclises under the reaction conditions.



Surprisingly, however, ethyl diazoacetate did not react with thioacetamide, which was recovered in quantitative yield from the reaction solution.

Thiourea condensed with diazoacetophenone, in a manner similar to thioacetamide, and gave in good yield 2-amino-4-phenylthiazole (XXXI). In the same way thiourea reacted with an ethanolic solution of ethyl diazoacetate to yield 2-amino-4-hydroxythiazole (XXXII).



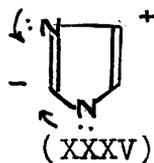
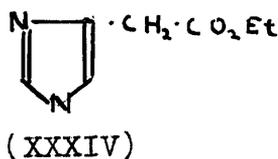
During the course of the work so far described an investigation of the reaction of ethyl diazoacetate with five membered heterocyclic ring systems was undertaken.

Jackson and Maske (32) have shown that diazoacetic ethyl ester reacts with indole to give a mixture of 3-indoleacetic acid and indylene-1:3-diacetic acid. Steinkopf and Jansen (36) have shown that the same diazo compound reacts with thiophene to give a product which they formulated as bicyclo- Δ^2 - α -penthiothiophene-5-carboxylic

ethyl ester (XXXIII). These authors consider that the reaction is due to addition of the diazo group to the ethylenic linkage in indole and thiophene.



It can, however, be considered that addition takes place at a centre of low electron density produced by resonance of the ring system. Thus it was found that ethyl diazoacetate condensed with imidazole to give ethyl imidazole-4-acetate (XXXIV), which was isolated from the reaction mixture as the hydrochloride of the free acid. An examination of imidazole (XXXV) shows that the 4(5)-position is deficient in electrons (i.e. possesses potential acidity). As the literature method for the preparation of imidazole-4-acetic acid (37) is somewhat tedious alternative methods were examined to confirm the structure of the reaction product. It was found that ethyl diazoacetate does not react with 4-methylimidazole; and therefore it can be concluded that in unsubstituted imidazole reaction with a diazo group can only occur at the potentially acidic 4(5)-position, and when imidazole is substituted in the 4-position, the acidity of carbon-5 is not sufficient to allow of reaction.



Ethyl diazoacetate did not react with hydantoin, which was recovered in quantitative yield from the reaction mixture.

When the work so far described had been almost completed, the communication of King and Miller (38) appeared describing the reaction of thioamides with diazo ketones, with the resultant formation of thiazoles by identical methods to those described in this thesis. In view of this published work, together with the lack of results showing promise of general application in the field of synthetic organic chemistry, it was decided to abandon this investigation.

EXPERIMENTAL

EXPERIMENTAL.

ω -Diazoacetophenone.— (a) cf. Arndt and Eistert, Ber., 1935, 68, 204; 1936, 69, 1805). Redistilled benzoyl chloride (6 g.) dissolved in dry ether (100 c.c.) was added dropwise with stirring, to an ethereal solution of diazomethane (300 c.c.; prepared from 20 g. N-nitrosomethylurea by the method of Org.Synth., 1935, 15, 4) when an immediate evolution of nitrogen occurred. The reaction mixture was allowed to stand at room-temperature for several hours, and concentrated to a bulk of 40 c.c. The reaction solution was cooled to -15° when ω -diazoacetophenone (4.5 g.) separated as large yellow elongated prisms, m.p. $47-49^{\circ}$ (decomp.). Further concentration of the mother liquors (8 c.c.) gave, on cooling to -15° , a mixture of diazoacetophenone and ω -chloroacetophenone (1.5 g.).

(b) (cf. Newman and Beal, J.Amer.Chem.Soc., 1949, 74, 1506). A solution of benzoyl chloride (14.1 g.) in dry ether (25 c.c.) was added during 20 minutes to a well stirred solution of diazomethane (4.2 g.; prepared from 16 g. N-nitrosomethylurea) and triethylamine (10.1 g.) in dry ether (235 c.c.) cooled in an ice-salt bath. A crystalline precipitate of triethylamine hydrochloride began to separate immediately. The mixture was mechanically stirred, at room temperature, for 12 hours;

the precipitated hydrochloride was collected (11.8 g,) and washed with a little dry ether. The solvent was removed under reduced pressure from the combined filtrate and washings to yield crude crystalline diazoacetophenone (15.2 g.). Crystallisation from light petroleum (b.p.40-60°) gave almost pure diazoketone, m.p.47-49° (decomp.) uncontaminated with ω -chloroacetophenone. The product from method (b) was purer and more pleasant to handle than that from (a).

Glycine ethyl ester hydrochloride.— Glycine (25.0 g.) was heated under reflux in dry ethanol (500 c.c.) and a steady stream of dry hydrogen chloride gas passed until a homogeneous solution was obtained. Heating was continued for 1 further hour. The reaction solution was allowed to stand overnight when the reaction mixture set to a solid mass of crystals. The product was separated by filtration; a further crop of glycine ester hydrochloride was obtained on reducing the mother liquors in bulk. The two crops were combined (43.7 g.; 90%) and crystallised from ethanolic ether, when the product separated as small needles, m.p.144°.

Ethyl diazoacetate.— (cf. Curtius, J.prakt.Chem., 1888, 38,401; Cohen, J., 1902, 600). Glycine ethyl ester hydrochloride (15 g.) was dissolved in water (30 c.c.) and sodium nitrite (11.0 g.) added. Dilute sulphuric acid

(1 c.c.; 2N) was added to the mixture which was then extracted with ether (9 c.c.). This procedure (addition of sulphuric acid and ether extraction) was repeated until the ether extracts were no longer coloured yellow. The combined ether extracts were dried over anhydrous sodium sulphate; removal of the ether gave ethyl diazoacetate (4.8 g.) as a yellow oil, b.p.39-40°/16 mm.

Diazoacetophenone and Urea.— (a) Urea (0.5 g.) was intimately mixed with diazoacetophenone (1.25 g.) and the mixture heated without a solvent to 130°, and maintained at this temperature for 2 hours. The heated mixture separated into two layers and little apparent reaction took place. After cooling the crushed gummy product was extracted with chloroform. Removal of the solvent from the chloroform solution gave only unchanged diazoketone. The residue obtained after the chloroform extraction was crystallised from methanol when unchanged urea (0.45 g.), m.p.138° alone or in admixture with a specimen of starting material was obtained.

(b) Urea (0.5 g.), diazoacetophenone (1.25 g.) and ethanol (20 c.c.) were heated together under reflux during 1 hour. The reaction solution was concentrated (5 c.c.), and on cooling crystals of urea (0.43 g.), m.p.138° separated. No other product could be isolated from the reaction mixture.

Ethyl diazoacetate and Urea.— Urea (1.2 g.), ethyl diazoacetate (2.3 g.) and ethanol (25 c.c.) were heated together under reflux for 2 hours. The reaction solution was reduced in bulk (10 c.c.) when unchanged urea (0.9 g.) separated. The filtrate was diluted with water and acidified with dilute sulphuric acid to destroy the excess of diazoacetic ester. The acidified solution was concentrated slightly and extracted with ether. The ether extract contained only a small quantity of urea (0.2 g.). The aqueous phase was made alkaline with dilute sodium hydroxide and re-extracted with ether; no further product was obtained from the latter solution.

S-Benzylthiuronium hydrochloride.— (cf. Donleavy, J. Amer. Chem. Soc., 1936, 58, 1004). A mixture of benzyl chloride (126 g.), thiourea (76 g.) and ethanol (200 c.c.) was gently warmed under reflux for 30 minutes, when a vigorous reaction took place. A homogeneous solution was rapidly obtained which, on cooling, set to a solid crystalline mass of S-benzylthiuronium hydrochloride (151 g.). The product was crystallised once from ethanol when it was obtained as prisms, m.p. 172-174°.

ω-Diazoacetophenone and S-Benzylthiuronium hydrochloride.— An intimate mixture of diazoacetophenone (1.0 g.) and S-benzylthiuronium hydrochloride (1.4 g.) was slowly

heated to 120°. Evolution of nitrogen commenced at 95°. The temperature was maintained at 120° until reaction had ceased. A red gum, possessing a strong smell of mercaptans, was obtained as product. The latter on treatment with methanol gave a colourless solid A (111 mg.), m.p.82-84°. The filtrate on addition of ether yielded unchanged S-benzylthiuronium hydrochloride (123 mg.).

A on crystallisation from ethanol gave benzylphenacyl sulphide as small prisms, m.p.89°, alone or in admixture with an authentic specimen, m.p.89°, prepared according to Wahl (Ber.,1922,55,1449) by the condensation of ω -bromoacetophenone with sodium benzyl mercaptan.

Found: C,73.8; H,6.1; S,12.7.

Calc. for $C_{15}H_{14}OS$: C,73.7; H,5.8; S,13.2%.

Treatment of A with Brady's reagent gave an orange precipitate of benzylphenacyl sulphide 2:4-dinitrophenyl-hydrazone which separated from ethanol as orange needles, m.p.168-169°, alone or in admixture with an authentic specimen, m.p.168-169°.

Found: C,59.4; H,4.3; N,12.7.

$C_{21}H_{18}N_4O_4$ requires: C,59.5; H,4.3; N,13.1%.

A (100 mg.) was dissolved in glacial acetic acid (5 c.c.) and 0.1N-potassium permanganate solution (70 c.c.) added. The mixture was allowed to stand at room temperature for 3 hours, and extracted with benzene

(3 x 20 c.c.). Removal of the solvent from the dried solution (calcium chloride) gave benzylphenacyl sulphone as a residue. The latter separated from ethanol as lustrous leaflets, m.p.112-113°, alone or when mixed with an authentic specimen of the sulphone (Wahl, loc. cit. gives m.p.113°).

Found: C,65.5; H,5.2.

Calc. for $C_{15}H_{14}O_3S$: C,65.7; H,5.1%.

Acetamidine hydrochloride.— A mixture of dry ethanolic ammonia (200 c.c.; 15%) and acetimido ethyl ether hydrochloride (95 g.; prepared from acetonitrile according to Org.Synth., Coll.Vol.I,5, in the stated yield) in methanol (50 c.c.) was mechanically stirred at room temperature. The precipitated ammonium chloride was separated by filtration, and the filtrate concentrated in bulk (100 c.c.). Acetamidine hydrochloride (34 g.) separated as prisms, m.p.165-166°; concentration of the mother liquors gave a further yield (9 g.) of product.

Acetamidine hydrochloride and diazoacetophenone.— An intimate mixture of diazoacetophenone (1.0 g.) and acetamidine hydrochloride (0.65 g.) were heated at 100° for 1 hour, and then at 120° for 3 hours. The reaction mixture was a red gum. The latter was dissolved in ethanol (5 c.c.) and ether (100 c.c.) added. Unchanged

acetamidine hydrochloride (0.5 g.) was precipitated; no other product could be isolated from the reaction mixture.

Benzimido methyl ether. — Dry hydrogen chloride was passed through a cooled solution of benzonitrile (51 c.c.) in methanol (25 g.) until an increase in weight of 21.3 g. had been observed. The reaction mixture was allowed to stand at room temperature for 48 hours, when the solid cake of benzimido methyl ether hydrochloride was collected (54 g.). The crushed hydrochloride (20 g.) was dissolved in water and a solution of potassium carbonate (100 c.c.; 10%) added. the free base was extracted with ether (3 x 30 c.c.), and the ethereal solution dried over sodium sulphate. Removal of the ether gave benzimido methyl ether as a colourless oil, b.p.78°/4 mm.

Benzimido methyl ether and diazoacetophenone. — A mixture of benzimido methyl ether (1.35 g.) and diazoacetophenone (1.46 g.) in methanol (20 c.c.) was heated under reflux for 2 hours. No evolution of nitrogen occurred. The reaction mixture was taken to dryness under reduced pressure, and the residue acidified with dilute hydrochloric acid to destroy the excess of diazoacetophenone. The benzimido methyl ether was recovered quantitatively as the hydrochloride.

Reaction of Diazoacetophenone with Amides.— A mixture of the amide (0.01 mole; formamide, acetamide, benzamide, or *p*-nitrobenzamide) and diazoacetophenone (1.46 g.; 0.01 mole) in methanol (20 c.c.) was heated under reflux for 3 hours. The solvent was removed under reduced pressure, and the residue extracted with ether (5 c.c.) to remove unchanged diazoacetophenone. In every case the amide was quantitatively recovered, unchanged.

Thioacetamide.— (cf. Hantysch, Ann., 1889, 250, 242).

Acetamide (9.0 g.) and phosphorus pentasulphide (48 g.) were intimately mixed and heated with benzene (80 c.c.) for 10 minutes on the water-bath. The yellow supernatant benzene solution was decanted, and evaporated. On cooling thioacetamide (7.5 g.) separated as colourless plates, m.p. 105-108°.

Diazoacetophenone and thioacetamide.— Thioacetamide (0.75 g.) was intimately mixed with diazoacetophenone (1.46 g.), and the mixture heated without a solvent at 120° until reaction ceased. The reaction product was an oil, which on storage solidified to a dark red crystalline mass (0.92 g.), m.p. 57-58°. The product on sublimation at 50°/10⁻³mm. gave a colourless sublimate. The latter on crystallisation from light petroleum (b.p. 100-120°) yielded 2-methyl-4-phenylthiazole as well defined needles, m.p. 67-71°, undepressed by mixing with

an authentic specimen, m.p.67-69°. The authentic specimen was prepared according to Hantsch, (Ann.,1889, 250,268) by the condensation of ω -bromoacetophenone with thioacetamide in ethanolic solution (Hantsch, loc. cit., gives m.p.68.5°).

Found: C,69.0; H,5.3; N,7.9; S,18.6.

Calc. for $C_{10}H_9NS$: C,68.6; H,5.1; N,8.0; S,18.3%.

Ethyl Diazoacetate and thioacetamide.— Thioacetamide (1.13 g.) and ethyl diazoacetate (4.5 g.) were refluxed together under dry methanol (25 c.c.) for 2 hours. The solvent was removed by distillation under reduced pressure. The oily residue crystallised from benzene as large square plates, m.p.107-108°, alone and in admixture with a specimen of thioacetamide.

Diazoacetophenone and thiourea.— Molecular proportions of thiourea (0.55 g.) and diazoacetophenone (1.0 g.) were heated together at 120° in the absence of a solvent. When evolution of nitrogen had ceased, the reaction mixture was cooled, and a dark red crystalline product (1.30 g.), m.p.140-144°, was obtained. The product (600 mg.) was extracted with dry chloroform and a small residue (43 mg.), m.p.174-176°, of unchanged thiourea was obtained. The filtrate (100 c.c.) was adsorbed on a column of alumina (Grade II; 1.65 x 37 cm.). The

column was eluted with the same solvent (100 c.c. fractions being collected). The first three fractions gave a yellow oil (125 mg.) which appeared to be unchanged diazoacetophenone. From fractions IV, V, VI, and VII was obtained a slightly discoloured crystalline solid (328 mg.), m.p.146-148°. The latter product was sublimed once at 100°/10⁻² mm. to give a colourless sublimate. The sublimate was crystallised from chloroform when 2-amino-4-phenylthiazole separated as needles, m.p.147-149°, alone and in admixture with an authentic specimen prepared as indicated below.

2-Amino-4-phenylthiazole.— (cf. Traumann, Ann.,1888, 249,38). ω -Bromoacetophenone (2.0 g.) in ethanol (50 c.c.) was added dropwise to a mechanically stirred solution of thiourea (0.75 g.) in ethanol (300 c.c.) at room temperature. After stirring for 2 hours the mixture was heated on the water bath for 30 minutes, and then evaporated to dryness. A residue consisting of yellow needles of 2-amino-4-phenylthiazole hydrobromide (1.5 g.) was obtained. The free base was liberated by boiling the hydrobromide with an excess of aqueous sodium hydrogen carbonate. The pale yellow residue, obtained on filtering the alkaline reaction mixture, separated from chloroform as colourless needles of 2-amino-4-phenylthiazole, m.p.147-150°.

Ethyl diazoacetate and Thiourea.— Ethyl diazoacetate (1.14 g.) and thiourea (0.75 g.) were heated together under reflux in ethanol (20 c.c.) for 2 hours. The solution was reduced in bulk (10 c.c.), diluted with water (5 c.c.) and boiled with activated charcoal to give a pale yellow filtrate which on cooling deposited 2-amino-4-hydroxythiazole (0.41 g.). The product separated from aqueous ethanol as small needles, m.p.233-237° (decomp.) (Andreasch, Monatsh.,1887,8,424, gives m.p.208° (decomp.); King and Miller, J.Amer.Chem.Soc.,1949,71,367, and Allan and van Allan, Org.Synth.,27,71, give m.p.233-238° (decomp.))

Found: C,30.7; H,3.8.

Calc. for $C_3H_4ONS_2$: C,31.0; H,3.45%.

Ethyl diazoacetate and imidazole.— Imidazole (3.4 g.) and ethyl diazoacetate (6.0 g.) were heated under reflux in dioxan (25 c.c.) for 6 hours, a trace of copper powder being present as a catalyst. The solvent was removed from the reaction mixture under reduced pressure. The residue, a brown gum, was dissolved in ethanol (10 c.c.) and the solution acidified to Congo red with dilute hydrochloric acid. The solution on evaporation to dryness gave a brown tarry solid. The latter on crystallisation from ethanol gave imidazole-4-acetic acid hydrochloride as colourless needles, m.p.197-202° (Pyman, J.,1911,680, gives m.p.225-226°).

Found: C,36.7; H,4.3; N,17.4; Cl,21.9.

Calc. for $C_5H_7N_2O_2Cl$: C,36.9; H,4.3; N,17.2; Cl,21.8%.

Ethyl diazoacetate and 4-methylimidazole.— 4-Methylimidazole (2.5 g.), diazoacetic ethyl ester (4.0 g.) and a trace of copper powder were heated together under reflux in ethanol (25 c.c.) for 6 hours. The green coloured reaction solution was filtered, and taken to dryness under reduced pressure. The residue was obtained as a slightly coloured gum. Part of the gum on treatment with dilute hydrochloric acid gave 4-methylimidazole as colourless, hygroscopic needles, m.p.248-250° (decomp.). The remainder of the gum was dissolved in ethanol (5 c.c.) and treated with a saturated ethanolic solution of picric acid, and the yellow precipitate collected. The latter separated from ethanol when 4-methylimidazole picrate was obtained as long yellow needles, m.p.148-150° (decomp.), alone or in admixture with a specimen of the picrate obtained from starting material. No other product could be isolated from the reaction mixture.

Ethyl diazoacetate and hydantoin.— Hydantoin (5.0 g.), ethyl diazoacetate (5.7 g.) and a trace of copper powder were refluxed together in ethanol (50 c.c.) for 8 hours. The dark red reaction mixture was filtered and taken to

dryness under reduced pressure to give a brown solid residue. The latter on crystallisation from methanol (charcoal) gave hydantoin, m.p. 217-220°, alone or in admixture with a specimen of starting material. No other product could be isolated from the reaction mixture.

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