T H E S I S

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requirements for the

DEGREE OF DOCTOR OF PHILOSOPHY

by

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CONTENTS.

Part 1.

Studies in the Pyrazolidine Field.

Part 2.

Dimerisation of Steroids.

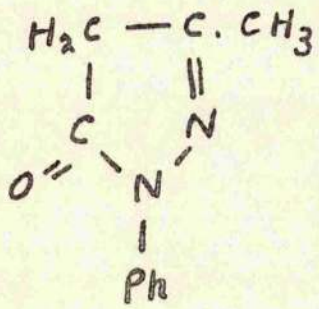
STUDIES IN THE PYRAZOLIDINE FIELD AND DIMERISATION OF STEROIDS.

PART ONE.

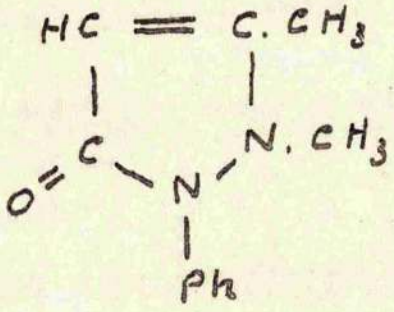
STUDIES IN THE PYRAZOLIDINE FIELD.

INTRODUCTION.

The first synthesis of a compound containing the 5-membered pyrazole ring system by Knorr[1] in 1883, involved the condensation of phenylhydrazine and ethyl acetoacetate and gave 3-methyl-5-oxo-1-phenylpyrazoline (I) as the main product. Since then the pyrazole molecule and the dihydro-pyrazole molecule, or pyrazoline group, have been studied intensively, particular emphasis being given to certain keto- derivatives of pyrazoline, the pyrazolones. This particular interest was brought about by Knorr with his discovery that 2,3-dimethyl-1-phenyl-5-pyrazolone (antipyrine, phenazone) (II), possessed interesting pharmacological properties. This discovery has resulted in a thorough investigation being made into the properties of the compounds in this group.



(I)



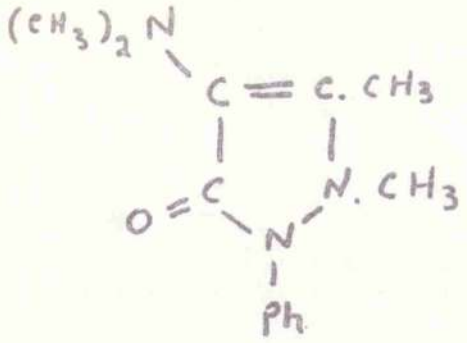
(II)

Antipyrine (II) is prepared by the action of methyl iodide on 3-methyl-5-oxo-1-phenylpyrazoline (I) in methanol[2] at 100°.

Its pharmacological action is similar to that of the salicylates and p-amino-phenol group of drugs, being an analgesic and antipyretic. It is toxic, and in certain cases where it has been used it has caused fatal agranulocytosis. As a result of this toxicity, it has been virtually abandonned as a drug in the U.S.A. and Canada, and replaced by salicylates, but it still finds limited use in Europe, excluding Britain.

Antipyrine is a colourless crystalline compound, soluble in water and decomposed by distillation at atmospheric pressure. Substitution in the molecule can take place at the 4-position, sulphonation giving the 4-sulphonic acid and N-bromosuccinimide giving 4-bromoantipyrine.

An important improvement on the drug antipyrine was the compound aminopyrine, or 2,3-dimethyl-4-dimethylamino-5-oxo-1-phenylpyrazoline (III)[3]. While this is a better antipyretic and analgesic than antipyrine, it has the disadvantage of being more toxic. It has been manufactured under the name pyramidon, being produced from antipyrine by the action of nitrous acid to give 4-nitroso-antipyrine (IV). Reduction of this latter compound with zinc gives 4-amino-antipyrine (V), which on treatment with methyl bromide in methanol gives the required product (III).



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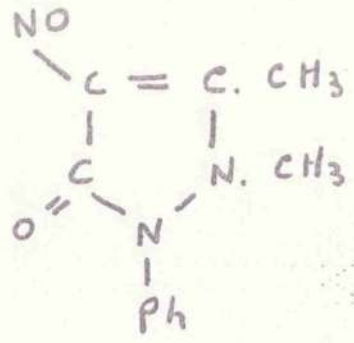

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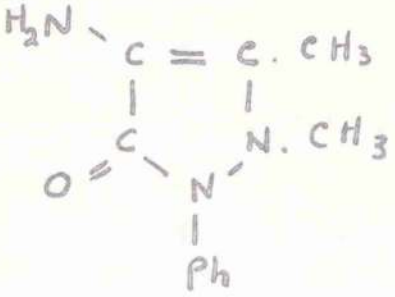
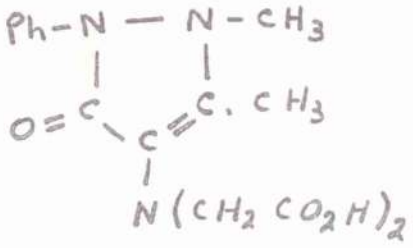


(V)

Methylation in the last stage of the synthesis of pyramidon has been done in a number of ways. If 4-amino-antipyrine (V) is treated with chloroacetic acid[4] and the resulting dicarboxylic acid (VI) is heated above its melting point, it loses carbon dioxide to give pyramidon (III).



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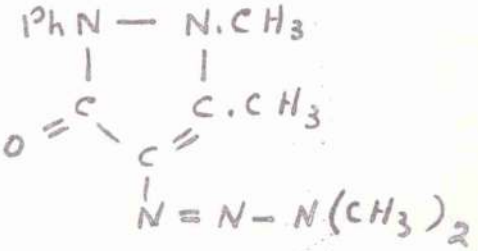
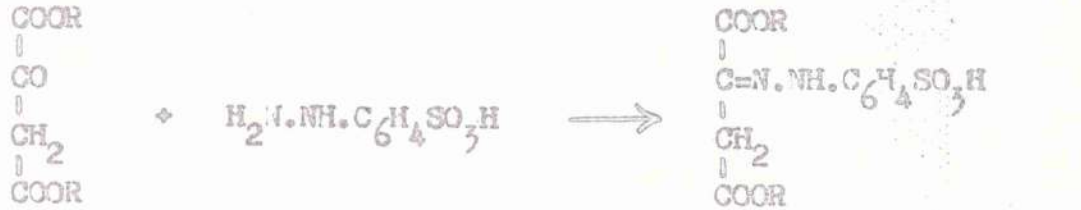


(VII)

An alternative method[5] involving diazotization of 4-aminoantipyrine (V) with nitrosodimethylamine gives the intermediate tri-azo compound (VII) which yields pyramidon (III) on loss of nitrogen.

The pharmacology of antipyrine, pyramidon, and related drugs has been extensively reviewed[6,7,8].

Interest in this field has been stimulated further by the discovery of certain pyrazole dyes. The important commercial dyes containing the pyrazole ring system are yellow-green and are used for wool. They are very fast and are available as the yellow components in two and three-coloured mixtures. The first known pyrazolone dye, tartrazine (X), is widely used in the colouration of foodstuffs[9]. It is obtained commercially from oxalacetic acid (VIII) and phenylhydrazine sulphonic acid, to give sulphophenylpyrazolone carboxylic acid (IX). This is then coupled with diazotised sulphanilic acid, to give tartrazine (X).

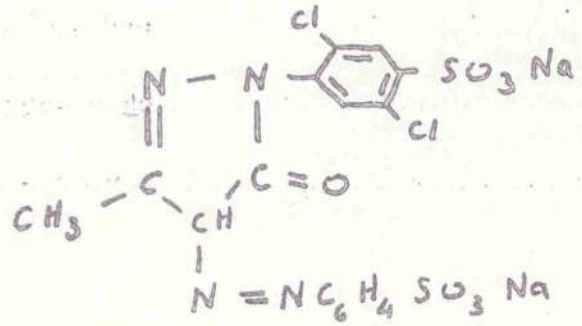


(VIII)

(IX)

(X)

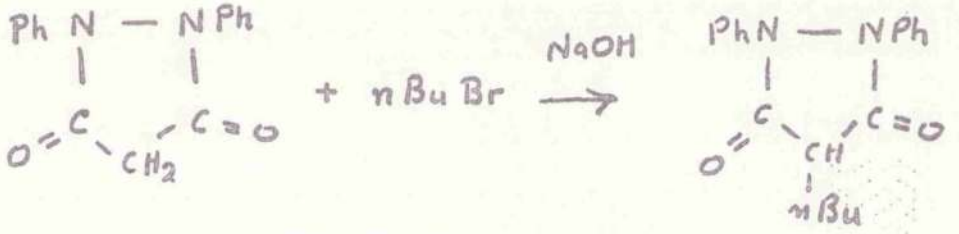
Xylene Light Yellow (XI) is also an important pyrazolone dye, but it is more expensive to manufacture.



(XI)

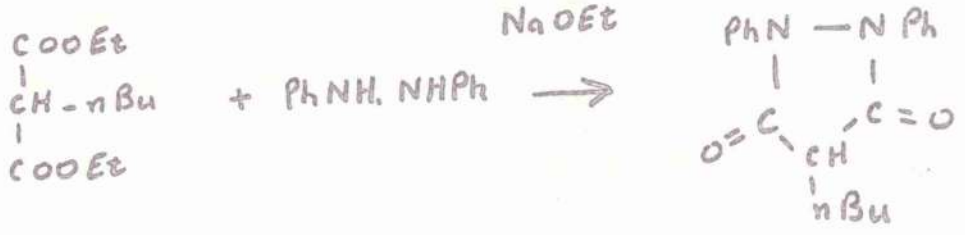
In recent years there has been a considerable amount of interest in the pyrazolidine group of compounds, due to the discovery that 1,2-diaryl-3,5-dioxopyrazolidines possess pharmacological properties similar to those of antipyrine. The most important of this group pharmacologically is phenylbutazone, or 4-n-butyl-3,5-dioxo-1,2-diphenylpyrazolidine (XII) which has been introduced into medicine under the name "butazolidine". As well as having important analgesic and antipyretic properties, it is valuable in the treatment of rheumatoid athritis. It is similar in its action to cortisone and was used in place of the latter since it is considerably cheaper[10]. Certain toxic effects have appeared[11-16] the most serious being agranulocytosis.

The synthesis of phenylbutazone was first carried out by Geigy[17] who treated 3,5-dioxo-1,2-diphenylpyrazolidine (XIII) with n-butyl bromide in the presence of sodium hydroxide.

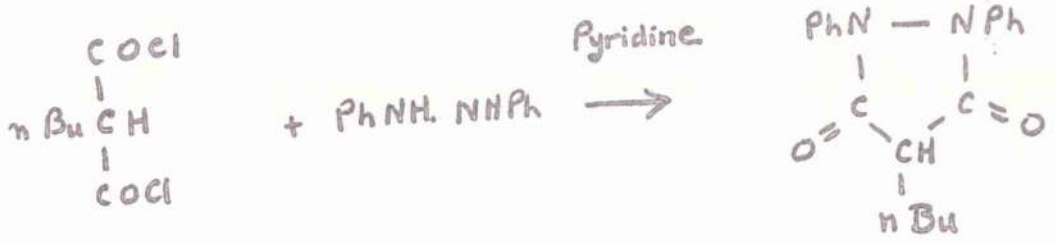


(XIII) (XII)

The two methods most commonly used for the preparation now are the condensation of ethyl n-butylmalonate (XIV) with hydrazobenzene in the presence of sodium ethoxide[18] and the condensation of n-butylmalonyl chloride (XV) in pyridine, with hydrazobenzene[19].



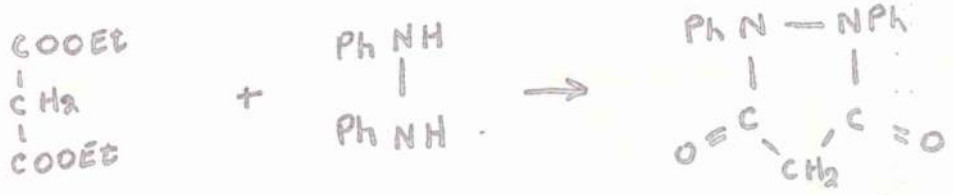
(XIV) (XII)



(XV) (XII)

Because of its toxicity, numerous attempts have been made to develop a less toxic drug from it with the same pharmacological action. Many compounds have been synthesised with different substituents in the 4-position[18] and with substituting groups in one or more of the phenyl rings[19] in attempts to improve the drug, but so far any reductions in toxicity have resulted in a reduction in pharmacological action.

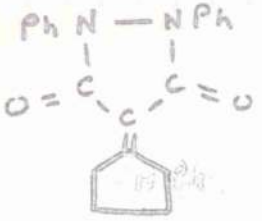
The parent compound of phenylbutazone is 3,5-dioxo-1,2-diphenylpyrazolidine (XIII). This was first synthesised by Tsumaki[20] by the condensation of hydrazobenzene and ethyl malonate in the presence of sodium ethoxide. It can also be prepared by the action of hydrazobenzene and malonyl chloride in the presence of pyridine.



(XIII)

(XVI) (XIII)

Tsumaki[20,21] has prepared a large number of derivatives of 3,5-dioxo-1,2-diphenylpyrazolidine (XIII) by condensing it with different aldehydes and ketones. These condensation products are usually highly coloured and are formed by substitution in the pyrazolidine ring in the 4-position. Cyclopentanone, cycloheptanone, cyclohexanone, benzaldehyde, and butyraldehyde have all been used in this way to give the corresponding cyclopentylidene (XVII), cycloheptylidene (XVIII), cyclohexylidene (XIX), benzylidene (XX), and butylidene (XXI) derivatives.



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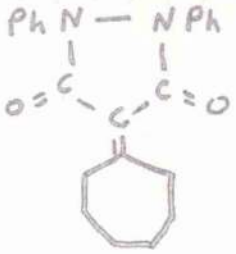
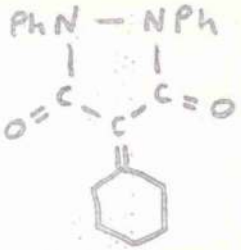


(XVIII)



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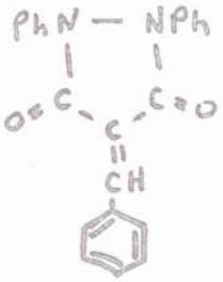

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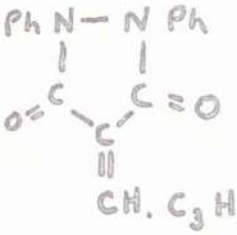
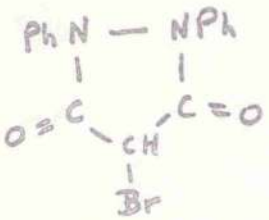


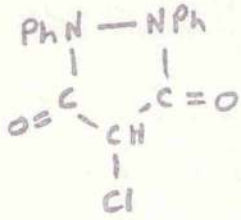
(XXI)

These compounds are all readily reduced by catalytic hydrogenation to the corresponding dihydro-derivatives[20,21].

4-Bromo-3,5-dioxo-1,2-diphenylpyrazolidine (XXII) has been prepared[22,23] by the action of bromine on 3,5-dioxo-1,2-diphenylpyrazolidine (XIII), and a 4-chloro-derivative[23] is also known. (XXIII).

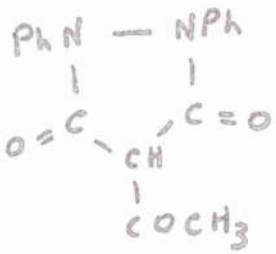


(XXII)



(XXIII)

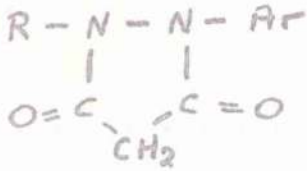
3,5-dioxo-1,2-diphenylpyrazolidine (XIII) can be acylated, using acetic anhydride in the presence of pyridine[24] when the alkali-soluble 4-acetyl-3,5-dioxo-1,2-diphenylpyrazolidine (XXIV) is formed. The acetyl derivative (XXIV) can also be prepared by the action of acetyl chloride in the presence of aluminium chloride as a catalyst[25]. Potassium carbonate or pyridine can also be used as catalysts, the product in each case being the 4-acetyl-3,5-dioxo-1,2-diphenylpyrazolidine (XXIV).



(XXIV)

THEORETICAL.

Although a large number of derivatives of 3,5-dioxo-1,2-diphenylpyrazolidine substituted in the benzene rings[19] and in the 4-position[18] have been prepared, none have been reported in which one of the keto- groups in the system has been replaced by an imino- group. A few 1-alkyl-2-aryl-3-imino-5-oxo-pyrazolidines (XXV) have been described[26,27] and these have been shown to have similar antipyretic effects to butazolidine.

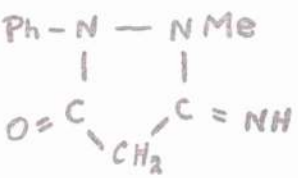


R = Alkyl

Ar = Aryl

(XXV)

These compounds are usually prepared by the alkylation of 1-aryl-3-imino-5-oxopyrazolidines and 2-Methyl-3-imino-5-oxo-1-phenylpyrazolidine (XXVI) has been prepared by methylation of 3-imino-5-oxo-1-phenylpyrazolidine[28] (XXVII). 2-Methyl-3-imino-5-oxo-1-phenylpyrazolidine (XXVI) can also be prepared by the Hofmann or Curtius methods[26,27] from 2-alkyl-1-aryl-5-pyrazolone-3-carboxylic acid (XXVIII).



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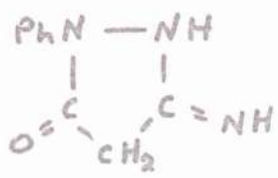

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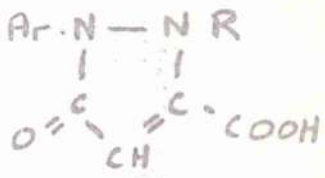
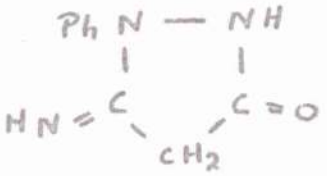


(XXVIII)

Imino-oxo-pyrazolidines can be prepared by a number of methods. One of the more popular involves the treatment of phenylhydrazine with ethyl cyanoacetate in the presence of sodium alkoxide as a condensing agent. This method was used by Conrad and Zart[29] to prepare a compound which they assumed to be 5-imino-3-oxo-1-phenylpyrazolidine (XXIX). Weisberger and Porter[30] pointed out that this reaction might lead to the isomeric 3-imino-5-oxo-1-phenylpyrazolidine (XXX). In order to establish clearly which compound had been formed, they started from 1-phenyl-3-carbethoxy-5-pyrazolone (XXXI)[31] which can be formed by ring closure of ethyl oxalacetate phenylhydrazone (XXXII)[31].



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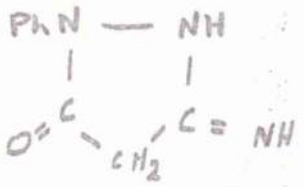
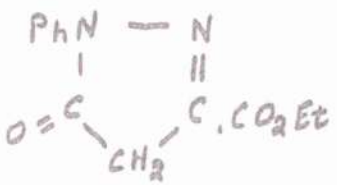
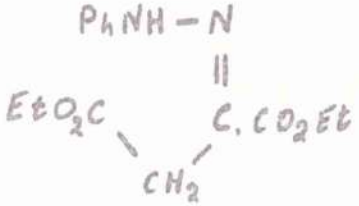


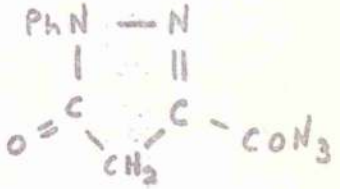
(XXX)



(XXXI)



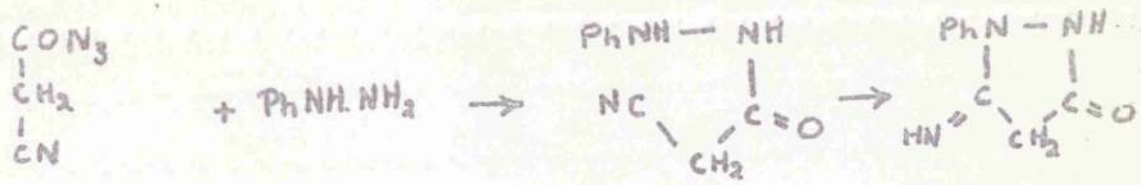
(XXXII)



(XXXIII)

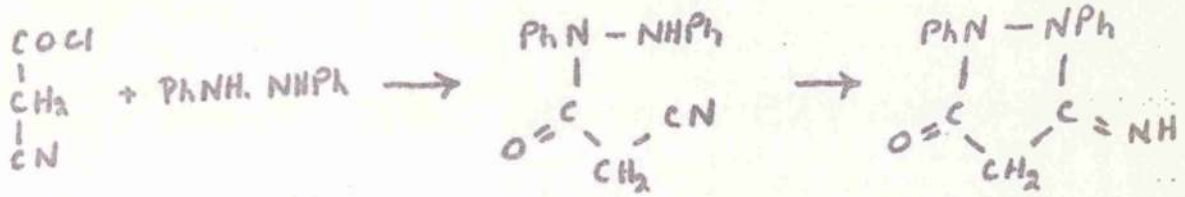
Weisberger and Porter treated 1-phenyl-3-carbethoxy-5-pyrazolone (XXXI) with nitrous acid to form the hydrazide and then the azide (XXXIII) and subjected the product to Curtius degradation. The compound formed was identical with that obtained by Conrad and Zart.

A more general synthesis of 5-imino-3-oxo-1-aryl-pyrazolidines is the condensation of cyanoacetyl chloride or azide (XXXIV) with a hydrazine derivative [32] such as phenylhydrazine as illustrated.



(XXXIV) (XXIX)

3-Imino-5-oxo-1,2-diphenylpyrazolidine (XXXV) is prepared in a similar manner[33] using cyanoacetyl chloride and hydrazobenzene (XXXVI).



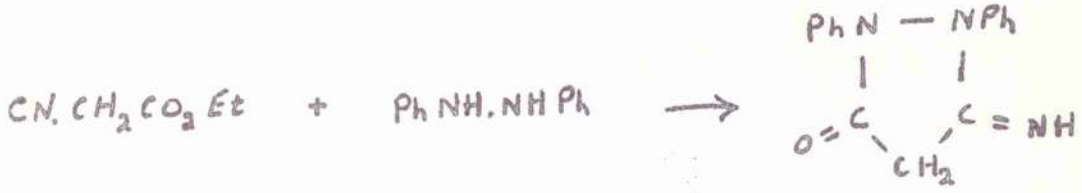
(XXXVI) (XXXVII) (XXXV)

The intermediate in this synthesis, N-cyanoacetylhydrazobenzene (XXXVII) has been described [34] as the product of reaction between hydrazobenzene (XXXVI), cyanoacetic acid, and phosphorus oxychloride in the presence of pyridine. It is more conveniently prepared by the reaction of cyanoacetyl chloride and hydrazobenzene in the presence of pyridine[35]. The objective of this work was to examine this synthesis, determine whether it was possible to adapt it for the preparation of 4-substituted derivatives and homologues of 3-imino-5-oxo-1,2-diphenylpyrazolidine (XXXV), and if so, to prepare some 4-substituted derivatives for comparison with the corresponding derivatives of 3,5-dioxo-1,2-diphenylpyrazolidine (XIII).

Using 1.5 mole of cyanoacetyl chloride per mole of hydrazobenzene, N-cyanoacetylhydrazobenzene was only obtained in 15% yield, and 30% of the hydrazobenzene was recovered. When 2.5 mole of the acid chloride was used per mole of hydrazobenzene, the yield of N-cyanoacetylhydrazobenzene was 30%. N-Cyanoacetylhydrazobenzene was cyclised to 3-imino-5-oxo-1,2-diphenylpyrazolidine (XXXV) by the action of aqueous

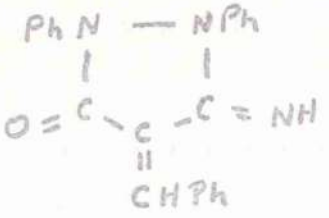
ethanolic sodium carbonate, sodium methoxide or ethoxide in the corresponding alcohol. 3-Imino-5-oxo-1,2-diphenylpyrazolidine (XXXV) was also isolated from the mother liquors of the acid chloride/hydrazobenzene reaction in 9% yield. In this synthesis, cyanoacetyl chloride sometimes decomposed by pyrolysis when being distilled, even under reduced pressure, and for this reason the preparation of the homologue, N-α-cyanopropionyl chloride was not attempted, since it would be difficult to purify. Consequently it was decided that this synthesis was not adaptable to the preparation of 4-substituted derivatives of 3-imino-5-oxo-1,2-diphenylpyrazolidine (XXXV).

An alternative procedure for the preparation of 3-imino-5-oxo-1,2-diphenylpyrazolidine (XXXV) involved the condensation of ethyl cyanoacetate (XXXVIII)[33] and hydrazobenzene in the presence of sodium ethoxide in a nitrogen atmosphere. Only about 8% of 3-imino-5-oxo-1,2-diphenylpyrazolidine (XXXV) was formed and most of the hydrazobenzene was recovered.

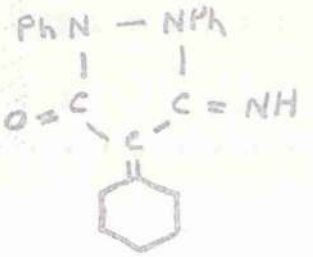


(XXXVIII) (XXXVI) (XXXV)

Using this synthesis, it was decided to attempt the preparation of 4-benzylidene-3-imino-5-oxo-1,2-diphenylpyrazolidine (XXXIX) and 4-cyclohexylidene-3-imino-5-oxo-1,2-diphenylpyrazolidine (XL) since the starting materials, ethyl benzylidene cyanoacetate (XLI) and ethyl cyclohexylidene cyanoacetate (XLII) are readily prepared from ethyl cyanoacetate with benzaldehyde[35] and cyclohexanone[36] respectively.



(XXXIX)



(XL)

(XLI)

(XLII)

Both ethyl benzylidene cyanoacetate (XLI) and ethyl cyclohexylidene cyanoacetate (XLII) were prepared in

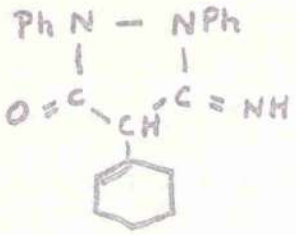
good yields, but when treated with hydrazobenzene in the presence of sodium ethoxide, no condensation took place, even on prolongued reflux.

It was found that 4-benzylidene-3-imino-5-oxo-1,2-diphenylpyrazolidine (XXXIX) could be prepared directly by the action of benzaldehyde on 3-imino-5-oxo-1,2-diphenyl-pyrazolidine (XXXVI), by refluxing the materials together using excess benzaldehyde as a solvent.

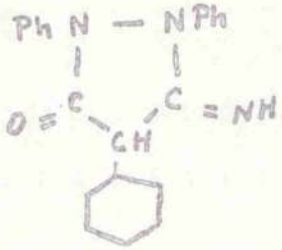
This preparation is similar to that used by Tsumaki[20,21] to prepare 4-benzylidene-3,5-dioxo-1,2-diphenylpyrazolidine (XX) and the product (XXXIX) is comparable to Tsumaki's in that it has 3 double bonds in conjugation. Unlike the dioxo-compound (XX), 4-benzylidene-3-imino-5-oxo-1,2-diphenyl-pyrazolidine (XXXIX) can not be reduced by catalytic hydrogenation, using either Raney nickel or platinum as catalysts, even at elevated temperatures and pressures.

Condensation in a similar manner of cyclohexanone and 3-imino-5-oxo-1,2-diphenylpyrazolidine (XXXV) did not yield 4-cyclohexylidene-3-imino-5-oxo-1,2-diphenylpyrazolidine (XL), As expected, but gave 4-cyclohexenyl-3-imino-5-oxo-1,2-diphenylpyrazolidine (XLIII), in which the double bond is not in conjugation with the carbonyl and imino-groups, but is in the ring. This is demonstrated by the ultraviolet absorption evidence, (see Tables A and B). 4-Cyclohexenyl-3-imino-5-oxo-1,2-diphenylpyrazolidine (XLIII)

shows absorption at 205 (ε = 29,000) and 255 mμ (ε = 21,750), whereas Tsumaki's compound (XIX) absorbs at 360 (ε = 7,020) and 372 (ε = 6,970). Catalytic hydrogenation of 4-cyclohexenyl-3-imino-5-oxo-1,2-diphenylpyrazolidine (XLIII) in the presence of platinum, gave 4-cyclohexyl-3-imino-5-oxo-1,2-diphenylpyrazolidine (XLIV).

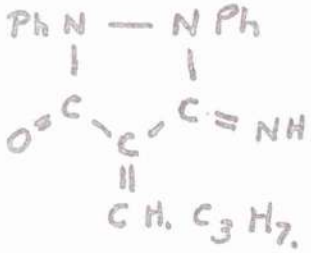


(XLIII)



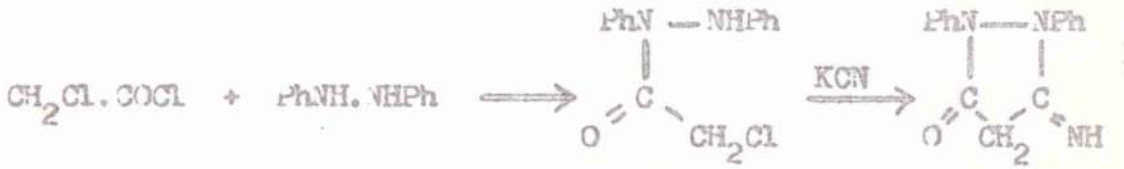
(XLIV)

4-n-Butylidene-3-imino-5-oxo-1,2-diphenylpyrazolidine (XLV) was prepared by the action of n-butyraldehyde on 3-imino-5-oxo-1,2-diphenylpyrazolidine (XXXV). It is similar to Tsumaki's product (XXI) in the dioxo series, in that the double bond is in conjugation with the carbonyl and imino-groups, but like 4-benzylidene-3-imino-5-oxo-1,2-diphenyl-pyrazolidine (XXXIX), it is not catalytically reduced by Raney nickel or platinum.



(XLV)

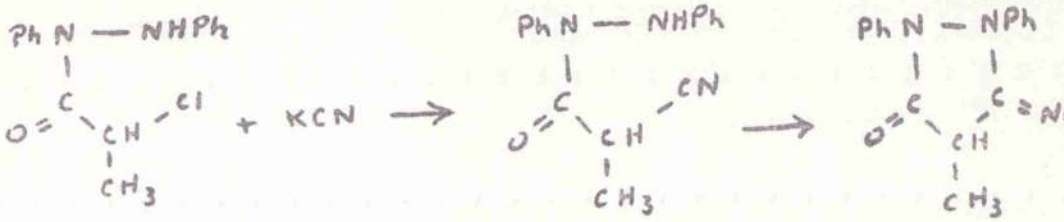
Since the two methods available for the preparation of 3-imino-5-oxo-1,2-diphenylpyrazolidine (XXXV) were not readily adaptable for the preparation of 4-substituted derivatives, it was decided to attempt the preparation of the compound (XXXV) from N-chloroacetylhydrazobenzene, replacing the chloro- group with a nitrile group, and cyclising the product. N-Chloroacetylhydrazobenzene (XLVI) was prepared by the action of chloroacetyl chloride on hydrazobenzene in the presence of pyridine. On refluxing N-chloroacetylhydrazobenzene (XLVI) with an aqueous ethanolic solution of potassium cyanide, 3-imino-5-oxo-1,2-diphenylpyrazolidine (XXXV) was formed without the isolation of the intermediate N-cyanoacetylhydrazobenzene (XXXVII).



(XLVI) (XXXV)

Since this method gave 3-imino-5-oxo-1,2-diphenylpyrazolidine (XXXV) in excellent yield, it was decided to use it for the preparation of 3-imino-4-methyl-5-oxo-1,2-diphenylpyrazolidine (XLVIII). N-α-Chloropropionylhydrazobenzene (XLVII) was prepared by the action of α-chloropropionyl chloride on

hydrazobenzene. Treatment of N-α-chloropropionylhydrazobenzene (XLVII) with aqueous ethanolic potassium cyanide gave 3-imino-4-methyl-5-oxo-1,2-diphenylpyrazolidine (XLVIII). In this synthesis, the intermediate N-α-cyanopropionylhydrazobenzene was not formed in a quantity sufficient to be isolated, but cyclised immediately it was produced in the presence of potassium cyanide.

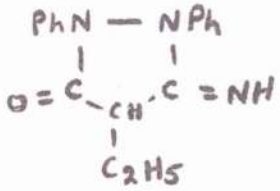


(XLVII) (XLIX) (XLVIII)

Using N-α-bromopropionylhydrazobenzene (L) in the same way, also gave 3-imino-4-methyl-5-oxo-1,2-diphenylpyrazolidine (XLVIII) in good yield. The starting material (L) in this case is prepared by the action of α-bromopropionyl bromide and hydrazobenzene[37] in ether, since an attempt to prepare N-α-bromopropionylhydrazobenzene (L) using pyridine and chloroform as solvents, gave bromopropionylanilide (LI) by splitting the hydrazobenzene group.

(L) (LI)

This synthesis gave excellent results with both N-α-chloropropionylhydrazobenzene (XLVII) and N-α-bromopropionylhydrazobenzene (L), but the cyclisation of N-α-chlorobutyrylhydrazobenzene and N-α-chlorocaproylhydrazobenzene with potassium cyanide[38] has given poor yields, if any reaction occurs at all. This is explained by the fact that a reductive dehalogenation reaction occurs in the presence of potassium cyanide and hydrazobenzene with the formation of N-butyrylhydrazobenzene and N-caproylhydrazobenzene[38]. In spite of this drawback, the synthesis has been extended to the preparation of 4-ethyl-3-imino-5-oxo-1,2-diphenylpyrazolidine (LII)[38] but there is a considerable decrease in the yield.

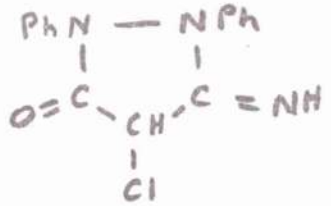


(LII)

It was decided to attempt the preparation of 4-chloro-3-imino-5-oxo-1,2-diphenylpyrazolidine (LIII) in the hope that this would provide a useful intermediate in the syntheses of other 4-substituted compounds. Initial reactions were carried out using phosphorus oxychloride

and 3-imino-5-oxo-1,2-diphenylpyrazolidine (XXXV) and varying the period of reflux from 5 to 10 hours, but in none of these cases could any solid be isolated from the resulting gum. A similar reaction with phosphorus pentachloride gave the same result.

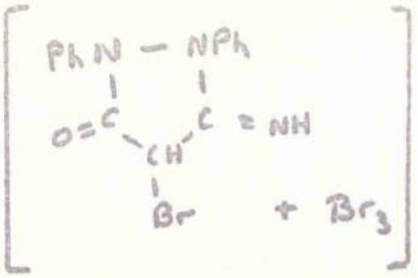
4-Chloro-3-imino-5-oxo-1,2-diphenylpyrazolidine (LIII) was finally obtained using phosphorus pentachloride and 3-imino-5-oxo-1,2-diphenylpyrazolidine (XXXV) and refluxing in chloroform solution. The product, (LIII), melted at 190° and showed infrared absorption at 3370 (NH), 3278 (OH), and 1640 cm^{-1} (CO). Ultraviolet absorption occurred at 206 (ε = 20,000) and 263 mμ (ε = 18,000) (see table A). A second compound, m.p. 183° was also isolated in this reaction in very small yield. It showed bands in the infrared spectrum at 3100, 3300, 1700, 1680, and 1590 cm^{-1}. It was obtained in poor yield along with an insoluble, infusible material, and neither was examined further.



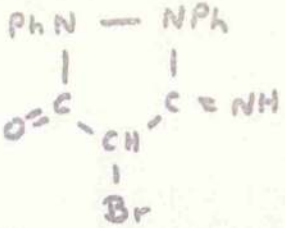
(LIII)

In view of the fact that phosphorus oxychloride and phosphorus pentachloride were not very successful as halogenating reagents, it was decided to brominate the 3-imino-5-oxo-1,2-diphenylpyrazolidine molecule, using a solution of bromine in chloroform and carrying out the reaction at room temperature. With an excess of bromine, yellow needles were formed which could not be recrystallised without decomposition. This material analysed for a tetrabromide, $C_{15}H_{12}ON_3Br_4$ (LIV). Its mode of formation and the fact that it is decomposed slowly on standing, suggest that it is similar to a compound prepared by Traubridge and Diehl[39] from pyridine and bromine in chloroform solution. They formulate their product as $C_5H_5N.Br_4$ but do not postulate a structural formula. A similar compound, formulated as $C_5H_5N.HBrBr_2$ has been prepared by Rosenmund and Kuhnhenn[40] but again the mode of attachment of the two bromine atoms is not known.

The tetrabromide from 3-imino-5-oxo-1,2-diphenylpyrazolidine has one bromine atom attached at the 4-position and the three other bromine atoms loosely attached, since on reduction with zinc and hydrochloric acid in ethanol solution, it gave 4-bromo-3-imino-5-oxo-1,2-diphenylpyrazolidine (LV) which could not be reduced further.

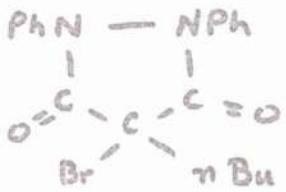


(LIV)



(LV)

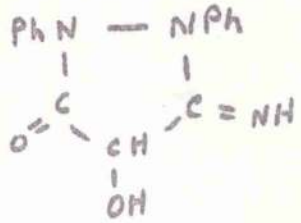
Both the tetrabromide (LIV), and 4-bromo-3-imino-5-oxo-1,2-diphenylpyrazolidine (LV) on treatment with an aqueous ethanolic solution of potassium cyanide, yielded 3-imino-5-oxo-1,2-diphenylpyrazolidine (XXXV). This reaction is similar to the action of potassium cyanide on bromo-butazolidine (LVI), which gives butazolidine as the major product[41].



(LVI)

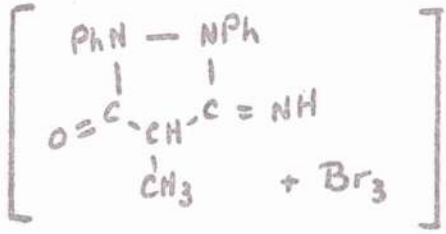
This reaction with potassium cyanide proceeds through the intermediate formation of cyanogen bromide, leaving 3-imino-5-oxo-1,2-diphenylpyrazolidine with a negative charge on the molecule. This in turn is stabilised by reacting with a hydrogen ion from the water present in the reaction mixture.

Treatment of the tetrabromide (LIV) with ethanolic potassium hydroxide solution gave 4-hydroxy-3-imino-5-oxo-1,2-diphenylpyrazolidine (LVII) along with an alkali-soluble material, m.p. 200°, which was shown to be a dimer by molecular weight determinations, but was not examined further.



(LVII)

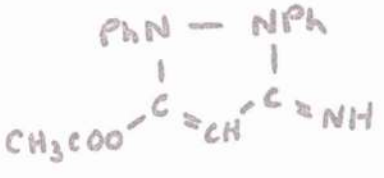
A similar reaction was carried out using 3-imino-4-methyl-5-oxo-1,2-diphenylpyrazolidine (XLVIII) and bromine in chloroform solution. In this case the product was a tribromide (LVIII), with the three bromine atoms loosely attached to the molecule and no substitution in the 4-position. This was demonstrated by treatment of the tribromide with a mixture of zinc and hydrochloric acid in ethanol. This gave 3-imino-4-methyl-5-oxo-1,2-diphenylpyrazolidine (XLVIII) with no bromine in the 4-position. Treatment of the tribromide (LVIII) with ethanolic potassium cyanide also gave 3-imino-4-methyl-5-oxo-1,2-diphenylpyrazolidine (XLVIII).



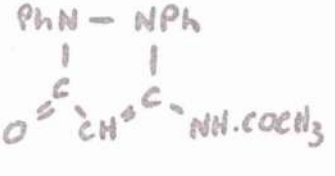
(LVIII)

In the bromination of 4-methyl-3-imino-5-oxo-1,2-diphenylpyrazolidine, the methyl group in the 4-position acts as a blocking group and hinders further substitution at that part of the molecule. All attempts to obtain a compound with two groups in the 4-position have been unsuccessful.

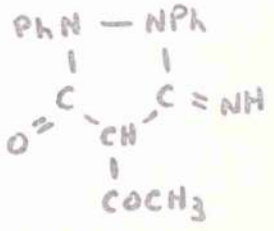
As a further method of putting substituent groups into the pyrazolidine molecule, it was decided to examine the products of acetylation. Previous attempts to acetylate 3-imino-5-oxo-1,2-diphenylpyrazolidine[42,43] have produced a series of products of varying complexity, some of which are very similar in their chemical properties, although not identical. Substitution using acetyl chloride or acetic anhydride can take place at one of three positions, as indicated in (LIX), (LX), and (LXI). Bimolecular condensations also take place, consequently the assignment of structures to the different products of acetylation is a matter of some difficulty.



(LIX)

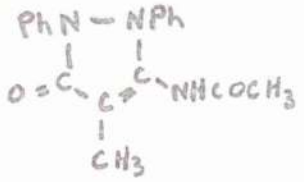


(LX)

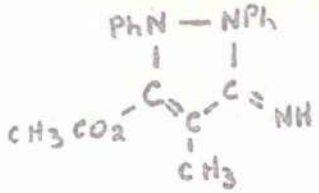


(LXI)

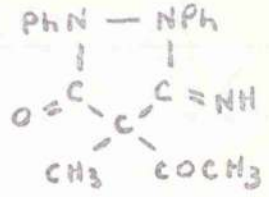
To simplify the problem of identifying and formulating the products, it was decided to attempt the acetylation of 4-methyl-3-imino-5-oxo-1,2-diphenylpyrazolidine (XLVIII). Since the ring system in this case is substituted in the 4-position, it was felt that there was not the same possibility of isomerism in the products, and hence the assignment of structural formulae would be simplified. In theory, there was the possibility of the formation of three mono-acetates (LXII), (LXIII), and (LXIV). There also existed the possibility of two diacetates, (LXV) and (LXVI).



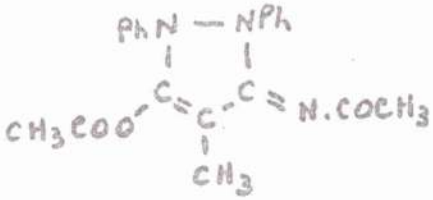
(LXII)



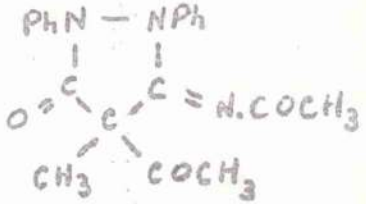
(LXIII)



(LXIX)



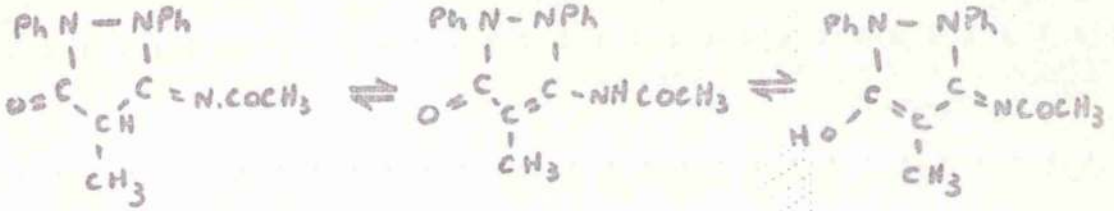
(LXV)



(LXVI)

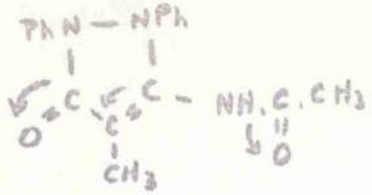
Initial attempts to acetylate 3-imino-4-methyl-5-oxo-1,2-diphenylpyrazolidine using acetyl chloride in the presence of pyridine resulted in the production of an alkali-soluble material which analysed for a mono-acetate.

On acidification of the alkaline solution, the acetate was recovered unchanged, showing that no hydrolysis had taken place. This acetate was found to give a red colouration with ferric chloride solution, indicating the presence of an enolic function in the molecule. Of the three possible mono-acetates, only 3-acetylimino-4-methyl-5-oxo-1,2-diphenylpyrazolidine (LXII) could be expected to show this property, since it can tautomerise as shown below :-



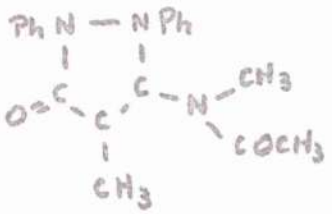
(LXII)

To confirm that the acetate formed was 3-acetylimino-4-methyl-5-oxo-1,2-diphenylpyrazolidine (LXII), an attempt was made to hydrolyse it. Aqueous sodium carbonate was found to have no effect and hydrolysis was only successful with sodium hydroxide solution on boiling for five hours. The reaction went in 50% yield. Of the three isomers, only an N- acetate would hydrolyse with so much difficulty. The solubility of the compound in alkali is explained by the fact that there are two carbonyl groups in the molecule, combining to withdraw electrons from the nitrogen atom in the 3-position. This atom has a low electron density as a result, and the hydrogen atom on it is therefore acidic (LXVII).

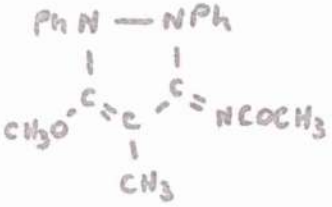


(LXVII)

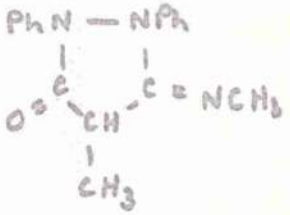
To confirm this idea the material was methylated by allowing it to stand in the presence of diazomethane for ten days. The product was a mono-methyl mono-acetate, and was shown to be 3-N-acetylmethylamino-4-methyl-5-oxo-1,2-diphenylpyrazoline (LXVIII). An alternative product of this reaction could be 3-acetylimino-4-methyl-5-methoxy-1,2-diphenyl-pyrazoline (LXIX), but this possibility has been eliminated since the product can be hydrolysed to give a material (LXX) producing a red colouration with ferric chloride solution.



(LXVIII)



(LXIX)



(LXX)

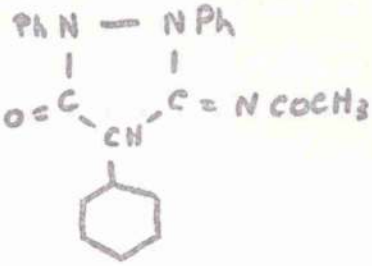
A product formed by the hydrolysis of 3-acetylimino-4-methyl-5-methoxy-1,2-diphenylpyrazoline (LXIX), would not give a ferric colouration because of the substitution on the OH group, so this formula has been rejected in favour of 3-N-acetylmethylamino-4-methyl-5-oxo-1,2-diphenylpyrazoline (LXVIII).

Further evidence that the material is 3-*N*-acetylmethylamino-4-methyl-5-oxo-1,2-diphenylpyrazoline (LXVIII) is that the infrared spectrum shows absorption bands corresponding to two carbonyl groups, at 1681 and 1658 cm^{-1}, whereas there is only one carbonyl group in 3-acetylimino-4-methyl-5-methoxy-1,2-diphenylpyrazoline (LXIX).

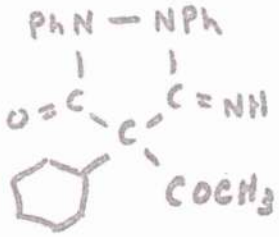
A second acetate was formed by treating 3-imino-4-methyl-5-oxo-1,2-diphenylpyrazolidine (XLVIII) with an excess of acetyl chloride and heating on a steam bath for five minutes, in the presence of pyridine. This material is not formed if pyridine is absent, even on prolongued reflux. This compound was found to be a diacetate. It could also be prepared by treatment of the mono-acetate (LXII) with acetic anhydride. To determine the position of the second acetate grouping, the compound was boiled with sodium carbonate solution. Partial hydrolysis gave the mono-acetate (LXII). The ease with which hydrolysis took place indicated the presence of an *O*-acetate grouping. The compound is therefore 3-acetylimino-5-acetoxy-4-methyl-1,2-diphenylpyrazoline (LXV) since the *C*-acetate (LXVI) would not hydrolyse so readily. The diacetate can be completely hydrolysed to the parent unsubstituted pyrazolidine on prolongued boiling with sodium hydroxide solution. It is insoluble in cold sodium hydroxide solution, but soluble on heating due to partial hydrolysis.

It does not give a colouration with ferric chloride solution. None of the other acetates theoretically possible, were isolated from these reactions.

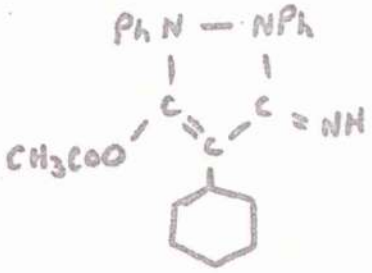
4-Cyclohexyl-3-imino-5-oxo-1,2-diphenylpyrazolidine (XLIV) was also acetylated using acetic anhydride and pyridine. This gave a mono-acetate which was shown to be the N-acetate (LXXI) since it gave a red colouration with ferric chloride solution and was difficult to hydrolyse. Neither the C-acetate (LXXII) or the O-acetate (LXXIII) would show these properties.



(LXXI)



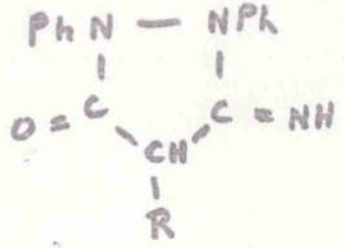
(LXXII)



(LXXIII)

Table A

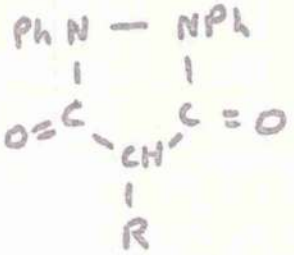
Ultraviolet absorption of 4-substituted imino-oxopyrazolidines.



Formula	R	λ max in ethanol
(XXXV)	H	206. 254.
(XLIII)	C_6H_9	205. 257.
(XLIV)	C_6H_{11}	204. 262.
(XLVIII)	CH_3	206. 264.
(LIII)	Cl	206. 263.
(LV)	Br	206. 261.
(LVIII)	OH	206. 224. 300.
(XXXIX)	PhCH=	206. 288.
(XLV)	C_3H_7CH=	245. 303. 370.

Table B.

Ultraviolet absorption of 4-substituted dioxopyrazolidines.



Formula	R	λ max in ethanol.
(XIII)	H	208, 249.
(XIX)	C_6H_9=	360, 372.
(XX)	PhCH=	206, 236, 334.

EXPERIMENTAL.

Infrared spectra were determined in nujol unless otherwise stated. Where two compounds are claimed to be identical, the identity was confirmed by infrared comparison. Ultraviolet spectra in alkali were determined in a mixture of equal parts of 2N NaOH and ethanol, and in acid, the spectra were obtained using a mixture of equal parts of 2N hydrochloric acid and ethanol.

N-Cyanoacetylhydrazobenzene. Since no experimental details were given in the literature method,[34] the following technique was used. - A well stirred solution of hydrazobenzene (13.8 g.) in chloroform (300 c.c.) and pyridine (100 c.c.) was treated at -10° with a solution of freshly prepared cyanoacetyl chloride[32] (21.5 g.:3 mole) in chloroform (75 c.c.) added over a period of 1 hr.. The reaction mixture was allowed to attain room temperature by standing for 3 hr., then kept overnight and poured into water (500 c.c.). The chloroform layer was washed with water (100 c.c.), hydrochloric acid (3 x 150 c.c.; 2N), aqueous sodium hydroxide solution (3 x 150 c.c.; 2N), and finally with water and dried (Na_2SO_4). Evaporation of the chloroform and crystallisation of the residue from ethanol gave N-cyanoacetylhydrazobenzene, (5.4 g.:29%) as plates,

m.p. 173° (lit.[34] m.p. 172-173°) (Found C,71.5; H,5.1% Calc. for $C_{15}H_{13}ON_3$ C,71.7; H,5.2%). λ max in ethanol 208 (ε= 16,000) and 237 mμ (ε = 18,000): λ max in alkali 254 mμ (ε = 23,900): λ max in acid 205 (ε = 36,000) and 236 mμ (ε = 24,000): ν max 3306 (NH), 2245 (CN), and 1667 cm^{-1} (CO).

3-Imino-5-oxo-1,2-diphenylpyrazolidine. -

(a). Concentration of the ethanolic mother liquors from the cyanoacetylhydrazobenzene preparation yielded 3-imino-5-oxo-1,2-diphenylpyrazolidine (1.6 g.;9%) as plates, m.p. 222°; it was sublimed at 200°/0.5 mm. for analysis. (Found C,71.45; H,5.2%; $C_{15}H_{13}ON_3$ requires C,71.7; H,5.2%) λ max in ethanol 206 (ε= 17,000) and 254 mμ (ε = 23,000): λ max in alkali 225 (ε = 61,000) and 255 mμ (ε = 22,000): λ max in acid 206 (ε = 19,000) and 252 mμ (ε = 22,000): ν max 3333 (NH), 1675 (CO), and 1639 (NH).

(b). A solution of N-cyanoacetylhydrazobenzene (500 mg.) in ethanol (18 c.c.) and aqueous sodium carbonate (18 c.c.) was refluxed for 4 hr.. The cooled solution on dilution with water (50c.c.) and extracting with chloroform (3 x 50 c.c.) gave a solid on evaporation of the solvent. Crystallisation of this residue from ethanol gave 3-imino-5-oxo-1,2-diphenyl-pyrazolidine (400 mg.; 80%), identical with the material produced in preparation (a), m.p. 222° (Found C,71.7; H,5.3%).

(c) A solution of N-cyanoacetylhydrazobenzene (500 mg.) in ethanol (18 c.c.) was refluxed with sodium ethoxide (from 20 mg. Na) for 3 hr., cooled, diluted with water and the product isolated using chloroform. Crystallisation from methylene chloride / hexane gave 3-imino-5-oxo-1,2-diphenylpyrazolidine (75 mg.) as prisms, m.p. 222°, (Found C,71.7; H,5.2%), identical with the material produced in preparation (a). A similar yield of the product was obtained using methanolic sodium methoxide.

(d). A solution of chloroacetylhydrazobenzene [44] (1.5 g.) in ethanol (25 c.c.) was refluxed with a solution of potassium cyanide (2.5 g.) in water (15 c.c.) for 7 hr.. The solution was diluted with water (50 c.c.) and extracted with chloroform (3 x 50 c.c.). The combined chloroform extracts were washed with water (2 x 25 c.c.), dried (Na_2SO_4) and evaporated. Crystallisation of the residue from chloroform / methanol gave 3-imino-5-oxo-1,2-diphenylpyrazolidine (0.8 g.: 57%), m.p. 222° alone or mixed with an authentic specimen.

Attempted preparation of 4-benzylidene-3-imino-5-oxo-1,2-diphenylpyrazolidine. - Sodium (2.0 g.) was dissolved in dry ethanol (50 c.c.) and ethyl benzylidene cyanoacetate[35] (2.0 g.) was added with hydrazobenzene (3.0 g.). The mixture was refluxed for 48 hr. on a water bath, filtered to free from suspended solid matter (m.p. above 360°) and the

ethanol was evaporated off. The residual material was dissolved in chloroform and the solution was washed with water (3 x 50 c.c.). The chloroform solution was evaporated to dryness and extracted with petrol until all azobenzene, m.p. 69°, was removed. A gummy material resulted from which no solid could be isolated.

4-Benzylidene-3-imino-5-oxo-1,2-diphenylpyrazolidine.

3-Imino-5-oxo-1,2-diphenylpyrazolidine (1.0 g.) was refluxed for 1 hr. with freshly distilled benzaldehyde (5.0 g.). The solution was diluted with ether, washed twice with saturated sodium bisulphite solution, once with water and dried (Na_2SO_4). An interfacial solid separated on washing and was removed by filtration before drying the ether. The ether was removed under vacuum, leaving a dark-red gum. Recrystallisation of the interfacial solid from chloroform / petrol gave yellow needles of 4-benzylidene-3-imino-5-oxo-1,2-diphenylpyrazolidine, m.p. 343°. (Found: C,77.34; H,5.1%; $C_{22}H_{18}ON_3$ requires C,77.6; H,5.3%). λ max in ethanol 206 (ε = 31,900) and 288 mμ (ε = 32,000); ν max 1710 (CO), 1600 (NH), 1560 (Ph) and 1380 cm^{-1}.

Attempted reduction of 4-benzylidene-3-imino-5-oxo-1,2-diphenylpyrazolidine. - (a). 4-Benzylidene-3-imino-5-oxo-1,2-diphenylpyrazolidine (0.5 g.) was dissolved in redistilled ethyl acetate and shaken with hydrogen at room temperature and atmospheric pressure with platinum black (0.3 g.) as catalyst. Filtration of the solution after 5 hr. and evaporation of the solvent resulted in the production of yellow crystals (m.p. 343°; 0.5 g.), identical to the starting material.

(b). 4-Benzylidene-3-imino-5-oxo-1,2-diphenylpyrazolidine (0.5 g.) was dissolved in ethanol (400 c.c.). Raney nickel catalyst (1.0 g.) was added and the mixture was shaken in an autoclave with hydrogen at 50 atmospheres and 135° for 7 hr.. Filtration and evaporation of the solvent resulted in the production of yellow needles, m.p. 343°, 0.5 g., identical to the starting material.

Attempted preparation of 4-cyclohexylidene-3-imino-5-oxo-1,2-diphenylpyrazolidine. - Ethyl cyclohexylidene cyanoacetate[36] (2.0 g.) and hydrazobenzene (3.0 g.) were refluxed for 48 hr in the presence of sodium ethoxide (from 2.0 g. sodium and 50 c.c. ethanol) on a water bath. The solution was evaporated to dryness, extracted with petrol to remove azobenzene (m.p. 68°), dissolved in chloroform, and washed with water. The chloroform solution was dried

(Na_2SO_4) and the solvent evaporated off, leaving an oily dark-red product from which no solid could be isolated.

4-Cyclohexenyl-3-imino-5-oxo-1,2-diphenyl-pyrazolidine. - 3-Imino-5-oxo-1,2-diphenylpyrazolidine (1.0 g.) was refluxed with cyclohexanone (10 c.c.) for 1 hr.. The solution was allowed to cool and petrol was added to precipitate the product as an oil. The material was washed with petrol and recrystallised from ethanol / petrol to give prisms of 4-cyclohexenyl-3-imino-5-oxo-1,2-diphenylpyrazolidine, m.p. 189°, (Found C,75.83; H,6.1%; $C_{21}H_{21}ON_3$ requires C,76.1; H,6.4%). λ max in ethanol 205 (ε = 27,000) and 257 mμ (ε = 23,100); λ max in alkali 228 (ε = 62,600) and 254 mμ (ε = 23,700); ν max 3400 (OH or NH), 1650 (CO), 1600 (NH), and 1570 cm^{-1}.

4-Cyclohexyl-3-imino-5-oxo-1,2-diphenylpyrazolidine. 4-Cyclohexenyl-3-imino-5-oxo-1,2-diphenylpyrazolidine (1.0 g.) was dissolved in redistilled ethyl acetate (250 c.c.) and platinum oxide was added (0.5 g.) as a catalyst. The mixture was shaken with hydrogen for several hours until no more gas was absorbed, filtered, and the solvent removed under vacuum, to give white prisms of 4-cyclohexyl-3-imino-5-oxo-1,2-diphenylpyrazolidine, m.p. 230°; 1.0 g. (Found C,75.24; H,6.77; N,12.94%: $C_{21}H_{23}ON_3$ requires C,75.64;

H,6.95; N,12.6). λ max in ethanol 204 (ε = 24,400) and 262 mμ (ε = 24,500); λ max in alkali 228 (ε = 13,200) and 263 mμ (ε = 20,700); ν max 3400 (OH or NH) 1660 (CO), 1590 and 1255 cm^{-1}.

4-n-Butylidene-3-imino-5-oxo-1,2-diphenylpyrazolidine.

3-Imino-5-oxo-1,2-diphenylpyrazolidine (1.0 g.) was refluxed with n-butyraldehyde (5.0 c.c.) for 2 hr., cooled, diluted with ether, and the solution was washed with a saturated solution of sodium bisulphite (3 x 50 c.c.), water and dried (Na_2SO_4). The ether was evaporated off and the residue was recrystallised from ethanol to give needles of 4-n-butylidene-3-imino-5-oxo-1,2-diphenylpyrazolidine, m.p. 196° (Found C,74.63; H,6.31; $C_{19}H_{19}ON_3$ requires C,74.73; H,6.27%). λ max in ethanol 245 (ε = 11,000), 303 (ε = 25,500) and 370 mμ (ε = 7,250); λ max in alkali 240 (ε = 11,200), 251 (ε = 11,200), 300 (ε = 17,000) and 370 mμ (ε = 6,900); ν max 3789 (NH), 1661 (CO), and 1502 cm^{-1}.

Attempted reduction of 4-butylidene-3-imino-5-oxo-1,2-diphenylpyrazolidine. - (a). 4-n-Butylidene-3-imino-5-oxo-1,2-diphenylpyrazolidine (500 mg.) was dissolved in ethyl acetate, and treated with hydrogen in the presence of platinum as catalyst, for 4 hrs.. When no more gas was

absorbed, the solution was filtered and concentrated. On standing, yellow needles were formed (m.p. 196°), which were found to be identical to the starting material.

(b). 4-n-Butylidene-3-imino-5-oxo-1,2-diphenylpyrazolidine (500 mg.) was dissolved in ethanol (400 c.c.). Raney nickel (1.0 g.) was added and the mixture was shaken in an autoclave with hydrogen at 50 atmospheres and 100° for 6 hr.. Filtration and evaporation of the solvent resulted in the production of yellow crystals (m.p. 196°), identical to the starting material.

α-Chloropropionylhydrazobenzene. - A solution of α-chloropropionyl chloride (40 g.) in chloroform (30 c.c.) was added dropwise to an ice-cooled solution of hydrazobenzene (25 g.) in chloroform (300 c.c.) and pyridine (100 c.c.) with stirring over 1 hr.. The ice bath was then removed and stirring continued for a further 2 hr.. The reaction solution was washed with hydrochloric acid (500 c.c.; 2 N), water (300 c.c.) and dried over anhydrous sodium sulphate. Concentration and cooling and crystallisation of the solid which separated, from ethanol gave α-chloropropionylhydrazobenzene (40 g.) as prisms, m.p. 149° (Found C,65.22; H,5.9; $C_{15}H_{15}ON_2Cl$ requires C,65.5; H,5.5%). λ max in ethanol 206 (ε = 28,000) and 238 mμ (ε = 20,000); ν max 3250 (NH), and 1642 cm^{-1} (CO).

3-Imino-4-methyl-5-oxo-1,2-diphenylpyrazolidine.

(a). A solution of α-chloropropionylhydrazobenzene (2.5 g.) and potassium cyanide (3.0 g.) in ethanol (25 c.c.) and water (8 c.c.) was refluxed for 5 hr.. The cooled solution was diluted with water and the product isolated using chloroform. 3-Imino-4-methyl-5-oxo-1,2-diphenylpyrazolidine (1.0 g.) separated as plates, m.p. 180°. (Found C,72.1; H,5.45%; $C_{16}H_{15}ON_3$ requires C,72.4; H,5.7%). λ max in ethanol 206 (ε = 22,000) and 264 (ε = 25,000); λ max in alkali 263 mμ (ε = 19,500); ν max 3874 (NH), 3278 (OH), and 1640 cm^{-1} (CO). The compound gave a red colouration with aqueous ferric chloride.

(b). α - Bromopropionylhydrazobenzene[37] (12 g.) when treated with potassium cyanide in the same way, also gave 3-imino-4-methyl-5-oxo-1,2-diphenylpyrazolidine (5.0 g.), m.p. and mixed m.p. 180°.

Attempted chlorination of 3-imino-5-oxo-1,2-diphenylpyrazolidine. (a). 3-Imino-5-oxo-1,2-diphenylpyrazolidine (0.5 g.) was refluxed for 1 hr. with phosphorus oxychloride (10 c.c.). The solution was allowed to cool, diluted with chloroform and washed thoroughly with water to remove acidic products. The chloroform solution was dried and the solvent was evaporated off, leaving a gummy residue, from which no solid could be isolated.

(b). The experiment described above was repeated using 3-imino-5-oxo-1,2-diphenylpyrazolidine (0.5 g.) and phosphorus pentachloride (1.5 g.) and refluxing for 1 hr.. Again no solid product could be isolated from the gummy residue.

4- Chloro-3-imino-5-oxo-1,2-diphenylpyrazolidine.

3-Imino-5-oxo-1,2-diphenylpyrazolidine (0.5 g.) was refluxed with phosphorus pentachloride (1.5 g.) in chloroform (20 c.c.) for 2 hr.. The solution was cooled, washed with water (3 x 40 c.c.), dried (Na_2SO_4) and the solvent removed. On treatment with methanol and ethanol, the gummy residue yielded initially a trace of a compound m.p. 183° after recrystallisation from ethanol, and the mother liquors on concentration gave prisms of 4-chloro-3-imino-5-oxo-1,2-diphenylpyrazolidine , m.p. 190°. (Found C,63.45; H,4.72; N,14.13; $C_{15}H_{12}ON_3Cl$ requires C,63.2; H,4.21; N,14.60%). λ max in ethanol 206 (ε = 20,000) and 263 mu (ε = 18,000). ν max 3340 (NH), 3278 (OH), and 1640 cm^{-1}(CO). A trace of a third compound m.p. above 360° was also isolated on further concentration of the mother liquors.

Bromination of 3-imino-5-oxo-1,2-diphenyl-pyrazolidine. - 3-Imino-5-oxo-1,2-diphenylpyrazolidine (1.0 g.) was dissolved in dry chloroform (30 c.c.) and a solution of bromine (2.0 c.c.) in chloroform (20 c.c.) was added, slowly

and with stirring. The solution was allowed to stand for 1 hr. when it deposited yellow needles of 4-bromo-3-imino-5-oxo-1,2-diphenylpyrazolidine tribromide, m.p. 130°, (0.7 g.). (Found C,28.9; H,2.2; N,5.9; Br,53.1%; $C_{15}H_{12}ON_3Br_4$ requires C,32.1; H,2.1; N,7.3; Br,55.0%). λ max in ethanol 205 (ε = 23,400), 240 (ε = 22,100), and 321 mμ (ε = 1,700); ν max 3340 (NH), 3100 (OH), 1650 (CO) and 1580 cm^{-1}.

Reduction of tetrabromide from 3-imino-5-oxo-1,2-diphenylpyrazolidine. - A solution of 4-bromo-3-imino-5-oxo-1,2-diphenylpyrazolidine tribromide (1.0 g.) in ethanol (10 c.c.) was reduced with zinc powder (0.5 g.) and hydrochloric acid (0.5 c.c.) on a steam bath for 15 minutes. The solution was filtered, diluted with water, and extracted with chloroform. The solution was concentrated and allowed to crystallise, when prisms of 4-bromo-3-imino-5-oxo-1,2-diphenylpyrazolidine (0.5 g.) were formed, m.p. 201°. (Found C,53.8; H,3.95; N,12.0; Br,23.67%; $C_{15}H_{12}ON_3Br$ requires C,54.5; H,3.63; N,12.7; Br,24.2%). λ max in ethanol 206 (ε = 4,900), and 261 mμ (ε = 4,600); ν max 3140 (OH or NH), 1670 (CO), 1610 (NH), and 1580 cm^{-1}.

Action of potassium cyanide on 4-bromo-3-imino-5-oxo-1,2-diphenylpyrazolidine tribromide. - 4-Bromo-3-imino-5-oxo-1,2-diphenylpyrazolidine tribromide (1.0 g.) was dissolved in ethanol (10 c.c.) and refluxed with an aqueous solution of potassium cyanide (2.0 g. in 6 c.c. water) for 3 hr.. The solution was allowed to cool, diluted with water, and extracted with chloroform. The chloroform solution was washed with water, dried and evaporated to small bulk, giving plates of 3-imino-5-oxo-1,2-diphenylpyrazolidine, (0.5 g.) m.p. 222° alone or mixed with an authentic sample.

Action of potassium cyanide on 4-bromo-3-imino-5-oxo-1,2-diphenylpyrazolidine. - A solution of 4-bromo-3-imino-5-oxo-1,2-diphenylpyrazolidine (1.0 g.) in ethanol (10 c.c.) was refluxed with a solution of potassium cyanide (2.0 g.) in water (8.0 c.c.) for 5 hr.. The solution was cooled, diluted with water and extracted with chloroform. On reducing the volume of the chloroform solution, plates of 3-imino-5-oxo-1,2-diphenylpyrazolidine, (0.7 g.), m.p. 222° were formed.

4-Hydroxy-3-imino-5-oxo-1,2-diphenylpyrazolidine. A solution of 4-bromo-3-imino-5-oxo-1,2-diphenyl-pyrazolidine tribromide (1.0 g.) in ethanol (10 c.c.)

was refluxed with an aqueous solution of potassium hydroxide (5%; 5.0 c.c.) for 1 hr.. The solution was cooled, diluted with water, and extracted with chloroform. The extract was evaporated down and allowed to crystallise, to give plates of 4-hydroxy-3-imino-5-oxo-1,2-diphenylpyrazolidine (0.2 g.) m.p. 255°; (Found C,68.4; H,4.9; $C_{15}H_{13}O_2N_3$ requires C,67.5; H,4.87%); λ max in ethanol 206 (ε = 33,100), 224 (ε = 23,200) and 300 mμ (ε = 20,500). ν max 3330 (OH or NH), 3170 (OH or NH), 1640 (CO), 1610 (NH), and 1460 cm^{-1}.

The alkaline solution was acidified (HCl) and extracted with chloroform. Evaporation of the chloroform solution yielded small prisms, m.p. 200°. (Found C,71.52; H,5.37; N,11.8%). λ max in ethanol 206 (E_{max} = 12,000), 226 (E_{max} = 10,000) and 305 (E_{max} = 5,700). νmax 1740 (CO), 1390, and 1235 cm^{-1}. Molecular weight of the compound was found to be 400.

Bromination of 4-methyl-5-oxo-3-imino-1,2-diphenylpyrazolidine. 3-Imino-4-methyl-5-oxo-1,2-diphenylpyrazolidine (0.7 g.) was dissolved in chloroform (10 c.c.) and treated with a solution of bromine (3.0 c.c.) in chloroform (10 c.c.) over a period of 30 minutes. The solution was allowed to stand overnight in a refrigerator to crystallise , when yellow needles of 3-imino-4-methyl-5-oxo-1,2-diphenylpyrazolidine tribromide were formed,

m.p. 140°. (Found C,37.1; H,2.23; N,7.0; Br,43.0%
$C_{16}H_{15}ON_3Br_3$ requires C,38.1; H,2.58; N,8.34; Br,47.6%).
λmax in ethanol 207 (ε = 18,000), 244 (ε = 15,700) and 321 mμ (ε = 1,700): ν max 3340 (NH), 3200 (OH), 1640 (CO) and 1580 cm^{-1}.

Action of potassium cyanide on 3-imino4-methyl-5-oxo-1,2-diphenylpyrazolidine tribromide. - 3-Imino-4-methyl-5-oxo-1,2-diphenylpyrazolidine tribromide (0.3 g.) in ethanol (10 c.c.) was refluxed for 5 hr. with a solution of potassium cyanide (1.0 g.) in water (5 c.c.). The solution was allowed to cool, diluted with water, and extracted with chloroform. The solvent was evaporated off and the solution was allowed to crystallise, giving plates of 3-imino-4-methyl-5-oxo-1,2-diphenylpyrazolidine, m.p. 180°, (0.1 g.), identical with an authentic specimen.

Reduction of 3-imino-4-methyl-5-oxo-1,2-diphenyl-pyrazolidine tribromide. - A solution of 3-imino-4-methyl-5-oxo-1,2-diphenylpyrazolidine tribromide (0.25 g.) in ethanol (5 c.c.) was reduced for 15 minutes with zinc (0.1 g.) and hydrochloric acid (2.0 c.c.). The solution was diluted with water, filtered, extracted with chloroform and the solvent removed. The gummy residue gave prisms on treatment with ether / chloroform. Recrystallisation of the material from

chloroform gave plates of 3-imino-4-methyl-5-oxo-1,2-diphenylpyrazolidine, m.p. 180°, identical to an authentic specimen.

3-Acetimino-4-methyl-5-oxo-1,2-diphenylpyrazolidine.

3-Imino-4-methyl-5-oxo-1,2-diphenylpyrazolidine (1.0 g.) was dissolved in dioxan (25 c.c.) and pyridine (5 c.c.). A solution of hydrochloric acid-free acetyl chloride (3 c.c.) in ether (20 c.c.) was added over a period of 30 minutes with cooling and stirring. The mixture was allowed to stand for 2 hr., diluted with chloroform, and washed with hydrochloric acid to remove pyridine. The chloroform solution was washed with water and extracted with sodium hydroxide solution (3 x 30 c.c.; 5%). The washed chloroform solution was evaporated to produce crystals of the starting material, 3-imino-4-methyl-5-oxo-1,2-diphenylpyrazolidine, m.p. 180°, (0.5 g.)

The alkali solution was acidified with dilute hydrochloric acid and extracted with chloroform (3 x 50 c.c.). The chloroform solution was washed with water (2 x 50 c.c.), dried, and evaporated down to give plates of 3-acetimino-4-methyl-5-oxo-1,2-diphenylpyrazolidine, m.p. 189°. (Found C, 70.1; H, 5.76; $C_{18}H_{17}O_2N_3$ requires C, 70.34; H, 5.58%). λ max in ethanol 205 (ε = 23,000), 242 (ε = 19,600) and 276 mμ (ε = 13,500). λ max in alkali 272 mμ (ε = 24,400). ν max 3195 (NH), 3003 (CH), 1685 (CO), 1681 (CO), 1658, 1637 (NH) and 1239 cm^{-1}.

Hydrolysis of 3-acetimino-4-methyl-5-oxo-1,2-diphenylpyrazolidine. - (a). 3-Acetimino-4-methyl-5-oxo-1,2-diphenylpyrazolidine (0.25 g.) was refluxed for 2 hr. with an aqueous solution of sodium carbonate (1.0 g.). The solution was acidified with hydrochloric acid and extracted with chloroform. Evaporation of the solvent yielded plates of the starting material, 3-acetimino-4-methyl-5-oxo-1,2-diphenylpyrazolidine, m.p. 189° (0.25 g.).

(b) 3-Acetimino-4-methyl-5-oxo-1,2-diphenylpyrazolidine (0.25 g.) was refluxed for 5 hr. with an aqueous solution of sodium hydroxide (5%; 5.0 c.c.). The solution was allowed to cool and extracted with chloroform. Evaporation of the chloroform solution yielded white plates of 3-imino-4-methyl-5-oxo-1,2-diphenylpyrazolidine, m.p. 180°, (0.15 g.) identical to an authentic sample. Acidification of the alkaline solution yielded the unhydrolysed material, 3-acetimino-4-methyl-5-oxo-1,2-diphenylpyrazolidine, m.p. 189°, 0.1 g.

Action of diazomethane on 3-acetimino-4-methyl-5-oxo-1,2-diphenylpyrazolidine. - 3-Acetimino-4-methyl-5-oxo-1,2-diphenylpyrazolidine (0.5 g.) was treated with an excess of diazomethane in ether solution and allowed to stand for 10 days in a refrigerator. The solution was treated with acetic acid to destroy excess of diazomethane,

and extracted with sodium hydroxide solution (5%), to remove unreacted starting material. The ether was evaporated off and the resulting gum was treated with acetone and petrol to give a solid, m.p. 117°, which was recrystallised from acetone/petrol, to give prisms of 3-N-methylacetylamino-4-methyl-5-oxo-1,2-diphenylpyrazoline, (0.4 g.), m.p. 123°. (Found C,71.43; H,6.21; N,11.75; $C_{19}H_{19}O_2N_3$ requires C,71.01; H,5.96; N,13.08%). ν max 1667 (CO), 1650 (CO), and 1610 cm^{-1} (NH).

3-Methylimino-4-methyl-5-oxo-1,2-diphenylpyrazolidine.

3-N-Methylacetylamino-4-methyl-5-oxo-1,2-diphenylpyrazoline (150 mg.) was refluxed with an ethanolic solution of potassium hydroxide with 5 c.c. of water, on a steam bath for 5 hr.. The solution was cooled, acidified with hydrochloric acid (2N.) and extracted with chloroform (3 x 15 c.c.). The solvent was evaporated off and the residue crystallised from methanol to give prisms of 3-methylimino-4-methyl-5-oxo-1,2-diphenylpyrazolidine, (100 mg.) m.p. 208°. (Found C,73.36; H,6.22; $C_{17}H_{17}ON_3$ requires C,73.51; H,5.8%). ν max 3210 (NH), 3000 (OH), 1660 (CO), 1650 and 1600 cm^{-1} (NH).

3-Acetimino-4-methyl-5-acetoxy-1,2-diphenyl-pyrazoline. - (a) 3-Imino-4-methyl-5-oxo-1,2-diphenylpyrazolidine (1.0 g.) was dissolved in chloroform (25 c.c.) and pyridine (5.c.c.) and a solution of acetyl chloride (6 c.c.) in chloroform (25 c.c.) was added. The solution boiled because of the heat generated in the reaction. The solution was heated on a steam bath for a further 5 minutes. The solution was washed with hydrochloric acid, water and extracted with sodium hydroxide (3 x 20 c.c.: 3 N.). The alkaline solution was acidified with hydrochloric acid (3 N) and extracted with chloroform. Evaporation of the chloroform solution gave no residue. The original chloroform solution was evaporated to dryness to give prisms of 3-acetimino-4-methyl-5-acetoxy-1,2-diphenylpyrazoline, (0.7 g.) m.p. 167°. (Found C,68.19; H,5.18; N,11.53; $C_{20}H_{19}O_3N_3$ requires C,68.75; H,5.48; N,12.03%). λmax in ethanol 209 (ε = 17,800), 240 (ε = 11,800) and 286 mμ (ε = 12,100). λmax in alkali 228 (ε = 49,000) and 278 mμ (ε = 17,000). λmax in acid 203 (ε = 14,000) 210 (ε = 11,000) and 257 mμ (ε = 15,000). ν max 1725, 1710, and 1667 cm^{-1} (CO).

(b) 3-Acetylimino-4-methyl-5-oxo-1,2-diphenylpyrazolidine (0.2 g.) was heated with acetic anhydride (5 c.c.) for 1 hr. on a steam bath. The solution was diluted with water and extracted with chloroform. The chloroform solution was evaporated to dryness to give a gum which on treatment with

methanol/water gave white prisms of 3-acetimino-4-methyl-5-acetoxy-1,2-diphenylpyrazoline (0.15 g.), m.p. 167°.

Hydrolysis of 3-acetimino-4-methyl-5-acetoxy-1,2-diphenylpyrazoline. - (a) 3-Acetimino-4-methyl-5-acetoxy-1,2-diphenylpyrazoline (250 mg.) was dissolved in ethanol (10 c.c.) and refluxed with aqueous sodium carbonate for 1 hr.. The solution was extracted with chloroform, after acidification with dilute hydrochloric acid, and the solvent was evaporated off, to give prisms of the partially hydrolysed material, 3-acetimino-4-methyl-5-oxo-1,2-diphenylpyrazolididine (200 mg.), m.p. 189°.

(b) 3-Acetimino-4-methyl-5-acetoxy-1,2-diphenylpyrazoline (250 mg.) was dissolved in ethanol (10 c.c.) and refluxed with aqueous sodium hydroxide (5%; 5 c.c.) for 5 hr.. The solution was acidified and extracted with chloroform. Evaporation of the chloroform solution yielded plates of 3-imino-4-methyl-5-oxo-1,2-diphenylpyrazolidine, (150 mg.), m.p. 180°.

3-Acetimino-4-cyclohexyl-5-oxo-1,2-diphenylpyrazolidine. - 3-Imino-4-cyclohexyl-5-oxo-1,2-diphenylpyrazolidine (250 mg.) was heated on a steam bath for 1 hr. with acetic anhydride (8 c.c.). The solution was allowed to cool and water was added to destroy excess of acetic anhydride. The material was allowed to crystallise from the aqueous

acetic acid solution. Initially white crystals of 3-acetimino-4-cyclohexyl-5-oxo-1,2-diphenylpyrazolidine (200 mg.) m.p. 308°, were formed. (Found C, 72.8; H, 6.5; $C_{23}H_{25}O_2N_3$ requires C, 73.5; H, 6.7%). λmax in ethanol 206 (ε = 21,000) 251 (ε = 13,000) and 278 mμ (ε = 13,000). λ max in alkali 277 mμ (ε = 19,000). λmax in acid 206 (ε = 18,000), 250 (ε = 11,000) and 280 mμ (ε = 11,000). ν max 3125 (NH), and 1704 cm^{-1} (CO). Further concentration of the mother liquors yielded crystals of the unchanged starting material.

Hydrolysis of 3-acetimino-4-cyclohexyl-5-oxo-1,2-diphenylpyrazolidine. - (a) 3-Acetimino-4-cyclohexyl-5-oxo-1,2-diphenylpyrazolidine (50 mg.) was dissolved in ethanol (5 c.c.) and sodium carbonate solution (5 c.c.; N) was added. The mixture was refluxed for 2 hr. on a steam bath, diluted and allowed to crystallise. The solid formed was recrystallised from ethanol and was shown to be identical to the starting material, 3-acetimino-4-cyclohexyl-5-oxo-1,2-diphenylpyrazolidine (50 mg.) m.p. 308°.

(b) The experiment was repeated using a solution of potassium hydroxide (5 c.c.; N) in place of the sodium carbonate solution. After refluxing for 2 hr. and working up the solution by extracting with chloroform, the product was again shown to be identical to the starting material, 3-acetimino-4-cyclohexyl-5-oxo-1,2-diphenylpyrazolidine.

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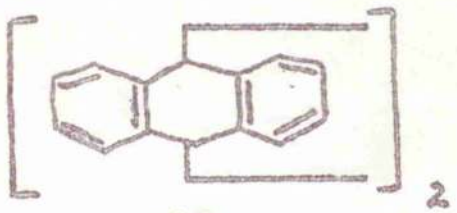
PART TWO.

DIMERISATION OF STEROIDS.

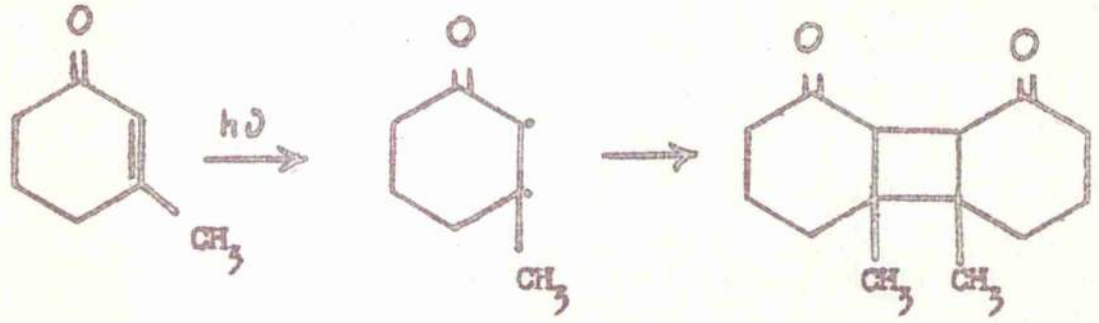
Photodimerisation of Steroids.

It has been known since 1867 that many compounds containing unsaturated systems undergo dimerisation when exposed to sunlight or ultraviolet light. The first photodimer of this type was obtained by Fritsche[1], who irradiated a solution of anthracene with sunlight and obtained an insoluble compound which was later shown to be dianthracene (I) by Elbs[2], and by Orndorff and Cameron[3].



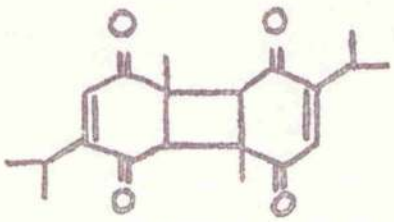
(I)

The photodimerisation of α-β unsaturated ketones has been studied extensively. With this type of compound the double bond is activated by the light energy to give a diradical and dimerisation occurs to give a cyclobutane derivative. In this way, Triebs[4] obtained a dimer (III) by irradiating a solution of 3-methylcyclohexenone (II).

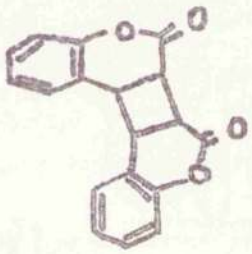


(II) (III)

Similar photodimers (IV), (V), (VI) and (VII), have been prepared from thymoquinone[5], coumarin[6], α-naphthaquinone[7], and 4-nitrophenylindone[8] respectively.



(IV)



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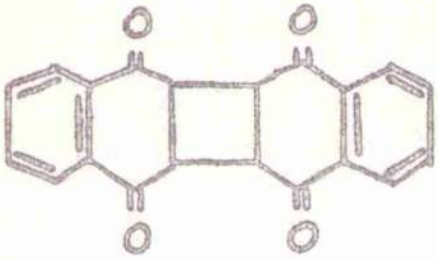
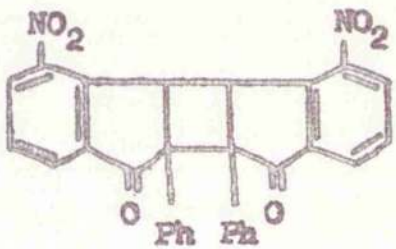
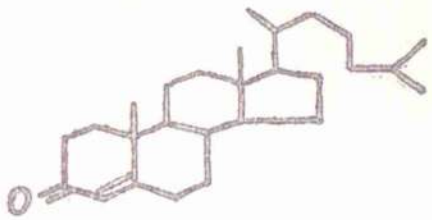


(VI)

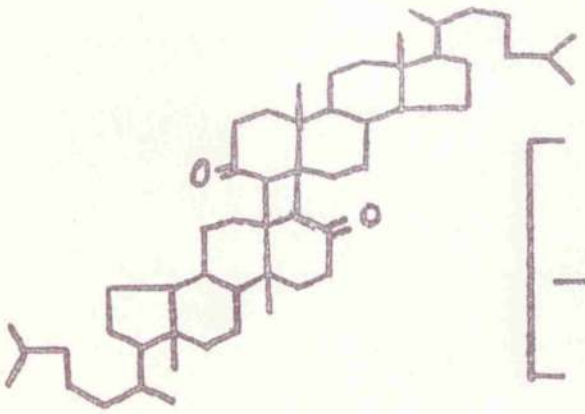


(VII)

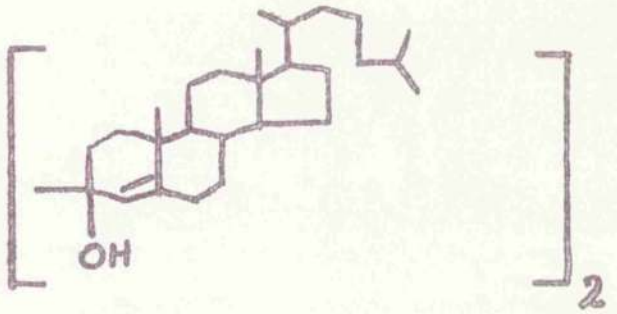
Irradiation of a solution of cholest-4-en-3-one (VIII) in hexane gives two products[9,10,11] one of which is the expected cyclobutane derivative (IX), and the other is a pinacol (X).



(VIII)

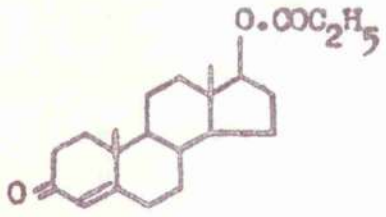


(IX)

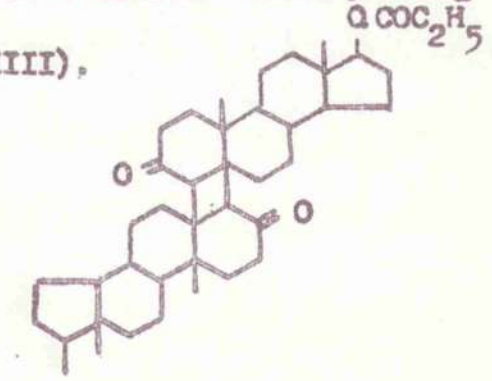


(X)

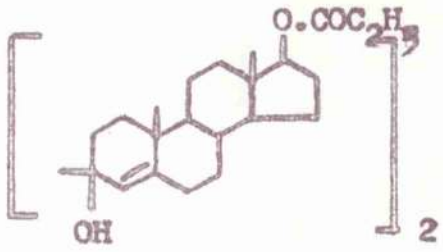
The pinacol (X) is a by-product formed by reduction of the free radical intermediate at the expense of the solvent, and is not formed by a typical photodimerisation reaction. Testosterone propionate (XI) has been found[10] to give a dimer (XII) in a similar manner, along with a trace of the pinacol (XIII).



(XI)

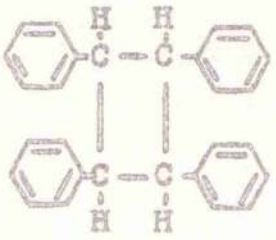


(XII)

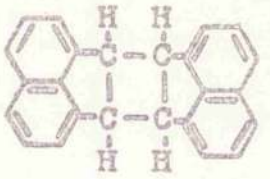


(XIII)

Cyclobutane derivatives are also obtained from other unsaturated systems where double bonds are activated. Stilbene dimerises[12] on exposure to sunlight to give 1,2,3,4,tetraphenylcyclobutane (XIV), and acenaphthylene also gives a dimer[13] (XV).

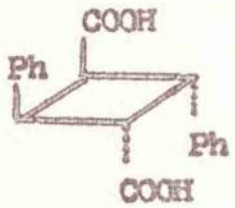


(XIV)

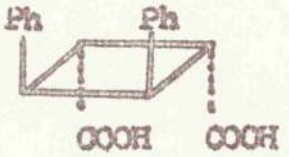


(XV)

Two significant points remain unanswered with regard to the structures of these cyclobutane derivatives. It has not been established whether the carbonyl groups are syn or anti about the cyclobutane ring in cases where this distiction can arise. Secondly, it is not known whether substituents lie on the same side or opposite sides of the plane of the cyclobutane ring. One case where this latter question has been solved is in the irradiation of cinnamic acid[14]. Here it has been found that the physical state of the material is important. Slowly recrystallised trans cinnamic acid on irradiation gives α-truxillic acid (XVI) but the meta stable form of the trans acid gives β-truxinic acid (XVII). Cis cinnamic acid gives β-truxinic acid (XVII)



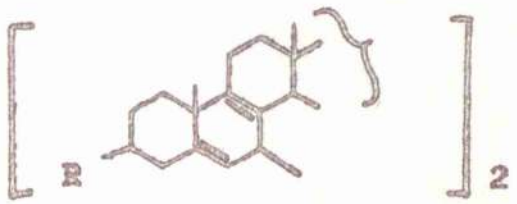
(XVI)



(XVII)

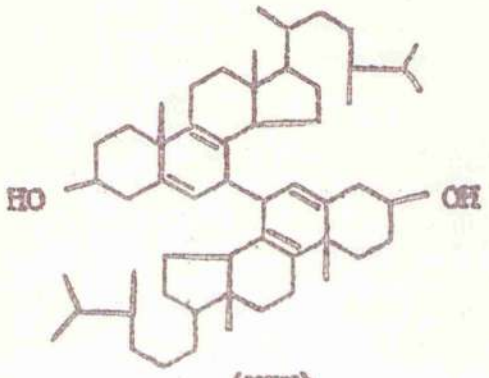
With the exception of the preparation of cholest-4-en-3-one pinacol (X), none of the dimerisations already discussed involve oxidation or reduction. Occasionally, however, photodimerisation is accompanied by an oxidation-reduction reaction.

An oxidative dimerisation by sunlight, of a $\Delta^{5,7}$ steroid in alcoholic solution in the presence of eosin, results in the production of a bis steroid. This bis steroid has been used as an intermediate in the preparation of a steroid with an aromatic ring B. The reaction was carried out by Mosettig and Scheer[15] who showed that the intermediate dimer (XVIII) had a structure in which the two steroid groups were linked between the 7 and 7' positions, with displacement of the double bonds to the 8 and 8' positions.



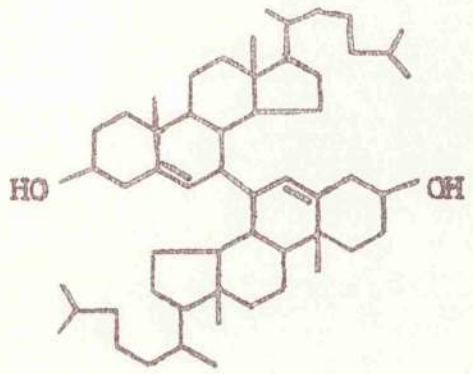
(XVIII)

Using these conditions, Windaus and Langer[16] prepared "22,23-dihydroergo pinacol" (XIX) from 22,23-dihydroergosterol. Similarly, ergosterol, ergosteryl acetate, and 7-dehydrocholesterol gave the corresponding "pinacols". These compounds are not true pinacols, but were unfortunately wrongly named when first prepared.



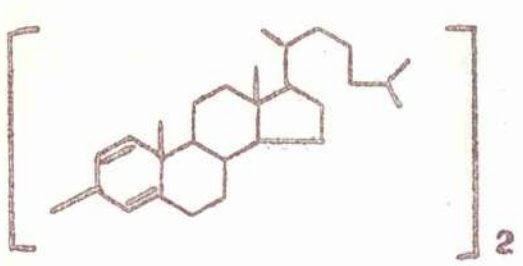
(XIX)

In 1940, de Fazi and Banchetti[17] claimed to have prepared a dimer by the ultraviolet irradiation of cholesterol in benzene solution in the presence of benzophenone as an oxidising agent. The dimer was believed to be 7,7'-bi(3β-hydroxycholest-5-enyl)(XX). Irradiation of cholesteryl acetate under similar conditions was said to give the diacetate of the dimer (XX), but more recent work by Bladon[18] using the conditions described gave no product. There is thus some doubt as to the nature of de Fazi's product, but it seems unlikely to be the compound which he claimed.

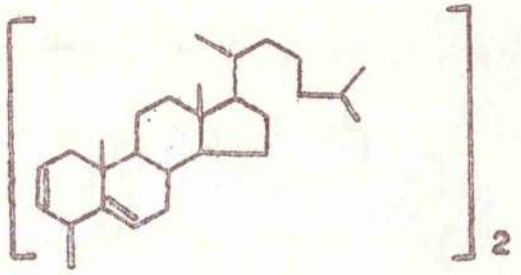


(XX)

Irradiation of cholesta-2,4-diene gives different products, depending on the conditions. Jacobsen and Nawrocki[19] reported the formation of 3,3'-bi(cholesta-1,4-dienyl) (XXI), when the irradiation was done in ethanol solution in the presence of rose bengal and absence of air. Later, Ushakov and Kosheleva[20] found that if the irradiation was done in the presence of fluorescein with sunlight, the product was the isomeric 4,4'-bi(cholesta-2,5-dienyl) (XXII)



(XXI)

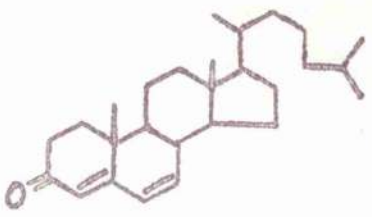


(XXII)

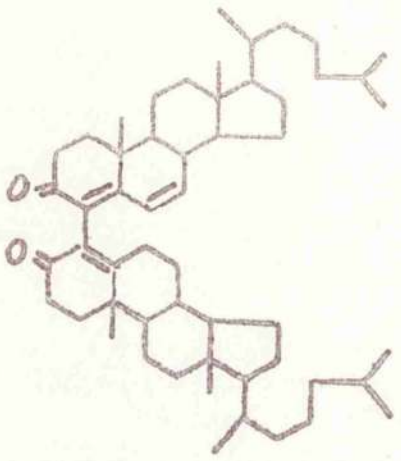
The Irradiation Product from Cholesta-4,6-dien-3-one.

In 1944, Ushakov and Kosheleva[21] reported the formation of a dimer when a solution of cholesta-4,6-dien-3-one (XXIII) in n-hexane was irradiated with ultraviolet light. The compound had m.p. 175 - 176°. and $[\alpha]_D$ +77.13°. The solvent for the optical rotation was not given and the work was done before ultraviolet and infrared spectrometers were available generally, so no absorption spectra were given. The molecular weight of the compound was not quoted.

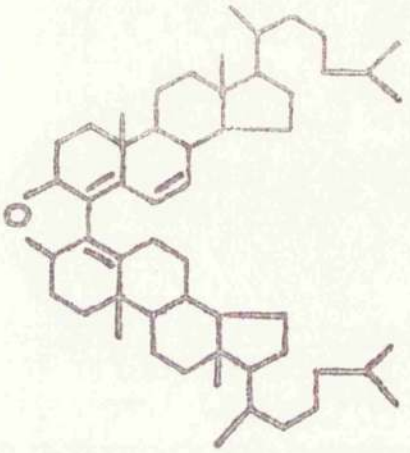
The unusual structure (XXIV) for the dimer was suggested by the Russian chemists to account for the formation on hydrogenation using palladium-charcoal catalyst, of a compound containing one less oxygen atom. They postulated that the selective reduction of the carbonyl groups, followed by elimination of water from the intermediate, gave the tetrahydrofuran derivative (XXV). The structure (XXIV) is open to question, and the problem merited further study.



(XXIII)



(XXIV)



(XXV)

It is understood that the photodimerisation reaction has been studied in Switzerland[22] but with inconclusive results, and no published work has appeared since that of Ushakov and Kosheleva.

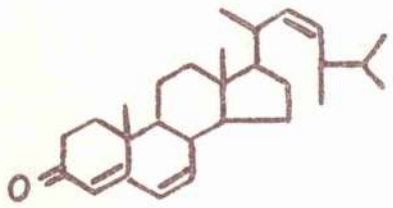
The irradiation was repeated using the conditions described and a compound was isolated which had m.p. 180°, $[\alpha]_D$ +38.4° (in chloroform). Using isopentane as a solvent instead of n-hexane, the same product was obtained, only much more readily, and with ethanol as solvent, the yield was further improved. In the absence of a direct comparison of the material with that obtained by Ushakov and Kosheleva, the question of their identity can not be settled definitely, but it is reasonable to assume that they are identical and that the difference in rotation is due to the use of a different solvent or to an arithmetical error on the part of the Russian workers.

The molecular weight of the compound has been difficult to determine, owing to the fact that the material is only slightly soluble in most solvents. Cryoscopic methods of determining the molecular weight failed because the compound came out of solution before the solvent crystallised. Using camphor as a solvent for a cryoscopic determination was unreliable since there is evidence that the material decomposes at elevated temperatures. This decomposition also explains the failure of ebullioscopic methods of determination.

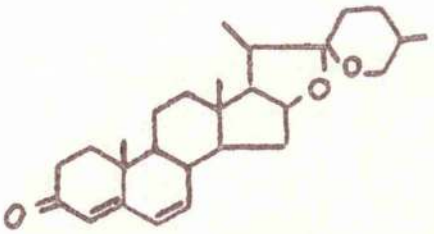
A value for the molecular weight was finally obtained by the light scattering method[23]. This gave a figure of the order of 1100, and since this is nearer the molecular weight of a trimer (1146) than of a dimer (764), it was believed for a time that the compound might be of the former type. However, experimental evidence, which will be quoted in detail later, completely excludes the possibility of the material being a trimer, or any polymer with an odd number of units. Since the formation of a photo-tetramer is unlikely, the more usual reaction being dimerisation, it was felt that the irradiation product from cholesta-4,6-diene-3-one was probably a dimer, and the discussion which follows is based on this assumption.

The ultraviolet absorption of the dimer is at 206 (ε = 9,500) and 256 mμ (ε = 10,400). These bands are ascribed to an isolated double bond and to an α-β unsaturated ketone group respectively. This shows that the structure (XXIV) suggested by Ushakov and Kosheleva is wrong, since a compound with such a structure would be expected to show absorption at 278 - 285 mμ due to the extended conjugation. In addition the formula which they postulated has no isolated double bonds. The infrared spectrum shows bands at 1670 and 1690 cm^{-1}, which are ascribed to the α-β unsaturated ketone group and to a saturated ketone group respectively.

Similar irradiation experiments were carried out with ethanolic solutions of ergosta-4,6,22-trien-3-one (XXVI) and $\Delta^{4,6}$ dehydrotigogenone (XXVII), both of which gave dimers.



(XXVI)



(XXVII)

The photodimer from ergosta-4,6,22-trien-3-one had m.p. 173°, $[\alpha]_D$ -9.6°, and showed absorption in the ultraviolet region at 206 (ε = 11,700), and 256 mμ (ε = 11,000). The dimer from $\Delta^{4,6}$ dehydrotigogenone had m.p. 190°, $[\alpha]_D$ -70°, and gave ultraviolet absorption bands at 204 (ε = 10,000), and 254 mμ (ε = 10,500). Both dimers gave two bands in the infrared carbonyl absorption region, similar to the bands given by the irradiation product of cholesta-4,6-dien-3-one.

It was concluded from the absorption evidence that the three products of irradiation had similar structures, a conclusion later confirmed by chemical evidence. The reactions discussed here on the dimer from cholesta-4,6-dien-3-one can be taken to apply to the other two irradiation products unless otherwise stated.

Pyrolysis of the dimer in vacuo resulted in the formation of the monomer, a reaction which confirmed the findings of Ushakov and Kosheleva[21] that the material is unstable to heat. Of the three dimers, that from $\Delta^{4,6}$ dehydrotigogenone is the most unstable, decomposing at its melting point (190°) to give the monomer, which crystallises and remelts at 205°.

The dimer also decomposed on treatment with perchloric acid, to give cholesta-4,6-dien-3-one, but was unaffected by alkali. This acid decomposition reaction occurred with all mineral acids and even chloroform was sufficiently acidic to cause decomposition if allowed to remain in contact with the material for a sufficient length of time. In spite of this it was still possible to use chloroform as a solvent for optical rotations, since the reaction under these conditions was extremely slow.

Treatment of the photodimer with lithium borohydride reduced the carbonyl groups to hydroxyl groups. Reduction of the double bonds did not occur, since the original photodimer was formed on oxidation of the reduced material. The ultraviolet absorption of the hydroxy compound was at 206 mμ (ε = 9,100), proving that the double bonds in the molecule were not in conjugation. The compound could be di-acetylated and dibenzoylated.

Pyrolysis of the hydroxy compound resulted in the production of cholesta-4,6-dien-3β-ol, and with slightly different conditions, gave cholesta-2,4,6-triene.

A similar pyrolysis of the acetate gave 3β-acetoxycholesta-4,6-diene. The hydroxycompound could not be reduced further by either Raney nickel or platinum catalysed hydrogenation.

Hydrogenation of the original photodimer with palladium black as a catalyst, in an attempt to reproduce the Russian chemists' results[21] gave a diketone with no double bonds in conjugation with the carbonyl groups. The compound, m.p. 280°, $[\alpha]_D$ +68.5°, had absorption in the ultraviolet spectrum at 207 mμ (ε = 8,600), and in the infrared region at 1720 and 1690 cm^{-1}. These results indicated that the double bond in conjugation with the carbonyl group had been reduced, but that the isolated double bond had been unaffected. No compound resembling the furan derivative (XXV) claimed by the Russians[21] was isolated.

Catalytic hydrogenation of the original irradiation product using Raney nickel gave a hydroxyketone, m.p.280°,$[\alpha]_D$ +93.7°. The hydroxyketone absorbed at 210 mμ (ε = 10,500) in the ultraviolet and gave a hydroxyl band and one at 1689 cm^{-1} in the infrared region of the spectrum. The compound was unaffected by heat and on oxidation with chromic acid it gave a diketone, identical with that obtained by hydrogenation of the dimer with palladium black as a catalyst. The hydroxyketone is thus

formed by reduction of the double bond in conjugation with the ketone, and by reduction of one of the ketone groups, more probably the originally α-β unsaturated ketone group.

The hydroxyketone formed an acetate on treatment with acetic anhydride and pyridine. This analysed for a mono-acetate of a dimer, but the analysis figures did not distinguish between this and a mono- or diacetate of a trimer. Consequently, the hydroxyketone was treated with p-iodobenzoyl-chloride in pyridine to give the p-iodobenzoate. The analysis figures and the calculated values of the three possible p-iodobenzoates are given in Table I.

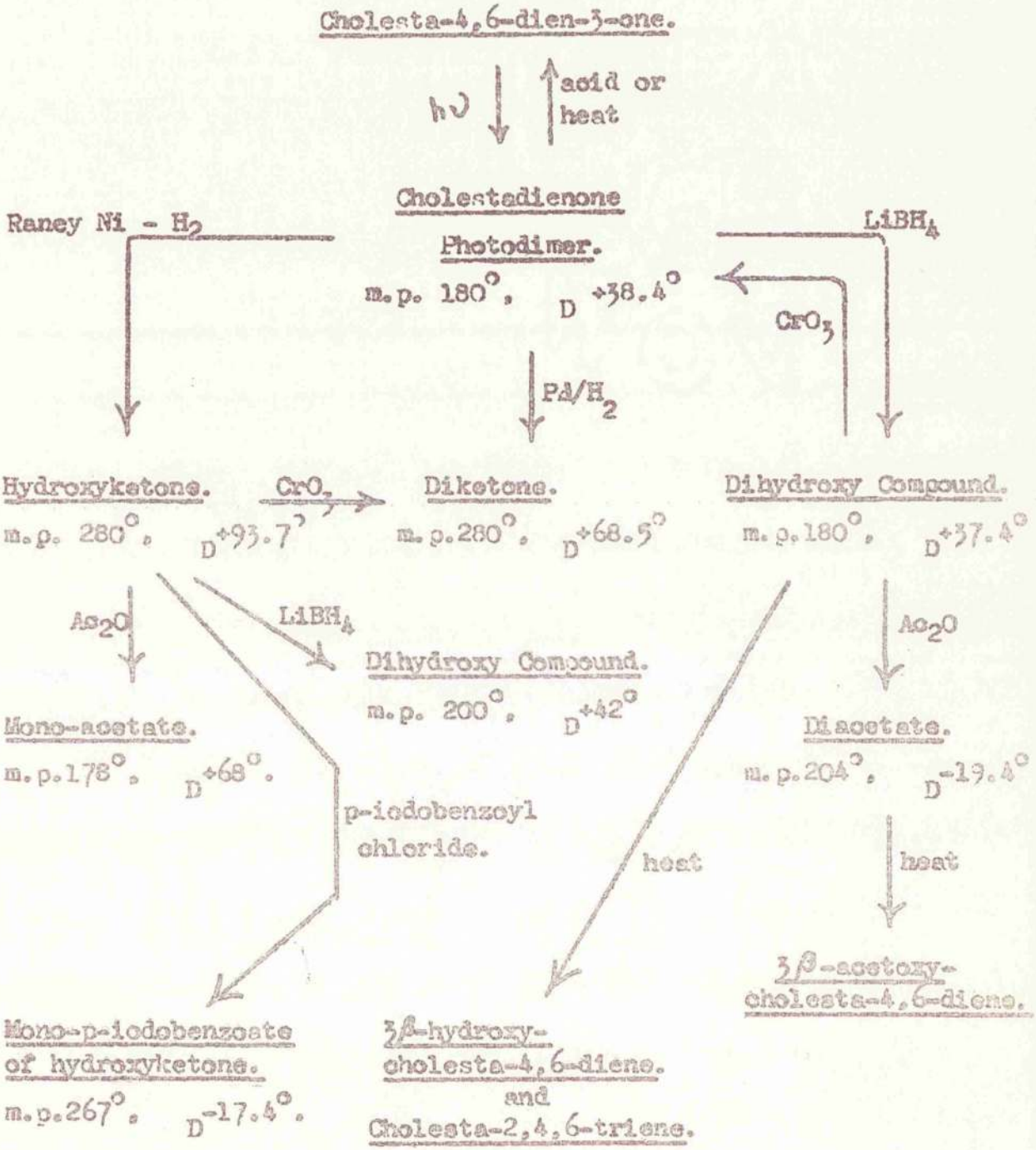
Table I.

Compound	Molecular Formula	C	H	I
Mono-p-iodobenzoate of a trimer.	$C_{88}H_{133}O_4I$	76.5	9.64	9.27
Di-p-iodobenzoate of a trimer.	$C_{95}H_{140}O_5I_2$	70.6	8.7	15.7
Mono-p-iodobenzoate of a dimer.	$C_{61}H_{91}O_3I$	73.2	9.13	12.7
	Found	73.2	9.13	11.7
		73.2	9.23	

Clearly the ester is the mono-p-iodobenzoate of a dimer, justifying the earlier assumption that the irradiation product of cholesta-4,6-dien-3-one was a photodimer. The p-iodobenzoate had m.p. 273°, $[\alpha]_D$ -17.4°, and showed absorption at 206 (ε = 10,800) and 259 mμ (ε = 10,200) in the ultraviolet region of the spectrum, and at 1718, 1700, and 1580 cm^{-1} in the infrared.

The hydroxyketone was reduced with lithium borohydride to give a dihydroxy compound with one double bond, m.p. 200°, $[\alpha]_D$ +42.0°.

The complete series of reactions carried out on the photodimer from cholesta-4,6-dien-3-one is outlined in the following table.


Cholesta-4,6-dien-3-one.
hν
acid or heat
Cholestadienone Photodimer.
m.p. 180°, D +38.4°
Raney Ni - H2
LiBH4
CrO3
Pd/H2
Hydroxyketone.
m.p. 280°, D +93.7°
CrO3
Diketone.
m.p. 280°, D +68.5°
Dihydroxy Compound.
m.p. 180°, D +37.4°
Ac2O
LiBH4
Dihydroxy Compound.
m.p. 200°, D +42°
Mono-acetate.
m.p. 178°, D +68°.
Diacetate.
m.p. 204°, D -19.4°
p-iodobenzoyl chloride.
heat
heat
3β-acetoxy-cholesta-4,6-diene.
Mono-p-iodobenzoate of hydroxyketone.
m.p. 267°, D -17.4°.
3β-hydroxy-cholesta-4,6-diene.
and
Cholesta-2,4,6-triene.

The nuclear magnetic resonance spectrum of the dimer from cholesta-4,6-dien-3-one is shown in Figure I. along with the integrated curve of the spectrum. The two peaks at 4.3 and 4.55 τ [24] are assigned to two olefinic protons. The doublet at 6.22 τ is assigned to a methine proton at C-4 which is subject to the influence of both the C-3 carbonyl group and the $\Delta^{4,}$ double bond (cf. [25]). The band at 9.05 τ is due to C-18 hydrogen atoms, and the two bands at 9.15 and 9.25 τ are due to C-19 protons.

The chemical evidence shows that the dimer has an unsymmetrical structure. This is unusual since photodimers normally exist in a symmetrical form. The compound contains a Δ^4 -3-ketone system with a 4-alkyl group, as shown by the ultraviolet absorption evidence[26]. The absence of a proton on this double bond is confirmed by the nuclear magnetic resonance spectrum, since a proton on a double bond, adjacent to a ketone, would show a band at 3.8 τ [27]. The evidence shows that the photodimer has the structure (XXVIII) but it is possible that subsequent information might favour an alternative possibility. The stereochemistry of the compound is not shown in the formula (XXVIII), but will be discussed later.

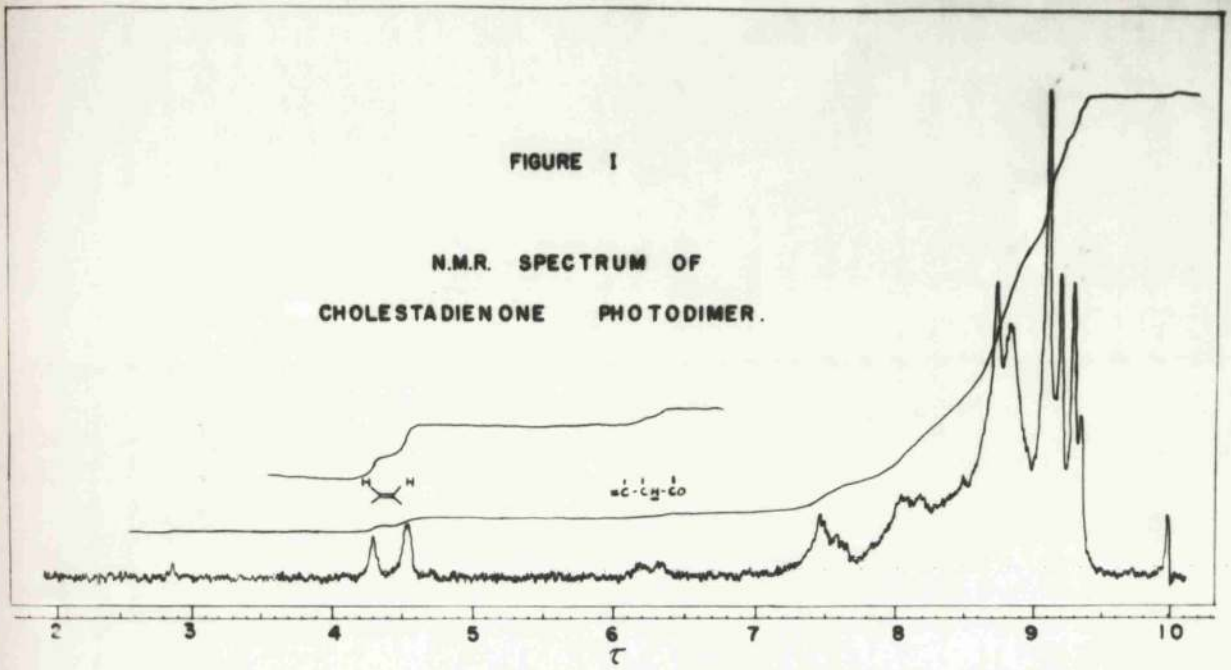


FIGURE I
N.M.R. SPECTRUM OF
CHOLESTADIENONE PHOTODIMER.
2
3
4
5
6
7
8
9
10
τ

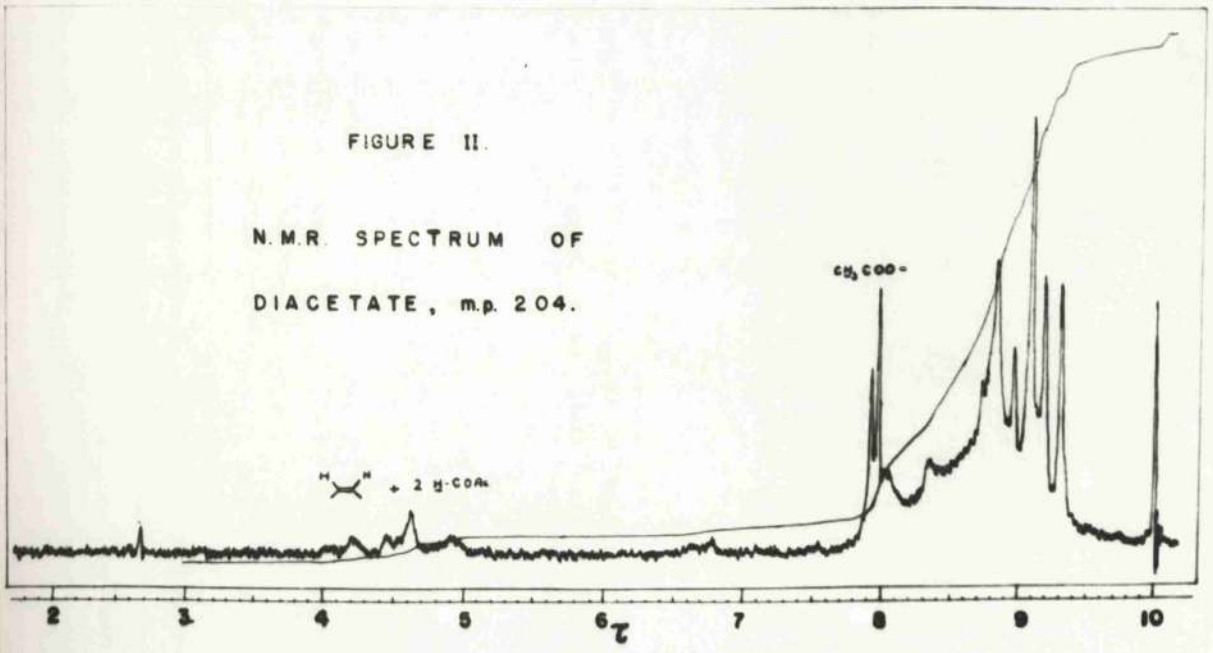


FIGURE II.
N.M.R. SPECTRUM OF
DIACETATE, m.p. 204.
2
3
4
5
6
7
8
9
10
τ

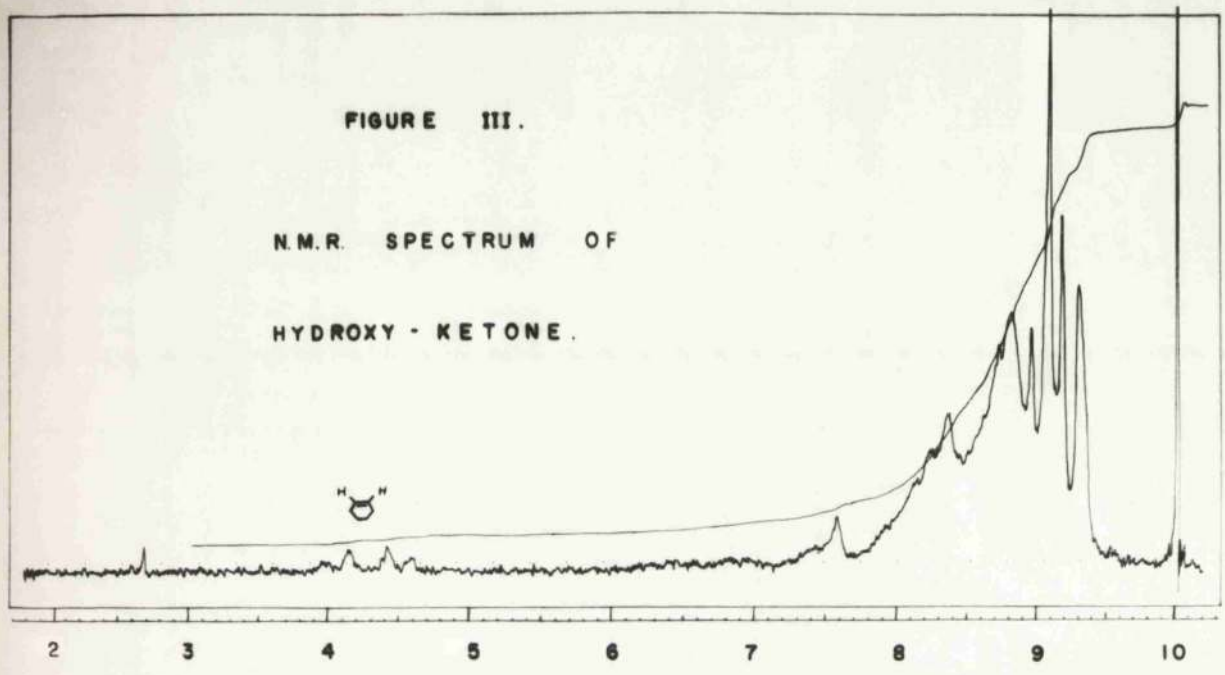


FIGURE III.

N.M.R. SPECTRUM OF

HYDROXY - KETONE.

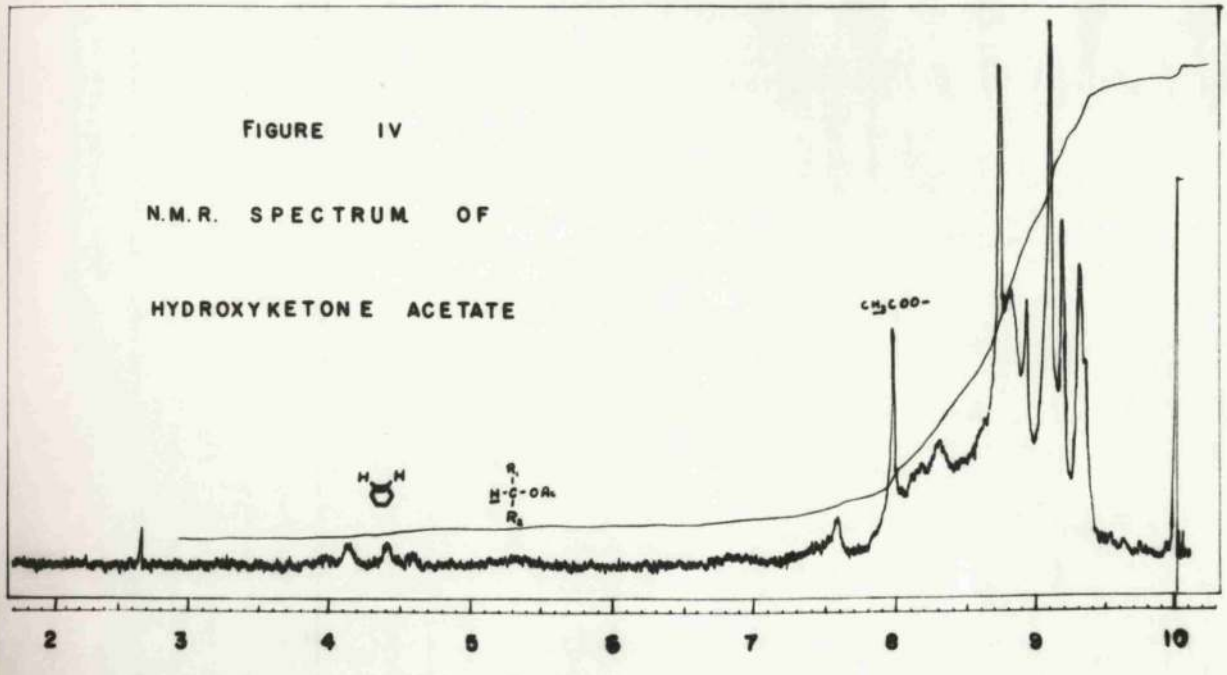
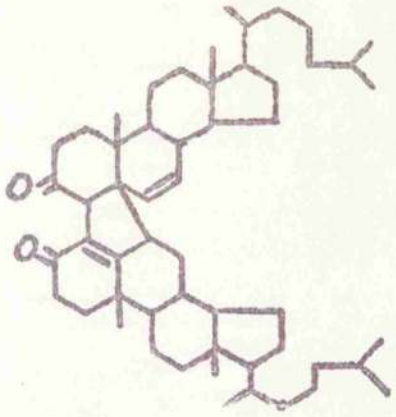


FIGURE IV

N.M.R. SPECTRUM OF

HYDROXYKETONE ACETATE

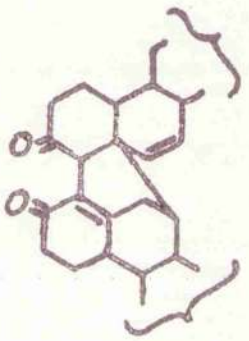


(XXVIII)

Any structure postulated for the dimer must have either one linkage between the two parts of the molecule and three double bonds, or two linkages and two double bonds. Since it is extremely difficult to accomodate three double bonds in the molecule and keep them out of conjugation, it was concluded that there were two bonds joining the two halves of the molecule, making another ring, and two double bonds, isolated from each other.

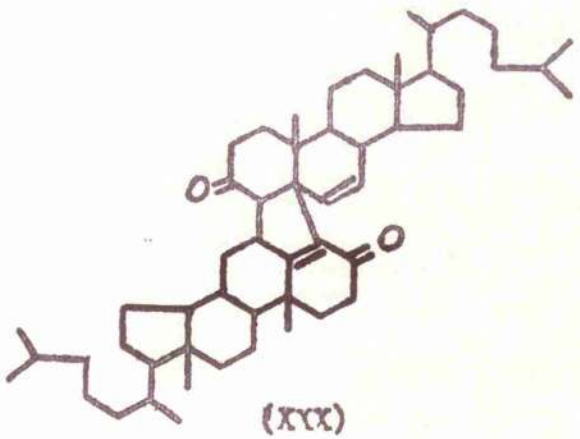
Since one of the double bonds in conjugation with the ketone group in the monomer has disappeared in the dimer, it is reasonable to conclude that the new ring is formed on the 4 and 5 position of one of the steroid groups. On the other half of the molecule, containing the α-β unsaturated ketone system, one of the bonds must join at the 4' position, as indicated by the ultraviolet and the nuclear magnetic resonance spectra. The other

linkage on this half of the molecule is believed to be on the 6' position, since a 7'-linkage would give a bridge structure (XXIX) containing a double bond adjacent to a bridge head and violating Bredt's Rule[28].



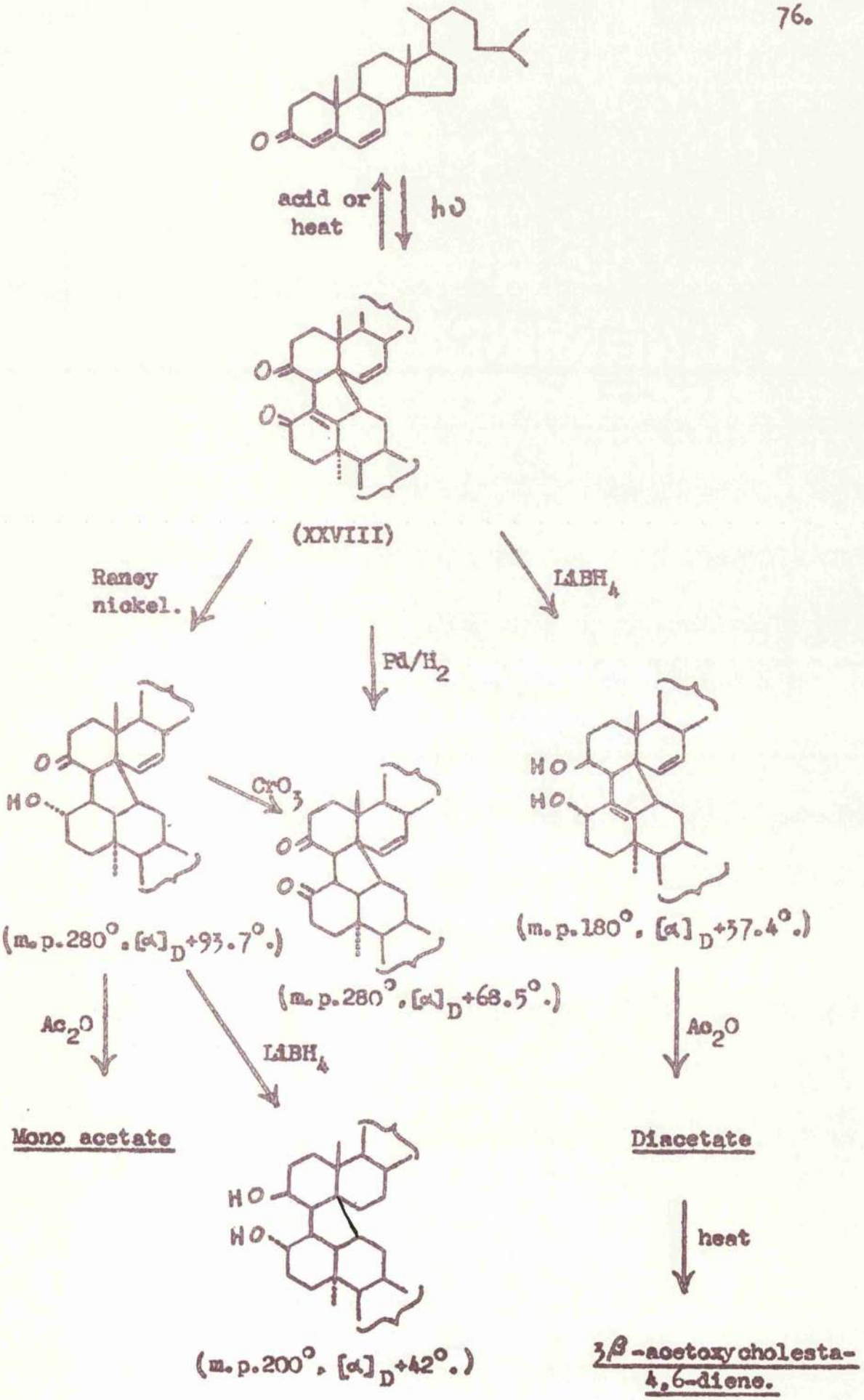
(XXIX)

The alternative 5-membered ring structure (XXX) is unsuitable since it does not explain the doublet at 6.22τ in the nuclear magnetic resonance spectrum.

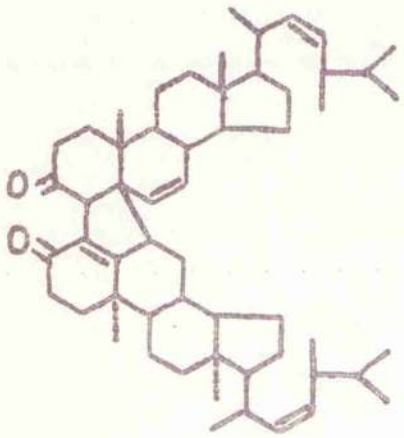


(XXX)

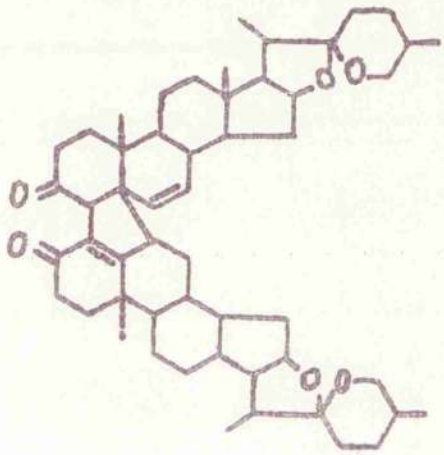
The reactions described previously can now be formulated on the basis of formula (XXVIII) as follows.


acid or heat
hυ
(XXVIII)
Raney nickel.
LiBH4
Pd/H2
CrO3
(m.p.280°. [α]D+93.7°.)
(m.p.280°. [α]D+68.5°.)
(m.p.180°. [α]D+37.4°.)
Ac2O
LiBH4
Ac2O
Mono acetate
Diacetate
heat
(m.p.200°. [α]D+42°.)
3β-acetoxycholesta-4,6-diene.

In the same way, it was concluded that the dimer from ergosta-4,6,22-trien-3-one could be represented by structure (XXXI), and that the dimer from $\Delta^{4,6}$dehydrotigogenone could be represented by structure (XXXII).

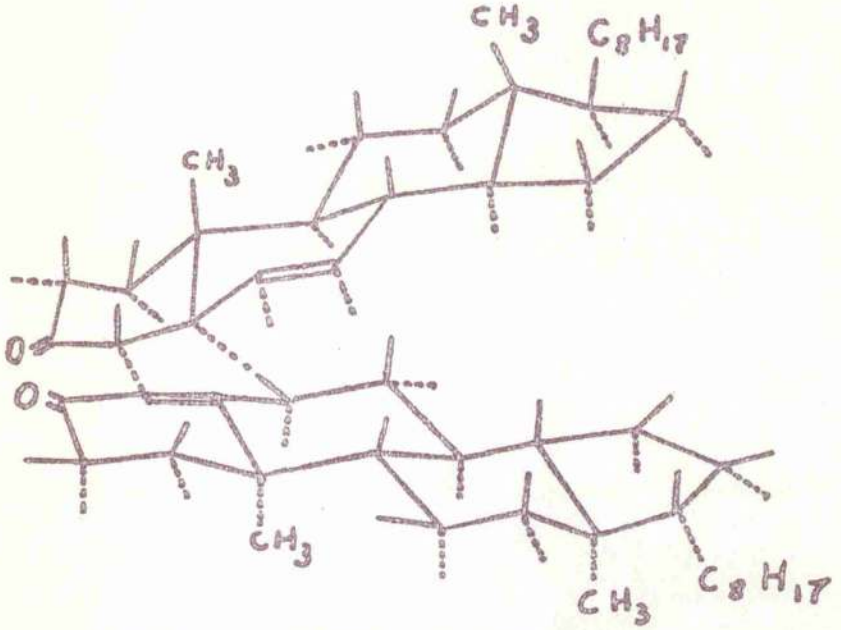


(XXXI)



(XXXII)

With Dreiding wire models, it was found that only one possible stereoisomer (XXXIII) of structure (XXVIII) could be formed without strain.



(XXXIII)

Structure (XXXIII) shows that the linkage in the 4-position is α orientated to the plane of the ring containing the saturated ketone group. This point is confirmed by the rotatory dispersion curve (Figure V) of the hydroxy ketone, which is similar to the rotatory dispersion curve of 4 α -methylcholestanone[29]. The dispersion curve of the dimer is also shown but no conclusions can be drawn from it.

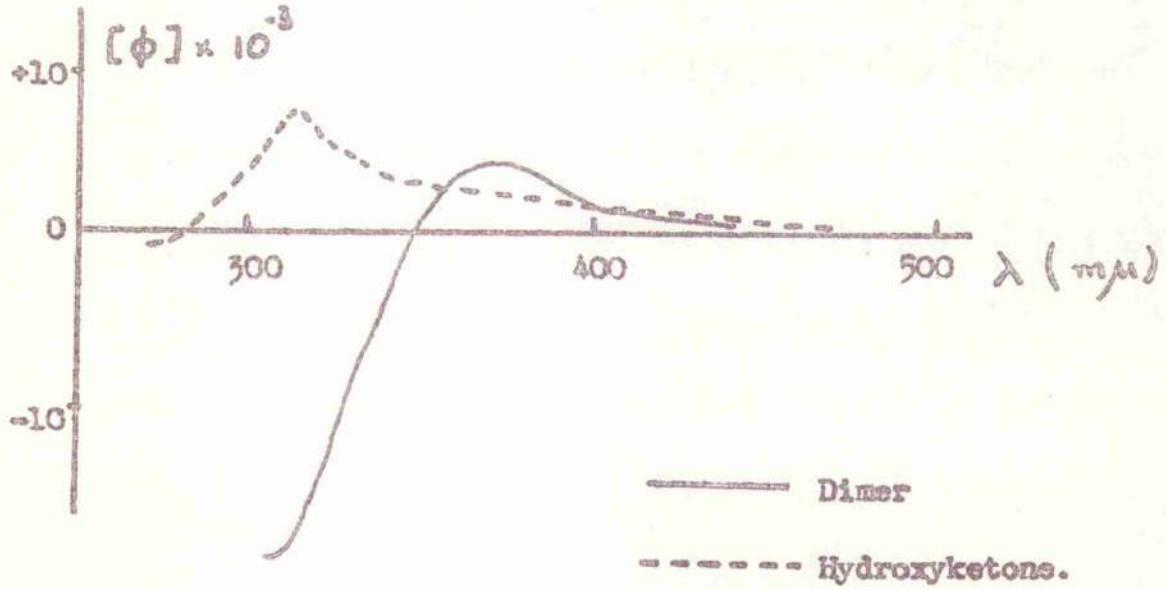


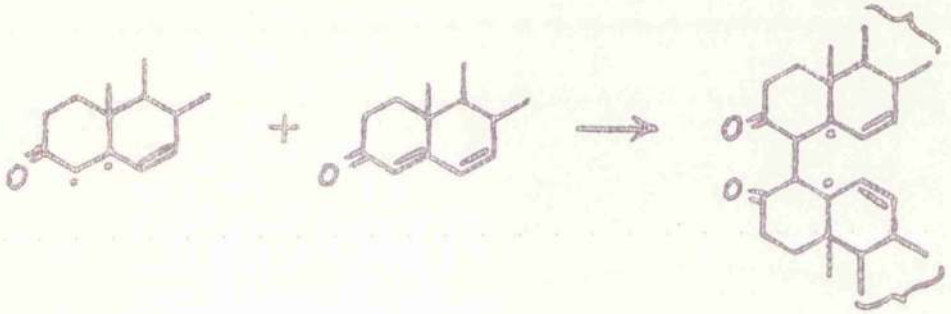
Figure V.

Optical Rotatory Dispersion Curves of Photodimer and Hydroxyketone from Chole-ta-4,6-dien-3-one.

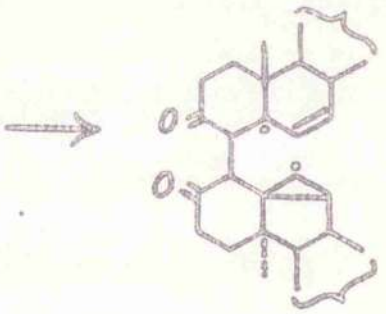
A possible mechanism of formation of the dimer during the irradiation process is outlined below.

(i)

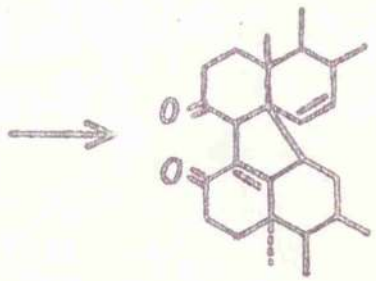
(ii)



(iii)



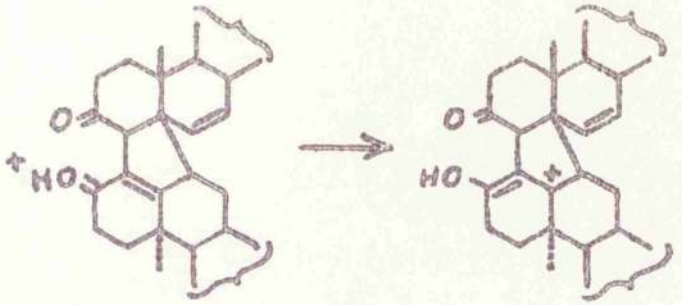
(iv)



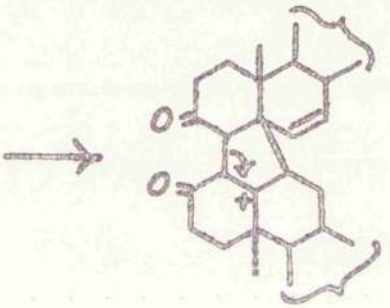
In order to obtain a bond between the 5 and 6' positions it is necessary to have some kind of cyclopropane intermediate.

A possible mechanism for the decomposition of the dimer by perchloric acid involves initial attack at the unsaturated carbonyl group by a hydrogen ion, followed by rearrangement, as shown.

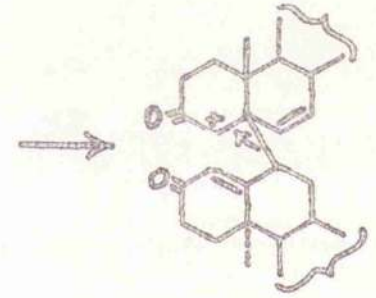
(i)



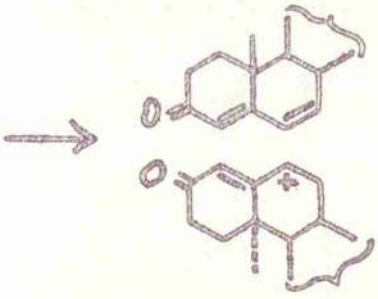
(ii)



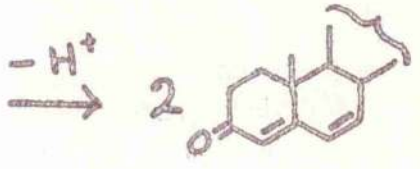
(iii)



(iv)

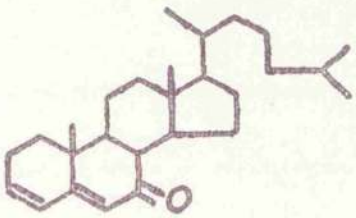


(v)



Stages (iii).(iv). and (v) of the above mechanism can be considered as a concerted rearrangement rather than a stepwise movement of electrons as shown.

A similar irradiation experiment was carried out with a solution of cholesta-3,5-dien-7-one (XXXIV) in ethanol. After several hours irradiation with ultraviolet light, an insoluble product separated, but much more slowly than with cholesta-4,6-dien-3-one.



(XXXIV)

This dimer had m.p. 256°. $[\alpha]_D$ -71.0°, and showed a band in the ultraviolet spectrum at 250 mμ (ε = 19,000). Infrared absorption occurred at 1650 cm^{-1} indicating the presence of an α-β unsaturated carbonyl group in the molecule. The high ultraviolet absorption at 250 mμ indicated that both carbonyl groups in the molecule were unsaturated, and this was confirmed by the absence of a band in the infrared spectrum corresponding to a saturated ketone group. The photodimer from cholesta-3,5-dien-7-one was almost completely insoluble in most organic solvents, consequently it was impossible to obtain a value for the molecular weight.

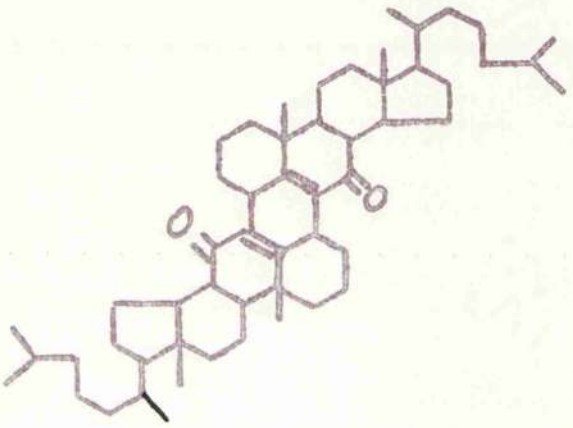
The dimer gave back cholesta-3,5-dien-7-one on heating under vacuum or on treatment with perchloric acid, but was more stable than the dimer from cholesta-4,6-dien3-one.

Reduction of the photodimer from cholesta-3,5-dien-7-one with lithium borohydride gave a compound m.p. 200°, $[\alpha]_D$ -24.5°, showing ultraviolet absorption at 208 mμ (ε = 9,700) and giving a band at 3400 cm^{-1} in the infrared region of the spectrum. This is an indication that the double bonds in the compound are isolated from each other. The dihydroxy compound thus formed gave a diacetate on treatment with acetic anhydride and pyridine, and gave cholest-5-en-7-one on pyrolysis.

Reduction of the photodimer with hydrogen in the presence of Raney nickel as a catalyst gave a hydroxyketone showing no absorption in the ultraviolet and giving bands at 3300 and 1700 cm^{-1} in the infrared spectrum. This compound is thus formed by reduction of both double bands and one carbonyl group.

The photodimer from cholesta-3,5-dien-7-one is best represented by structure (XXXV), which can be made in Dreiding wire models without any strain.

Structures joined by 7 or 8 membered rings violate Bredt's Rule[28] by having a double bond adjacent to a bridge head in a small ring system. The compound was too insoluble to have the structure confirmed by nuclear magnetic resonance spectra.

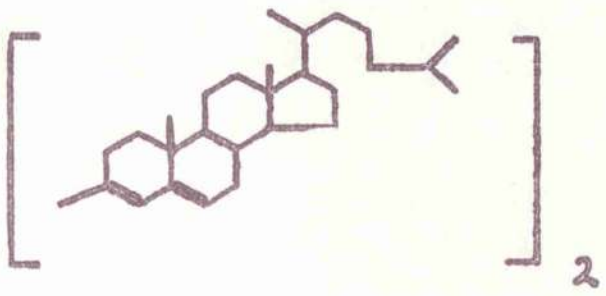


(XXXV)

Reductive Dimerisation of Steroids.

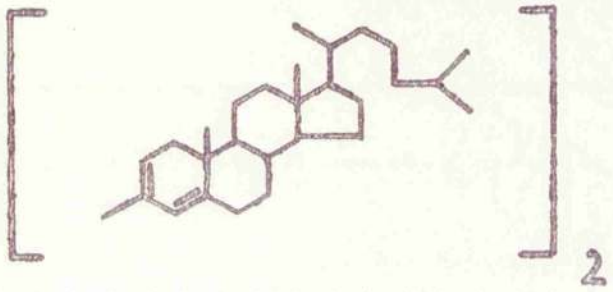
Many dimerisation reactions of steroids are known which involve reduction and dimerisation simultaneously. These reactions are rarely photo-dimerisations, the only known exception being the reaction reported by Butenandt et al[10,11] for the preparation of cholestenone pinacol (X) and testosterone propionate pinacol (XIII) mentioned previously.

The earliest reported reduction demerisation was in 1906, when Windaus[30] reduced cholest-4-en-3-one by zinc and ethanol or by sodium amalgam. He obtained 3,3'-bi(3β-hydroxycholest-4-enyl) (X), already mentioned. By treatment of the pinacol with mineral acid, Windaus obtained the dehydrated product, a hydrocarbon with he showed to be 3,3'-bi(cholesta-3,5-dienyl) (XXXVI).



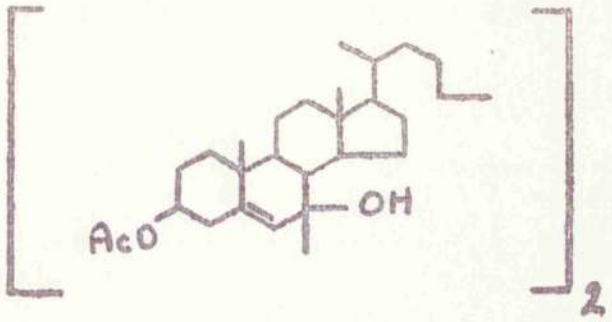
(XXXVI)

Dolou, Chopin and Raoul[31] also obtained 3,3'-bi(cholesta-3,5-dienyl) (XXXVI) along with the isomeric 3,3'-bi(cholesta-2,4-dienyl) (XXXVII), by the action of concentrated sulphuric acid on cholesterol.



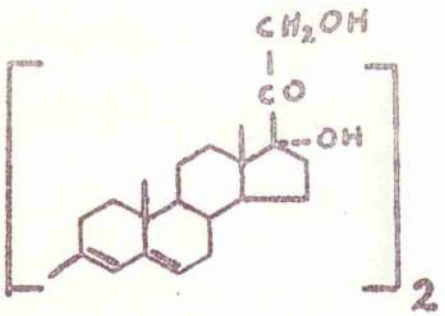
(XXXVII)

The reductive dimerisation of cholestenone has been further studied by Squire[32] using sodium amalgam, and an improved method of preparation by Bladon, Cornforth and Jaeger[33] involved electrolytically reducing cholestenone in a alcoholic solution of sodium acetate using a mercury cathode at 20°C. A similar reduction at a higher temperature in acetic acid solution gave the dehydrated compound, 3,3'-bi(cholesta-3,5-dienyl) (XXXVI) directly. Using the same conditions, 7-oxocholesteryl acetate yielded a pinacol[33](XXXVIII).

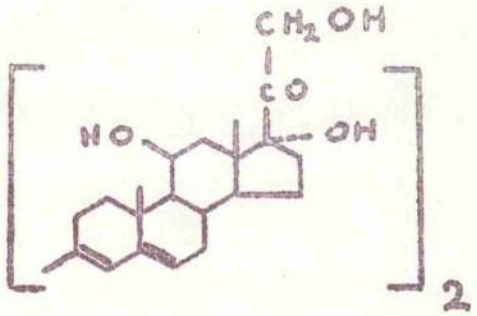


(XXXVIII)

The method of electrolytic reduction employed by Bladon et al.[33] had been used extensively in polarographic studies[34,35] but although a large number of steroids have been reduced, few products have been isolated. Kabasakalian and McGlotten[36] reduced cortisone and hydrocortisone by this method to obtain the tetraenes (XXXIX) and (XL).



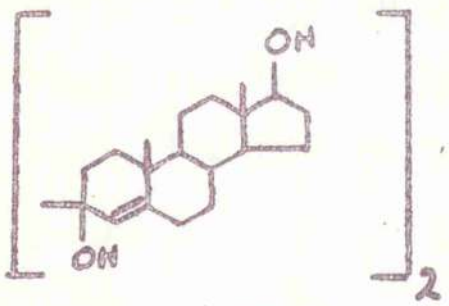
(XXXIX)



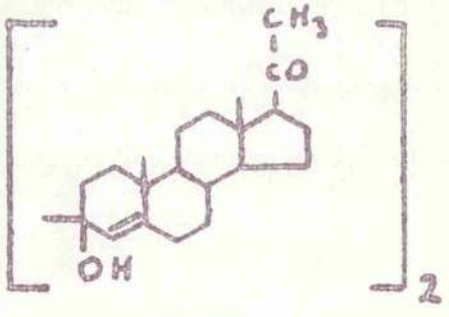
(XL)

A similar reduction[36] of prednisone and prednisolone is also reported to have given the corresponding products, absorbing at 316 mμ in the ultraviolet, but no formulae have been proposed for these.

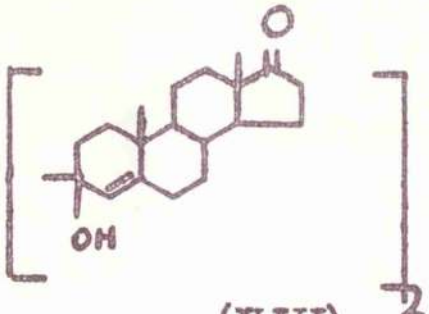
The reduction of a Δ^4-3-ketone steroid to a pinacol gives rise to two asymmetric carbon atoms, and there is thus the possibility of formation of three compounds, one with both hydroxyl groups in the α-configuration, one with both in the β-configuration, and one with one in the α and the other in the β-configuration. The isolation of two pinacols from the one ketone was claimed by Lund[37] in 1957. He obtained, in a series of reactions, cholestenone pinacol (X), testosterone pinacol (XLI), progesterone pinacol (XLII), androstendione pinacol (XLIII), and two isomeric pinacols, (XLIV) from 17β-hydroxyandrosta-1,4-dien-3-one.



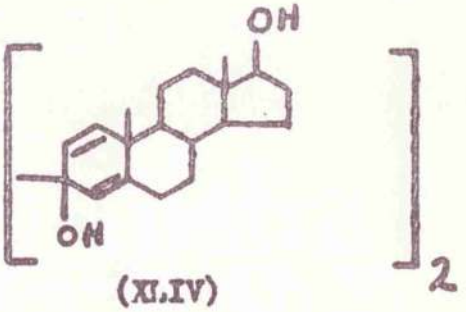
(XLI)



(XLII)



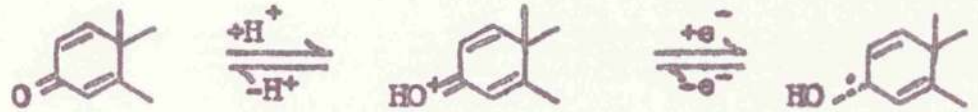
(XLIII)



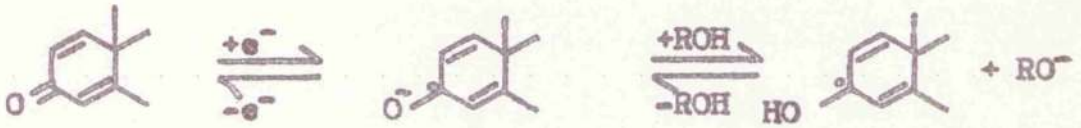
(XLIV)

Lund's explanation for the formation of the two pinacols, involves a radical mechanism:-

In acid solution:



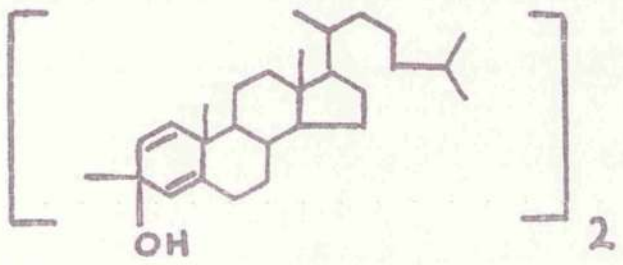
In alkaline solution:



These radicals are assumed to dimerise by a slow reaction to give the two isomeric pinacols. This mechanism has been criricized[33] because it assumes that the radicals will retain their configuration during the slow dimerisation process, and it has been pointed out that this is not necessarily the case. The configurations of the other pinacols have not been suggested. Lund[37] did not report the dehydration reaction of the pinacols.

In 1957, Burn, Kirk, and Petrow[38] reported the formation of a hydrocarbon, $C_{27}H_{44-46}$, m.p. 196°, and showing ultraviolet absorption at 342, 360, and 378 mμ, by debromination of 1,2-dibromocholest-4-en-3-one, using zinc. No structural formula was proposed for the

hydrocarbon, but Petrow and his co-workers assumed that it was a monomer. However it is probable that this hydrocarbon is the product of dehydration of cholesta-1,4-dien-3-one pinacol (XLV), which is a likely intermediate.

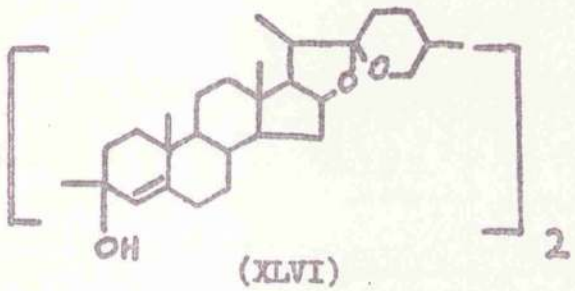


(XLV)

It was to clarify this point and to investigate the dehydration reaction of pinacols in general that the following investigations were carried out.

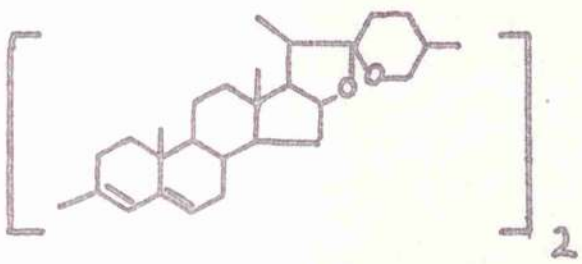
Earlier work[33,36] had shown that when a Δ^4-3-ketone system is reduced to a pinacol, and the product dehydrated, the reaction goes smoothly to give a conjugated $\Delta^{3,5}$ double bond system, as in the preparation of 3,3'-bi(cholesta-3,5-dienyl) (XXXVI)[30,33], and in the preparation of the tetraenes (XXXIX) and (XL) from cortisone and hydrocortisone[36]. To confirm this work, it was decided to prepare the pinacol from diosgenone, or 25D-spirost-4-en-3-one. An electrolytic reduction

using the method of Bladon et al.[33] gave the pinacol, 3,3'-bi(25D-3β-hydroxyspirost-4-enyl) (XLVI), m.p. 280°, $[\alpha]_D$ -56.1°.



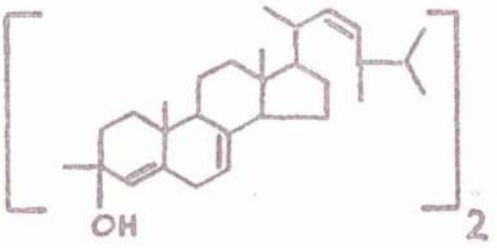
(XLVI)

Dehydration of 3,3'-bi(25D-3β-hydroxyspirost-4-enyl) (XLVI), using hydrochloric acid, gave the expected product, 3,3'-bi(25D-spirosta-3,5-dienyl) (XLVII), m.p. above 360°, $[\alpha]_D$ -27.5°. The compound absorbed in the ultraviolet region of the spectrum at 300 (ε = 31,900), 310 (ε = 45,700), and 324 mμ (ε = 42,600). The absorption is similar to that of 3,3'-bi(cholesta-3,5-dienyl) (XXXVI)[33] which shows bands at 298 (ε = 32,000), 311 (ε = 41,540) and 326 mμ (ε = 30,000). The wavelength of maximal absorption calculated from Woodward's Rules[26] is 316 mμ.

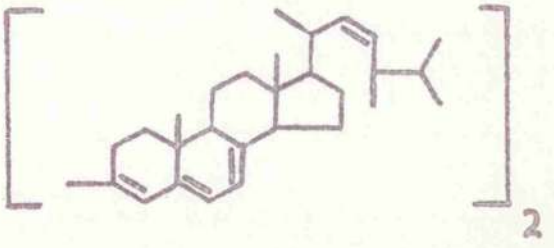


(XLVII)

In the same way, it was found that the pinacol from ergosta-4,7,22-trien-3-one, 3,3'-bi(3β-hydroxyergosta-4,7,22-trienyl) (XLVIII), m.p. 240°, $[\alpha]_D$ -11.2°, underwent dehydration, the isolated Δ^4 double bond being replaced by a $\Delta^{3,5}$ double bond system, going into conjugation with the Δ^7 double bond already there to give the unsaturated hydrocarbon, 3,3'-bi(ergosta-3,5,7,22-tetraenyl) (XLIX), m.p. 234°, $[\alpha]_D$ +449°. The ultraviolet absorption of the hexaene system in 3,3'-bi(ergosta-3,5,7,22-tetraenyl)(XLIX) occurred at 351 (ε = 19,500), 366 (ε = 26,300), 386 (ε = 24,800), 422 (ε = 11,200) and 446 mμ (ε = 9,400).



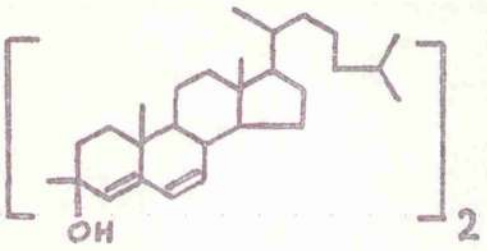
(XLVIII)



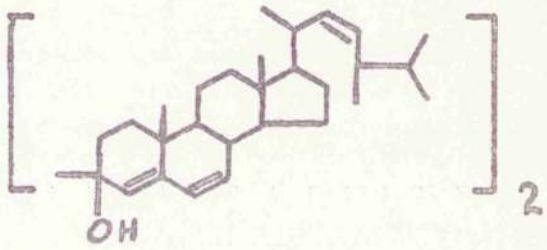
(XLIX)

There are no earlier reports describing the dehydration of pinacols containing a conjugated $\Delta^{4,6}$ diene system, so it was decided to prepare the pinacols

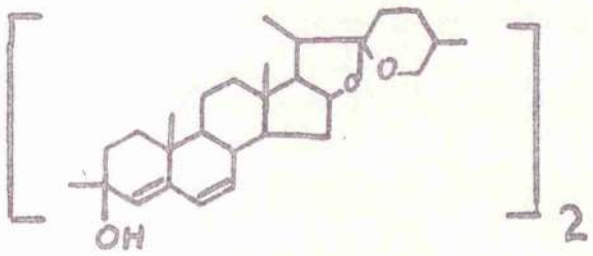
from cholesta-4,6-dien-3-one, ergosta-4,6,22-trien-3-one, and $\Delta^{4,6}$ dehydrotigogenone. The three pinacols (L), (LI), and (LII) were prepared by electrolytic reduction and showed absorption in the ultraviolet at 206, and 234 mμ, as expected.



(L)



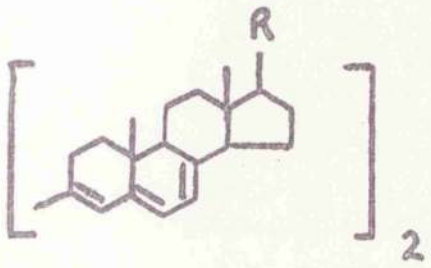
(LI)



(LII)

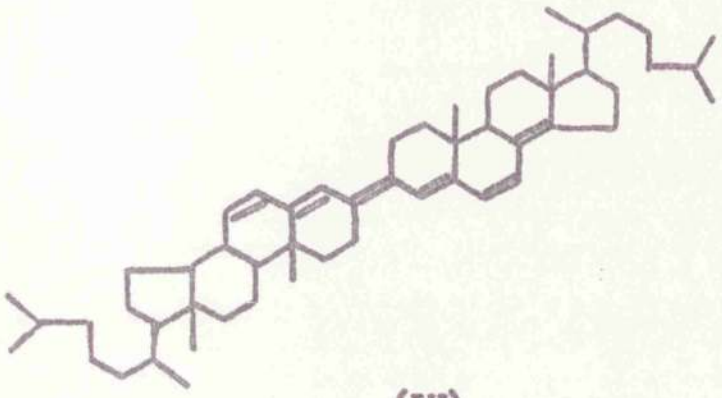
Dehydration of the pinacols (L), (LI), and (LII) yielded yellow crystals, showing ultraviolet absorption at 360, 374, and 390 mμ. The calculated absorption[26] for a conjugated hexaene is of the order of 472 mμ for a symmetrical structure (LIV), and although Woodward's Rules are known to be inaccurate for highly conjugated systems,

it was felt that the discrepancy was too great for the dehydration products to have this structure (LIV).

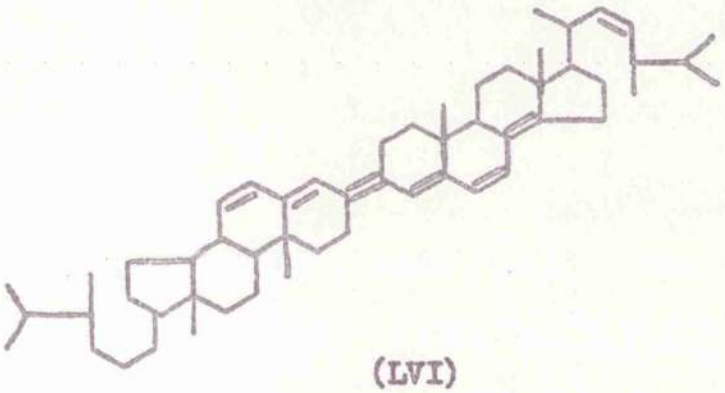


(LIV)

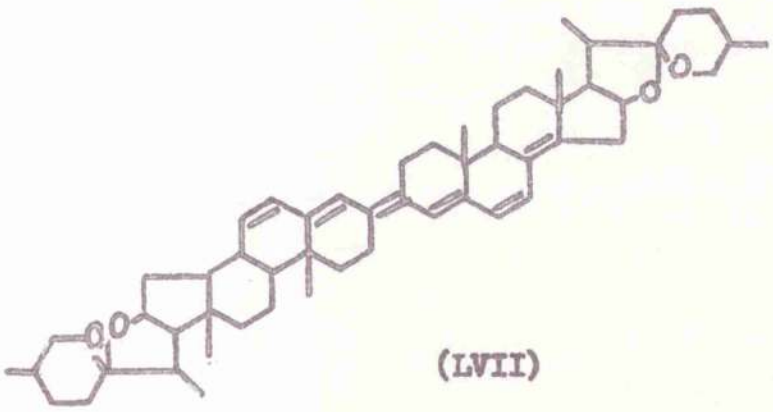
The dehydration products have been formulated as the unsymmetrical structures (LV),(LVI), and (LVII). These have a calculated ultraviolet absorption of 404 mμ which corresponds reasonably well to the found values. It is interesting to note that the dehydration product (LVI) from 3,3'-bi(3β-hydroxyergosta-4,6,22-trienyl) could not be converted into 3,3'-bi(ergosta-3,5,7,22-tetraenyl) (XLIX), or vice versa. The high optical rotation of 3,3'-bi(ergosta-3,5,7,22-tetraenyl) (XLIX) of +449° is not shown by the unsymmetrical dehydration product (LVI) from 3,3'-bi(3β-hydroxyergosta-4,6,22-trienyl) which has $[\alpha]_D$ +3°.



(LV)



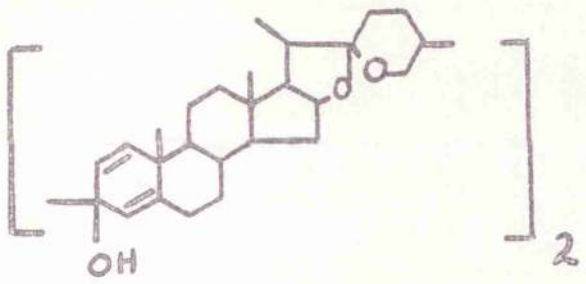
(LVI)



(LVII)

The molecules probably exist in the trans form about the double bond joining the two halves, since this would involve less strain, but this is not certain.

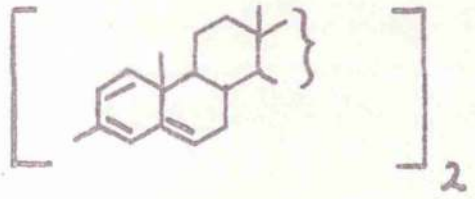
A study of the compounds containing a $\Delta^{1,4}$ diene system was carried out by preparing the pinacols from cholesta-1,4-dien-3-one, and from 25D-spirosta-1,4-dien-3-one, by electrolytic reduction. 3,3'-Bi(3β-hydroxycholesta-1,4-dienyl) (XLV) had m.p. 130° with decomposition, and $[\alpha]_D$ +68.1°. 3,3'-Bi(25D-3β-hydroxyspirosta-1,4-dienyl) (LVIII) had mp. 250°, and $[\alpha]_D$ -49.7°.



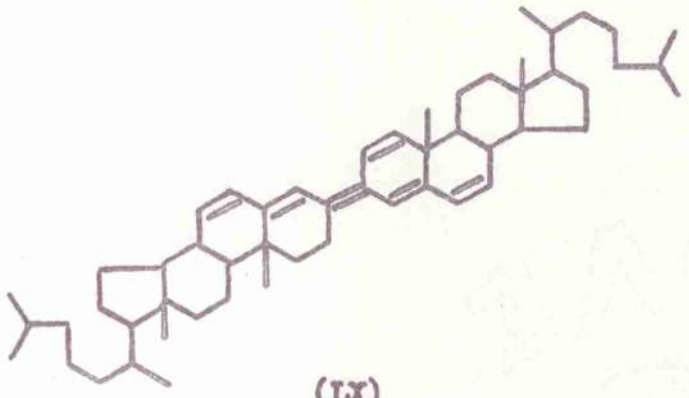
(LVIII)

Dehydration of 3,3'-bi(3β-hydroxycholesta-1,4-dienyl) (XLV) gave a yellow crystalline material, m.p. 196°, $[\alpha]_D$ +14.5°, showing absorption in the ultraviolet at 342 (ε = 9,000), 360 (ε = 12,600), and 378 mμ (ε = 12,500), identical with that obtained by Petrow and his co-workers[38].

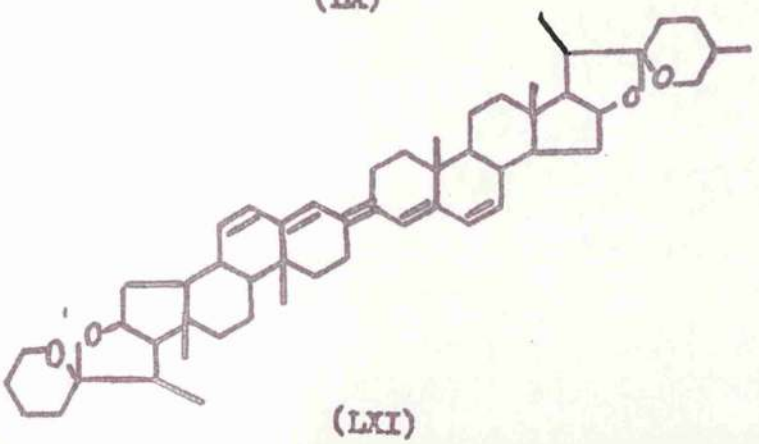
Dehydration of 3,3'-bi(25D-3β-hydroxyspirosta-1,4-dienyl) (LVIII) gave a similar product, m.p. above 360°. $[\alpha]_D$ -47.2°, and showing ultraviolet absorption at 340 (ε = 15,500), 360 (ε = 21,400), and 376 mμ (ε = 32,800). It is apparent that some rearrangement of the molecule takes place on dehydration, since the expected dehydration product (LIX) would show absorption at about 316 mμ. It is postulated that the dehydration products can best be represented by structures (LX) and (LXI).



(LIX)

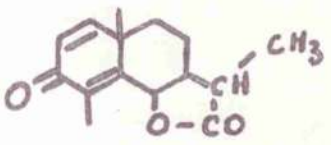


(LX)

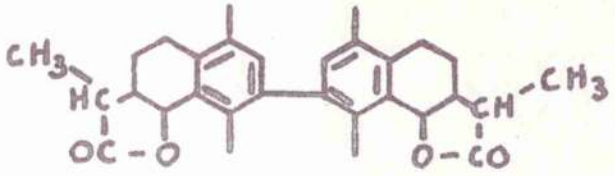


(LXI)

The calculated value (354 mμ) for maximal absorption of these structures (LX) and (LXI) is reasonably close to the found value. It is not easy to explain the migration of the double bond from the 1 to the 6 position, but it most probably occurs by an attack at the 1 position by a hydrogen ion during the dehydration reaction. It is interesting to note that in the dehydration and dimerisation which occurs on treatment of santonin (LXII) with zinc and acetic acid, the rings A are aromatised[39,40] with a migration of the angular methyl groups to the 1-positions, to give a biphenyl derivative (LXIII). In this instance the intermediate pinacol has not been isolated. It is clear however that no aromatisation occurs in the steroid 1,4-dien-3-one system which has just been considered.



(LXII)



(LXIII)

EXPERIMENTAL

Part Two.

Cholesta-4,6-dien-3-one.[41,42,43]

Cholesterol (20g.) and p-benzoquinone (120 g.) were dissolved in dry toluene (1200 c.c.) and boiled. 200 c.c. of toluene were distilled off and aluminium isopropoxide (20 g.) was added. The mixture was refluxed for 45 min. and allowed to cool. Sulphur dioxide was passed in for 1 hr. to reduce the excess of p-benzoquinone, and the solution was filtered. The residue of quinhydrone was washed with dilute sulphuric acid (2N) and ether. The filtrate and washings were mixed and washed with dilute sulphuric acid (6 x 2N), and then with water. The ether layer was washed with potassium hydroxide solution, care being taken to prevent the formation of an emulsion, and finally with water and dried (Na_2SO_4). The ether was evaporated off, the residue was dissolved in benzene and the solution was chromatographed on alumina (500 g.), washing through with benzene, benzene-ether (1:1), and finally with ether. The combined fractions, after removal of solvent yielded a yellow gum from which cholesta-4,6-dien-3-one was isolated by treatment with acetone. The product was recrystallised from methylated spirit to give the pure material, m.p. 82°, $[\alpha]_D$ +55°, λ_{max} in ethanol, 285 mμ (ε = 27,000), ν_{max} 2890, 1666, 1622, 1460 and 1370 cm^{-1}.

Irradiation of Cholesta-4,6-dien-3-one.[21]

(a) Cholesta-4,6-dien-3-one (1.0 g.) was dissolved in isopentane (10 c.c.) and irradiated for 3 hr. in a quartz flask with a mercury lamp (Hanovia UVS 500, Model XII). The material which came out of solution was filtered off at intervals, washed with isopentane, and recrystallised from chloroform-acetone to give the dimer, (0.5 g.), m.p. 180°, $[\alpha]_D$ +38.4°. (Found: C, 85.1; H, 11.48. $C_{54}H_{84}O_2$ requires C, 84.8; H, 11.1%.) λ_{max} in ethanol 206 (ε = 9,500) and 256 mμ (ε = 10,400). ν_{max} 2900, 1690, 1670, 1600, 1462, and 1380 cm^{-1}.

(b) A solution of cholesta-4,6-dien-3-one (1.0 g.) in ethanol (30 c.c.) was irradiated for a period of 2 hr. by a Hanovia UVS 500 mercury lamp. The solution was cooled and filtered off at 30 min. intervals. The combined solid was recrystallised from ethanol to give plates of the dimer (0.7 g.), m.p. 180°, $[\alpha]_D$ +38.4°. λ_{max} in ethanol 206 (ε = 9,600) and 256 mμ (ε = 10,500). ν_{max} 2900, 1690, 1670, 1600, 1462, and 1380 cm^{-1}.

Pyrolysis of Dimer from Cholesta-4,6-dien-3-one.

The dimer (30 mg.) was heated in vacuo at 200°, on a heating block for 30 min.. The product of pyrolysis sublimed and was collected on the cold part of the tube. The material was found to be identical with

cholesta-4,6-dien-3-one, m.p. and mixed m.p. 82°. λ_{max} in ethanol 285 mμ (ε = 26,000), ν_{max} 2900, 1666, 1622, 1582, 1462, 1370 cm^{-1}.

Action of Perchloric acid on Dimer from Cholesta-4,6-dien-3-one. The dimer (200 mg.) was dissolved in ethanol (10 c.c.) and perchloric acid (2 c.c.; N.) was added. The solution was allowed to stand for 4 hr., diluted with water and extracted with chloroform. The extract was washed with water to remove excess of acid, dried (Na_2SO_4), and the solvent was removed. The residue was recrystallised from methylated spirits to give prisms of cholesta-4,6-dien-3-one, (125 mg.), m.p. 82°, $[\alpha]_D$ +35°. λ_{max} in ethanol 285 mμ (ε = 26,000), ν_{max} 2890, 1666, 1622, 1460, 1370 cm^{-1}.

Action of potassium hydroxide on Dimer from Cholesta-4,6-dien-3-one. The dimer (200 mg.) was dissolved in ethanol (10 c.c.) and a solution of potassium hydroxide (200 mg.) in ethanol (5 c.c.) was added. The solution was refluxed for 3 hr. and diluted with water. The solution was extracted with chloroform, the extract was washed with water to remove alkali, and the solvent was removed after drying (Na_2SO_4). The product crystallised to give the starting material (200 mg.), m.p. 180°, $[\alpha]_D$ +38°. λ_{max} in ethanol 206 (ε = 9,000), and 256 mμ (ε = 10,000). ν_{max} 2900, 1690, 1670, 1600, 1460, and 1380 cm^{-1}.

Reduction of Dimer from Cholesta-4,6-dien-3-one using Lithium Borohydride. The dimer (1.0 g.) was dissolved in dioxan (15 c.c.) and an excess of lithium borohydride (1.0 g.) was added. The mixture was refluxed for 5 hr. and allowed to stand overnight. The solution was diluted with water and the precipitated organic material was filtered off, dissolved in chloroform and washed with water to remove traces of inorganic material. The chloroform solution was dried (Na_2SO_4) and evaporated to dryness. The product was recrystallised from acetone-methanol to give the pure dihydroxy compound (0.75 g.) m.p. 180°, $[\alpha]_D$ +37.4°. (Found: C, 83.75; H, 11.7. $C_{54}H_{88}O_2$ requires C,84.3; H, 11.5%.) λ_{max} in ethanol 208 mμ (ϵ = 11,000). ν_{max} 3333, 2850, 1470, 1380, 1030, and 750 cm^{-1}.

Acetylation of Dihydroxy Compound. The dihydroxy compound (1.0 g.) prepared in the previous experiment, was dissolved in pyridine (5.0 c.c.) and acetic anhydride (5.0 c.c.) was added. The mixture was allowed to stand at room temperature for 3 hr., diluted with water and extracted with chloroform. The chloroform extract was washed with dilute hydrochloric acid to remove pyridine, washed with water, dried over anhydrous sodium sulphate, and evaporated to dryness. The residue was recrystallised from acetone to give plates of the diacetate (0.8 g.),

m.p. 204°, $[\alpha]_D$ -19.4°. (Found C, 81.9; H, 11.1. $C_{58}H_{92}O_4$ requires C, 81.7; H, 10.8%.) λ_{max} in ethanol 206 mμ (ε = 13,000). ν_{max} 2860, 1730, 1470, 1370, 1250, and 1030 cm^{-1}.

Benzoylation of the Dihydroxy Compound. The dihydroxy compound (0.5 g.) was dissolved in pyridine (5.0 c.c.) and benzoyl chloride (1.5 c.c.) was added. The solution was allowed to stand overnight, diluted with water, and extracted several times with chloroform. The chloroform solution was washed with hydrochloric acid (3 x 10 c.c.; 2N), water, and evaporated to dryness after drying over anhydrous sodium sulphate. The residue was dissolved in benzene (5.0 c.c.) and chromatographed on alumina (40 g.). The combined eluates were evaporated to dryness and the residue was crystallised from acetone-chloroform to give plates of the dibenzoate, (0.4 g.) m.p. 215°. (Found; C, 83.0; H, 9.7. $C_{68}H_{96}O_4$ requires C, 83.6; H, 9.8%.) λ_{max} in ethanol 206 (ε = 26,300) 230 (ε = 28,100) and 270 mμ (ε = 2,500). ν_{max} 2860, 1710, 1370, and 1260 cm^{-1}.

Oxidation of Dihydroxy Compound. The dihydroxy compound (0.5 g.) was dissolved in pyridine (5.0 c.c.) and a solution of chromic acid (0.3 g.) in pyridine (5.0 c.c.) was added. The mixture was allowed to stand overnight, diluted with hydrochloric acid and sulphur dioxide was passed in to destroy the chromic acid present in excess.

The solution was extracted with chloroform and the extract was washed with dilute hydrochloric acid and water, dried over anhydrous sodium sulphate and evaporated to dryness. The residue was recrystallised from acetone-methanol to give a material (0.4 g.) m.p. 180°, $[\alpha]_D$ +38.0°, identical with the original photodimer. λ_{max} in ethanol 204 (ε = 9,200), and 257 mμ (ε = 9,800). ν_{max} 2900, 1690, 1670, 1600, 1462, and 1380 cm^{-1}.

Pyrolysis of Dihydroxy Compound. (a) The dihydroxy compound (40 mg.) was heated at 200° under a vacuum of 0.1 mm. on a heating block for 30 min.. The product of pyrolysis sublimed at this temperature and collected on the cold part of the tube. Recrystallisation from chloroform-acetone gave cholesta-2,4,6-triene, (30 mg.) m.p. 72°, $[\alpha]_D$ -6°. λ_{max} in ethanol 296 (ε = 11,000), and 306 mμ (ε = 12,300). ν_{max} 2890, 1460 and 1370 cm^{-1}.

(b) A second sample of the dihydroxy compound (0.2 g.) was heated at 200° under a vacuum of 0.1 mm. for 15 min.. The product of pyrolysis sublimed and was collected on the cold part of the tube. The material obtained was dissolved in benzene and chromatographed on alumina (10 g.). Two materials were eluted from the column, the first being cholest-4-en-3-one (55 mg.) m.p. 82°, $[\alpha]_D$ +89°. λ_{max} in ethanol 241 mμ (ε = 18,000), ν_{max} 2900, 1670, 1570 and 1380 cm^{-1}. The second material from the column was

3β-hydroxycholesta-4,6-diene (60 mg.) m.p. 127°, $[\alpha]_D$ -38°, λ_{max} in ethanol 234 (ε = 17,000), 239 (ε = 18,600), and 248 mμ (ε = 11,800). ν_{max} 3300, 2900, 1470, and 1380 cm^{-1}.

Attempted Catalytic Hydrogenation of Dihydroxy Compound. (a) The dihydroxy compound (0.25 g.) was dissolved in ethyl acetate (20 c.c.), mixed with a pre-reduced sample of palladium charcoal (20% Pd, 0.2 g.), and stirred in the presence of hydrogen until no more gas was taken up. The solution was filtered, and the solvent evaporated off. The residue was recrystallised from methylated spirit to give the pure product (0.2 g.), m.p. 180°, $[\alpha]_D$ +33.4°, identical with the starting material. (b) The dihydroxy compound (0.25 g.) was dissolved in ethanol and stirred with Raney nickel (0.2 g.) and hydrogen. When no more gas was taken up, the solution was filtered and evaporated to dryness. The residue was recrystallised from methylated spirit to give prisms, m.p. 180°, $[\alpha]_D$ +34°, identical with the starting material.

Catalytic Hydrogenation of the Photodimer from Cholesta-4,6-dien-3-one. (a) The dimer from cholesta-4,6-dien-3-one (0.5 g.) was dissolved in ethyl acetate (30 c.c.) and mixed with a prereduced sample of palladium charcoal catalyst (20% Pd; 0.5 g.). The solution was magnetically stirred under hydrogen until no more gas was

taken up. The solution was filtered and the ethyl acetate solution was allowed to crystallise, giving needles, m.p. 191°. The compound was recrystallised from acetone-chloroform, to give the pure reduced diketone, (0.3 g.), m.p. 280°, $[\alpha]_D$ +68.5°. (Found: C, 84.3, 84.3; H, 11.5, 10.8. $C_{54}H_{86}O_2$ requires C, 84.5; H, 11.2%.) λ_{max} in ethanol 207 mμ (ε = 8,600). ν_{max} 2910, 2860, 1720, 1690, 1460, 1385, and 1047 cm^{-1}. The mother liquors, on standing, gave crystals of the starting material (0.2 g.) m.p. 180°.

(b) The dimer from cholesta-4,6-dien-3-one (0.5 g.) was dissolved in ethanol (30 c.c.) and mixed with a pre-reduced sample of Raney nickel (0.3 g.). The solution was magnetically stirred in the presence of hydrogen until no more of the gas was taken up. The solution was filtered and evaporated to dryness. The product was crystallised from ethyl acetate to give needles (0.4 g.) of the hydroxy ketone, m.p. 280°, $[\alpha]_D$ +93.7°. (Found: C, 84.0; H, 11.57. $C_{54}H_{88}O_2$ requires C, 84.3; H, 11.53%.). λ_{max} in ethanol 210 mμ (ε = 10,500). ν_{max} 3500, 2925, 2860, 1689, 1465, 1385, 1049, 1300, 1020, and 970 cm^{-1}.

Oxidation of Hydroxy Ketone. The hydroxy ketone (150 mg.) prepared in the previous experiment, was dissolved in pyridine (5 c.c.) and chromic acid (150 mg.)

was added. The solution was allowed to stand overnight, diluted with water and extracted with chloroform. The chloroform solution was washed thoroughly with dilute hydrochloric acid to remove pyridine, with water and finally dried over anhydrous sodium sulphate. The chloroform was evaporated off, the residue was dissolved in benzene and chromatographed on an alumina column (10 g.), the eluates being combined and evaporated to dryness to give the diketone (100 mg.), m.p. 280°, $[\alpha]_D$ +68.5°, identical with the sample prepared by the hydrogenation of the dimer with palladium as catalyst, already described. (Found: C, 84.3; H, 11.5. Calc for $C_{54}H_{86}O_2$ C, 84.5; H, 11.2%.). λ_{max} in ethanol 206 mμ (ε = 7,000). ν_{max} 2940, 2860, 1715, 1695, 1460, 1385, and 1047 cm^{-1}.

Acetylation of Hydroxy Ketone. The hydroxy ketone (150 mg.) was dissolved in pyridine (5 c.c.) and a solution of acetic anhydride (2 c.c.) in pyridine (1 c.c.) was added. The solution was allowed to stand overnight, diluted with water and extracted with chloroform. The chloroform extract was washed with dilute hydrochloric acid to remove excess of pyridine, washed with water and dried over anhydrous sodium sulphate. The chloroform was evaporated down and the solution was chromatographed on alumina (10g.) in benzene (5 c.c.). Evaporation of the

solvent after chromatography yielded the acetate (150 mg.) m.p. 178°, $[\alpha]_D$ +68°. (Found: C, 83.2; H, 11.4. $C_{56}H_{90}O_3$ requires C, 83.0; H, 11.1%.) λ_{max} in ethanol 210 mμ (ε = 10,500), ν_{max} 2940, 2860, 1742, 1710, 1470, 1390, 1248, and 1030 cm^{-1}.

p-Iodobenzoylation of Hydroxy Ketone. The hydroxy ketone (0.75 g.) was dissolved in pyridine (25 c.c.) and p-iodobenzoyl chloride (1.0 g.) was added. The solution was allowed to stand overnight, then heated for 1 hr. on a steam bath, and allowed to cool. The p-iodobenzoic anhydride which crystallised out at this stage was filtered off. Water was added and the solution was allowed to stand for 2 hr.. The solution was then poured into water (50 c.c.) and the precipitated organic material was filtered off. The solid was dissolved in chloroform, and the solution was washed with dilute hydrochloric acid to remove pyridine. The solution was evaporated to dryness and the solid was recrystallised from chloroform-acetone to give needles of the p-iodobenzoate (0.75 g.), m.p. 267°, $[\alpha]_D$ -17.4°. (Found: C, 73.19, 73.26; H, 9.13, 9.23, I, 11.68; $C_{61}H_{91}IO_3$ requires C, 73.2; H, 9.12; I, 12.7%.) λ_{max} in ethanol 206 (ε = 10,800), and 259 mμ (ε = 10,200). ν_{max} 2940, 1718, 1700, 1580, 1470, 1370, 1270, 1175, 1120, 1010, 860, and 755 cm^{-1}.

Reduction of the Hydroxy Ketone. The hydroxy ketone (0.2 g.) was dissolved in dioxan (10 c.c.) and heated for 3 hr. with lithium borohydride (1.0 g.) on a steam bath. The solution was diluted with water and the precipitated organic material was filtered off and dissolved in chloroform. The chloroform solution was washed with water and evaporated to dryness to give the dihydroxy compound, (0.18 g.), m.p. 200°, $[\alpha]_D$ +42°. (Found; C, 84.6; H, 11.8. $C_{54}H_{90}O_2$ requires C, 84.2; H, 11.7%.) λ_{max} in ethanol 208 mμ (ε = 2,000). ν_{max} 3400, 2940, 2860, 1460, 1385, and 1040 cm^{-1}.

Preparation of ergosta-4,7,22-trien-3-one.[44,45,46,47]

(a) Cyclohexanone (296 c.c.;280 g.; 0.285 mol.) and toluene (1.7 l.) were refluxed in a 5 litre flask and dried by the Dean and Stark method for 1 hr.. Ergosterol (100 g.) was added and the solution was again boiled until dry. Aluminium isopropoxide (27.2 g.; 0.133 mol.) was added rapidly to the boiling solution with stirring, and refluxing was continued for a further 15 min.. The solution was cooled to 15°, and poured into hydrochloric acid (1 litre, 2N) at 5°. The two layers were separated, and the acid layer was washed twice with ether (500 c.c.). The toluene and ether solutions were combined and washed

with sodium bicarbonate solution and water. The solution was then steam-distilled to remove all solvent and the residual water was decanted off from the impure product. The material was dissolved in benzene and chromatographed on alumina (250 g.), eluting with benzene, and finally with ether-benzene (1:9). The residual material from these fractions, after removal of solvent, was dissolved in acetone, evaporated to 150 c.c. and allowed to crystallise overnight at -5°. Needles of ergosta-4,7,22-trien-3-one (30 g.), m.p. 129°, $[\alpha]_D$ -10° separated out. λ_{max} in ethanol 206 (ε = 8,900) and 238 mμ (ε = 15,900), ν_{max} 2940, 1680, 1610, 1450, 1260, 1220, 1180, 965, 870, 847, 830, and 770 cm^{-1}.

(b) Ergosterol (100 g.) was dissolved in benzene (2.4 l.) and acetone (1000 c.c.) and boiled. 400 c.c. of solvent was distilled off and aluminium isopropoxide (120 g.) was added. The solution was refluxed for 9 hr., cooled, and washed with dilute hydrochloric acid (3 x 500 c.c.; N). The acid was washed with ether (2 x 500 c.c.) and the combined organic layer was washed with potassium bicarbonate solution (500 c.c.) and then with water and dried. The ether and benzene were distilled off and the residual solid was chromatographed on alumina (1000 g.) eluting with benzene. The material from the column was recrystallised from acetone to give ergosta-4,7,22-trien-3-one (56 g.), m.p. 129°, $[\alpha]_D$ -10°.

Preparation of Ergosta-4,6,22-trien-3-one.[44,48]

Ergosta-4,7,22-trien-3-one (20 g.) was stirred under reflux with methanol (1 litre) in a 2-litre 3-necked flask until all solid had dissolved. 1 c.c. concentrated hydrochloric acid was added and a precipitate of 3-methoxy-3,5,7,22-ergostatetraene was formed. An additional 60 c.c. of concentrated hydrochloric acid was added dropwise over a period of 15 min. and the solution was boiled for a further 1.5 hr.. The solution was cooled and sodium bicarbonate (60 g.) was added. The precipitated sodium chloride was filtered off, and the solution was concentrated to a thick slurry, poured into water (750 c.c. and extracted with petrol (b.p. 40-60). The petrol solution was washed with water and dried (Na_2SO_4), and concentrated to 60 c.c.. The solution was allowed to crystallise at -5° for 12 hr., to give ergosta-4,6,22-trien-3-one (15 g.), m.p. 107°, $[\alpha]_D$ -26°. λ_{max} in ethanol 206 (ε = 27,700), and 284 mμ (ε = 29,000). ν_{max} 2940, 1670, 1610, 1585, 1450, 1370, 1260, 1220, 1180, 1020, 965, 875, 775 and 757 cm^{-1}.

Irradiation of Ergosta-4,6,22-trien-3-one.

Ergosta-4,6,22-trien-3-one (1.0 g.) was dissolved in ethanol (15 c.c.) and irradiated by ultraviolet light in the manner already described for a period of 12 hr., filtering at intervals of 2 hr.. Needles were formed

and were recrystallised from methanol to give plates of the dimer (0.7 g.), m.p. 173°, $[\alpha]_D$ -9.6°. (Found: C, 85.6; H, 10.5. $C_{56}H_{84}O_2$ requires C, 85.4; H, 10.5%.).

λ_{max} in ethanol 206 (ε = 11,700), and 256 mμ (ε = 11,000)

ν_{max} 2920, 2850, 1685, 1660, 1585, 1450, 1370, 1360, 1260, 1220, 1020, 980, 885, and 775 cm^{-1}.

Pyrolysis of Dimer from Ergosta-4,6,22-trien-3-one. The dimer from ergosta-4,6,22-trien-3-one (0.5 g.) was heated at 250° under a vacuum of 0.1 mm. on a heating block for 30 min.. The sublimate which formed on the cold part of the tube was crystallised from petrol to give ergosta-4,6,22-trien-3-one (0.4 g.), m.p. 107°, $[\alpha]_D$ -26°.

λ_{max} in ethanol 206 (ε = 21,700), and 284 mμ (ε = 29,000).

ν_{max} 2940, 1670, 1610, 1585, 1450, 1370, 1260, 1220, 1180, 1020, 965, 875, 775, and 757 cm^{-1}.

Action of Lithium Borohydride on Dimer from Ergosta-4,6,22-trien-3-one. The dimer from ergosta-4,6,22-trien-3-one (0.5 g.) was dissolved in tetrahydrofuran (25 c.c.) and refluxed with lithium borohydride (0.5 g.) for 5 hr.. The solution was diluted with water and the precipitated organic solid was filtered off, dissolved in chloroform (50 c.c.) and the chloroform solution was washed with water (3 x 50 c.c.), dried, and the solvent removed. The residual solid was recrystallised from chloroform-acetone

to give prisms of the dihydroxy compound (0.4 g.), m.p. 165°, $[\alpha]_D$ -11.4°. (Found: C, 84.9; H, 11.4. $C_{56}H_{88}O_2$ requires C, 84.8; H, 11.1%.) λ_{max} in ethanol 206 mμ (ε = 12,400), ν_{max} 3400, 2960, 1460, 1380, 1020, and 970 cm^{-1}.

Action of Raney nickel and Hydrogen on Dimer from Ergosta-4,6,22-trien-3-one. The dimer from ergosta-4,6,22-trien-3-one (0.5 g.) was dissolved in ethanol (100 c.c.) and a pre-reduced sample of Raney nickel (0.5 g.) was added. The solution was magnetically stirred in the presence of hydrogen for 6 hr., filtered and the solvent evaporated down to 20 c.c. and allowed to crystallise. Prisms of the hydroxy ketone (0.4 g.) m.p. 160°, $[\alpha]_D$ +36.4°, were formed. (Found: C, 84.7; H, 11.2. $C_{56}H_{88}O_2$ requires C, 84.8; H, 11.1%). λ_{max} in ethanol 204 mμ (ε = 3,800), ν_{max} 3300, 2960, 1690, 1465, 1380, 1055 cm^{-1}.

Preparation of $\Delta^{4,6}$ dehydrotigogenone.[41,49]

Diosgenin (20 g.) and p-benzoquinone (120 g.) were dissolved in toluene (1200 c.c.) and the solution was boiled, 200 c.c. of the toluene being distilled off. Aluminium isopropoxide (20 g.) was added, the mixture was refluxed for 15 min. allowed to cool, and sulphur dioxide was passed in for 1 hr. to reduce the excess of quinone. The solution was filtered

and the residue of quinhydrone was washed with sulphuric acid (200 c.c.;N) and ether (250 c.c.). The filtrate and washings were combined and washed with dilute sulphuric acid (6 x 400 c.c.;N) with water, (4 x 400 c.c.) and dried (Na_2SO_4). The solvent was evaporated off and the residue was dissolved in benzene and chromatographed on alumina (700 g.). The combined ether and ether-methanol fractions, after evaporation of the solvent, gave crystals of $\Delta^{4,6}$ dehydrotigogenone (15 g.), m.p. 205°, $[\alpha]_D$-64.5°. λ_{max} in ethanol 204 (ε = 12,850) and 284 mμ (ε = 28,000). ν_{max} 2900, 2850, 1670, 1615, 1590, 1460, 1380, 1050, 990, 905, 895, 800, and 760 cm^{-1}.

Irradiation of $\Delta^{4,6}$ dehydrotigogenone.

A solution of $\Delta^{4,6}$ dehydrotigogenone (5.0 g.) in ethanol (100 c.c.) was irradiated by ultraviolet light for a period of 9 hr., filtering at intervals of 2 hr.. The solid formed was recrystallised from chloroform-methanol to give fine needles of the dimer (4.0 g.), m.p. 190°, decomposing and remelting at 203°, $[\alpha]_D$ -70°. (Found: C, 78.7; H, 9.2. $C_{54}H_{76}O_6$ requires C, 79.0; H, 9.3%.). λ_{max} in ethanol 204 (ε = 10,400), and 254 mμ (ε = 10,500). ν_{max} 2950, 1700, 1670, 1610, 1460, 1380, 1250, 1180, 1060, 990, 905, 800, and 740 cm^{-1}.

Preparation of Cholesteryl Acetate. Cholesterol (300 g.) and acetic anhydride (800 c.c.) were refluxed together for 1.5 hr. and the solution was allowed to cool and crystallise. The solid was filtered off from the excess of acetic anhydride, washed with ethanol and allowed to dry. The compound was recrystallised from ethanol to give cholesteryl acetate (40 g.) m.p. 116°, $[\alpha]_D$ -47°.

Preparation of 7-ketocholesteryl acetate.[50] Chromic acid (15 g.) was added as a solid to a stirred solution of cholesteryl acetate (21.4 g.) in glacial acetic acid (230 c.c.) maintained at 50-55° over a period of 2 hr.. Stirring was continued for a further hour at the same temperature, and 70 c.c. of the acetic acid was removed by vacuum distillation. Water (10 c.c.) and ethanol (5 c.c.) were added and the solution was allowed to stand overnight. The crystals were filtered off and washed with 85% aq. acetic acid before drying in vacuo over potassium hydroxide. The material was dissolved in ether and washed with dilute hydrochloric acid, water, aqueous potassium bicarbonate and again with water, and dried. The ether was evaporated to dryness and the residue was dissolved in hot acetone, evaporated till crystals formed and methanol was added, to give crystals of 7-ketocholesteryl acetate (5.2 g.), m.p. 161°, $[\alpha]_D$ -35°.

Preparation of Cholesta-3,5-dien-7-one.[51,52]

(a) 7-Ketocholesteryl acetate (5 g.) was mixed with a saturated solution of hydrogen bromide in glacial acetic acid (50 c.c.) and the mixture was allowed to stand for 36 hr. at room temperature. The solution was diluted with water and extracted with ether. The etherial solution was washed with water, aqueous sodium bicarbonate, and water again, then dried. The ether was evaporated off and the residue was dissolved in benzene (25 c.c.), and chromatographed on alumina (100 g.). Combination of the fractions from the column after evaporation of the solvent gave a yellow gum, from which cholesta-3,5-dien-7-one (3.5 g.) m.p. 114°, $[\alpha]_D$ -210°, was obtained on treatment with, and recrystallisation from acetone. λ_{max} in ethanol 278 mμ (ε = 23,000), ν_{max} 2870, 1640, 1450, and 1370 cm^{-1}.

(b) 7-Ketocholesteryl acetate (361 mg.) was treated with a solution of hydrogen bromide in glacial acetic acid (5.0 c.c.) and heated on a steam bath for 10 min. at 100°, before being allowed to stand for 4 hr.. The solution was diluted with water and extracted with chloroform. The chloroform solution was washed with water, aqueous sodium bicarbonate and again with water before being dried over anhydrous sodium sulphate. The chloroform was evaporated off, and the residue was dissolved in

benzene and chromatographed on alumina (15 g.). The product, after evaporation of the benzene was recrystallised twice from acetone-methanol to give prisms of cholesta-3,5-dien-7-one (200 mg.), m.p. 114°, $[\alpha]_D$ -210°. λ_{max} in ethanol 278 mμ (ε = 23,000), ν_{max} 2870, 1640, 1450, and 1370 cm^{-1}.

Ultraviolet Irradiation of Cholesta-3,5-dien-7-one.

(a) Cholesta-3,5-dien-7-one (0.5 g.) was dissolved in the minimum volume of cyclohexane and irradiated with ultraviolet light from a mercury lamp (Hanovia UVS 500, Model XII) in a quartz flask fitted with a reflux condenser for a total of 13 hr.. The solid product formed during the irradiation was filtered off at intervals of 2 hr.. The compound was recrystallised from chloroform-isopentane to give the pure dimer (0.25 g.) m.p. 258°, $[\alpha]_D$ -71°. (Found: C, 84.7; H,11.2. $C_{54}H_{84}O_2$ requires C, 84.7; H, 11.1%) λ_{max} in chloroform 250 mμ (ε = 19,200), ν_{max} 2870, 1650, 1600, 1450, and 1370 cm^{-1}.

(b) The experiment was repeated as above using isopentane as solvent in place of cyclohexane. The dimer was formed much more readily under these conditions. The material was filtered off, washed with isopentane and recrystallised from chloroform to give the pure material (0.3 g.) m.p. 258°, $[\alpha]_D$ -71°.

(c) A solution of cholesta-3,5-dien-7-one (0.5 g.) in ethanol (20 c.c.) was irradiated for 2 hr. in the manner described above. Recrystallisation of the product from ethanol gave plates of the dimer, (0.35 g.) m.p. 258°, $[\alpha]_D$ -71.0°. λ_{max} in ethanol 250 mμ (ε = 19,000), ν_{max} 2870, 1650, 1600, 1450, and 1370 cm^{-1}.

Pyrolysis of Dimer from Cholesta-3,5-dien-7-one. The dimer from cholesta-3,5-dien-7-one (0.2 g.) was heated under a vacuum of 0.1 mm. for 30 min. at 250°. The product of pyrolysis sublimed and was collected on the cold part of the tube. The material was found to be cholesta-3,5-dien-7-one (0.18 g.), m.p. and mixed m.p. 114°, $[\alpha]_D$ -210°, λ_{max} in ethanol 278 mμ (ε = 23,000), ν_{max} 2870, 1640, 1450, and 1370 cm^{-1}.

Reduction of Dimer from Cholesta-3,5-dien-7-one by Lithium Borohydride. The dimer from cholesta-3,5-dien-7-one (0.5 g.) was dissolved in tetrahydrofuran and refluxed with lithium borohydride (0.5g.) for 3 hr., then allowed to stand overnight. The solution was diluted with water and the precipitated solid was filtered off and dissolved in chloroform. The chloroform solution was washed with water to remove inorganic material and dried over anhydrous sodium sulphate. The solvent was evaporated off and the residue was recrystallised from chloroform-acetone, to give

needles of the dihydroxy compound (0.4 g.), m.p. 200°, $[\alpha]_D$ -24.5°. (Found: C, 83.8; H, 11.3. $C_{54}H_{88}O_2$ requires C, 84.3; H, 11.5%). λ_{max} in ethanol 208 mμ (ε = 9,700), ν_{max} 3400, 1450, 1370 and 1310 cm^{-1}.

Acetylation of the Dihydroxy Compound.

The dihydroxy compound(0.5 g.) was dissolved in pyridine (2 c.c.) and acetic anhydride (1.0 c.c.) was added. The solution was allowed to stand overnight, diluted with water (10 c.c.) and extracted with chloroform. The extract was washed with water, dilute hydrochloric acid (3 x 25 c.c.; 3N.) and again with water. The solution was evaporated to dryness and the residue was crystallised from chloroform-acetone to give plates of the diacetate (0.3 g.), m.p. 205°, $[\alpha]_D$ +42.2°. (Found: C, 81.0; H, 10.8. $C_{58}H_{92}O_4$ requires C, 81.6; H, 10.8%.) λ_{max} in ethanol 210 mμ (ε = 47,000), ν_{max} 2860, 1720, 1460,,1365, 1240, and 1020 cm^{-1}.

Pyrolysis of Dihydroxy Compound. The dihydroxy compound (50 mg.) was heated under a vacuum of 0.1 mm. on a heating block for 45 min. at 250°. The product which sublimed and collected on the cold part of the tube was recrystallised from acetone-chloroform to give cholest-5-en-7-one (40 mg.) m.p. 130°, λ_{max} in ethanol 250 mμ (ε = 15,000). ν_{max} 2900, 1685, 1460, and 1370 cm^{-1}.

Hydrogenation of Photodimer from Cholesta-3,5-dien-7-one. The dimer from cholesta-3,5-dien-7-one (0.2 g.) was dissolved in ethanol (50 c.c.) and a sample of pre-reduced Raney nickel (0.3 g.) was added as a catalyst. The mixture was stirred in the presence of hydrogen until no more gas was taken up. The solution was filtered, and evaporated down to 7 c.c., then left to crystallise. Needles of the reduced compound were formed (0.18 g.), m.p. 284°, $[\alpha]_D$ +7.8°. (Found: C, 84.0; H, 11.9. $C_{54}H_{90}O_2$ requires C, 84.2; H, 11.7%). λ_{max} in ethanol 208 mμ (ε = 1,000), ν_{max} 3300, 2900, 1700, 1460, 1380, 1040, 1015 cm^{-1}.

Preparation of 4-dehydrotigogenone.[53] Diosgenin (50 g.) was dissolved in benzene (1200 c.c.) and acetone (500 c.c.) and boiled. 200 c.c. of the solvent were distilled off and aluminium isopropoxide (60 g.) was added. The solution was refluxed for 9 hr., cooled and washed with dilute hydrochloric acid (2 x 500 c.c.: N.). The acid was washed with ether (2 x 500 c.c.) and the combined organic layer was washed with saturated potassium bicarbonate solution (500 c.c.), water, and dried. The ether and benzene were distilled off, and the residual solid was recrystallised from acetone-methylene chloride to give 4-dehydrotigogenone (40 g.), m.p. 186°, $[\alpha]_D$ -20°, λ_{max} in ethahol 204 mμ (ε = 16,100). ν_{max} 2950, 1680, 1610, 1460, 1380, 1180, 1060, 990, 909, and 870, cm^{-1}.

Electrolytic reduction of 4-Dehydrotigogenone.

4-Dehydrotigogenone (6.0 g.) was dissolved in ethanol (750 c.c.) along with hydrated sodium acetate (12 g.). The solution was placed in a cell consisting of a 1 litre beaker and a current of 3 amps. D.C. (200 V.) was passed through for 3 hr., using a mercury cathode and 4 carbon rods as an anode. The solution was kept at 20° throughout the experiment by surrounding the cell with a bath containing acetone and solid carbon dioxide. The ethanol solution was poured into water (3 litres.) and the organic material was filtered off, dissolved in benzene and dried (Na_2SO_4). The solution was chromatographed on alumina (250 g.). The initial fractions eluted from the column with benzene consisted of 4-dehydrotigogenone, m.p. 186°, $[\alpha]_D$ -20°. Further elution of the column with ether-methanol and recrystallisation from benzene-acetone gave 3,3'-bi(25D-3β-hydroxyspirost-4-enyl) (1.5 g.), m.p. 280°, $[\alpha]_D$ -56.1°. (Found: C, 78.1; H, 9.98. $C_{54}H_{82}O_6$ requires C, 78.3; H, 9.96%). λ_{max} in ethanol 206 mμ (ε = 10,400). ν_{max} 3400, 2980, 1460, 1380, 1215, 1180, 1065, 1010, 990, 980, 920, and 900 cm^{-1}.

Dehydration of 3,3'-bi(25D-3β-hydroxyspirost-4-enyl).

The pinacol (0.5 g.) prepared in the previous reaction was dissolved in chloroform (50 c.c.) and methanol (5 c.c.) and concentrated hydrochloric acid (1.0 c.c.) was added.

The mixture was shaken and allowed to stand at room temperature for 24 hr., with occasional shaking. The chloroform solution was washed with sodium bicarbonate solution (20 c.c.) and water (3 x 30 c.c.) and dried (Na_2SO_4). The solvent was evaporated off and the residue was recrystallised from chloroform-methanol to give yellow prisms of 3,3'-bi(25D-spirosta-3,5-dienyl) (0.3 g.), m.p. above 360°, $[\alpha]_D$ -27.5°. (Found: C, 82.0, H, 9.6. $C_{54}H_{78}O_4$ requires C, 82.1; H, 9.8%). λ_{max} in chloroform 300 (ε = 31,900), 310 (ε = 45,700), and 324 mμ (ε = 42,600). ν_{max} 2980, 1460, 1380, 1240, 1180, 1070, 1055, 980, 900, and 865 cm^{-1}.

Electrolytic Reduction of Ergosta-4,7,22-trien-3-one.

A solution of ergosta-4,7,22-trien-3-one (1.0 g.) in ethanol (750 c.c.) with sodium acetate (12 g.) was reduced electrolytically in the manner described, at 15°. The ethanol solution was poured into water and the organic material filtered off, dissolved in benzene, and dried (Na_2SO_4). The solvent was removed. The residue would not crystallise from benzene-acetone, but was found to crystallise readily from acetone-water, to give prisms of 3,3'-bi(3β-hydroxyergosta-4,7,22-trienyl) (0.8 g.), m.p. 240°, $[\alpha]_D$ -11.2°., as a dihydrate. (Found: C, 81.9;

H, 10.7. $C_{56}H_{86}O_2.2H_2O$ requires C, 81.4; H, 10.9%). λ_{max} in ethanol 209 mμ (ε = 14,400), ν_{max} 3390, 2950, 1460, 1380, 1310, 1150, 1030, 1010, 970, 850, and 807 cm^{-1}.

Dehydration of 3,3'-bi(3β-hydroxyergosta-4,7,22-trienyl). A solution of 3,3'-bi(3β-hydroxy-ergosta-4,7,22-trienyl) (200 mg.) in chloroform (10 c.c.) and methanol (5 c.c.) was boiled for 15 min. with a few drops of concentrated hydrochloric acid. The solution was allowed to cool, washed with a saturated solution of sodium bicarbonate (3 x 30 c.c.) and water (2 x 30 c.c.) and dried (Na_2SO_4). The solvent was removed, and the residue was dissolved in benzene and chromatographed on alumina (10 g.). The fractions eluted with benzene were combined and recrystallised from light petroleum (b.p.40-60) to give yellow crystals of the dehydration product, 3,3'-bi(ergosta-3,5,7,22-tetraenyl) (150 mg.), m.p. 234° $[\alpha]_D$ +449°. (Found: C, 89.5; H, 10.9. $C_{56}H_{82}$ requires C, 89.2; H, 10.8%). λ_{max} in chloroform 351 (ε = 19,500), 366 (ε = 26,300), 386 (ε = 24,800), 422 (ε = 11,200) and 446 mμ (ε = 9,400). ν_{max} 2980, 2930, 1455, 1370, 1160, 1020, 965, 872, 805, and 775 cm^{-1}.

Electrolytic Reduction of Cholesta-4,6-dien-3-one. Cholesta-4,6-dien-3-one (2.0 g.) was dissolved in ethanol (750 c.c.) and reduced electrolytically in the manner

already described, at 15° for 3 hr.. The solution was diluted with water and extracted with benzene. The extract was dried (Na_2SO_4), concentrated to small bulk and chromatographed on alumina (80 g.). The first three fractions from the column gave unchanged starting material (0.7 g.). The remaining fractions, on evaporation to dryness, gave a gum which would not crystallise from acetone-benzene, but which crystallised readily with acetone-water, to give 3,3'-bi(3β-hydroxycholesta-4,6-dienyl) dihydrate (1.0 g.), m.p. 152°, $[\alpha]_D$ +36.6°. (Found: C, 80.8; H, 10.8. $C_{54}H_{86}O_2.2H_2O$ requires C, 80.8; H, 11.2%). λ_{max} in ethanol 208 (ε = 8,600), and 236 mμ (ε = 9,100). ν_{max} 3450, 2940, 2860, 1470, 1380, 1260, 1170, 1060, 1015, 870, 770, and 755 cm^{-1}.

Dehydration of 3,3'-bi(3β-hydroxycholesta-4,6-dienyl). The pinacol (0.5 g.) prepared in the previous experiment was dissolved in acetone (10 c.c.) and chloroform(5.0 c.c.) and concentrated hydrochloric acid (1.0 c.c.) was added. The solution was heated on a steam bath for 5 min., diluted with water and extracted with benzene. The extract was washed with water, dried over anhydrous sodium sulphate and evaporated to small bulk. The residual solution was chromatographed on alumina (17 g.), the fraction eluted with benzene being collected and evaporated. Crystallisation of the residue gave

yellow prisms of 3,3'(cholesta-4',6'-dienylidene) cholesta-4,6,8-triene, (0.4 g.) m.p. 214°, $[\alpha]_D$ +7°. (Found: C, 88.5; H, 11.4. $C_{54}H_{82}$ requires C, 88.7; H, 11.3%.) λ_{max} in chloroform 360 (ε = 39,000), 374 (ε = 55,600), and 392 mμ (ε = 53,600), ν_{max} 2965, 2900, 1470, 1385, 1308, 1260, 1110, 946, 977, 870, 755, and 740 cm^{-1}.

Electrolytic Reduction of Ergosta-4,6,22-trien-3-one. A solution of ergosta-4,6,22-trien-3-one (1.0 g.) and sodium acetate (12 g.) in ethanol (750 c.c.) was reduced electrolytically for 3 hr. at 15°. The solution was poured into water and extracted with benzene. The extract was washed with water, dried (Na_2SO_4), concentrated and chromatographed on alumina (25 g.) to give 3,3'-bi(3β-hydroxy-ergosta-4,6,22-trienyl) (0.7 g.) on recrystallisation from benzene-acetone. The compound had mp. 180°, $[\alpha]_D$ -12.1°. (Found: C, 85.3; H, 11.3. $C_{56}H_{86}O_2$ requires C, 85.2; H, 11.0%). λ_{max} in ethanol 206 (ε = 10,000), and 234 (ε = 10,900). ν_{max} 3450, 2900, 1470, 1380, 1260, 1170, 1060, 870, 770, and 755 cm^{-1}.

Dehydration of 3,3'-bi(3β-hydroxyergosta-4,6,22-trienyl). 3,3'-Bi(3β-hydroxyergosta-4,6,22-trienyl) (0.3 g.) was dissolved in chloroform (10 c.c.) and methanol (5.0 c.c.), and treated with a drop of concentrated hydrochloric acid. The solution was boiled and allowed to cool, washed with saturated sodium bicarbonate solution

(3 x 20 c.c.), water (2 x 20 c.c.), and dried over anhydrous sodium sulphate. The solvent was evaporated off and the residual solid was recrystallised from light petroleum (b.p. 40-60°), to give yellow prisms of 3,3'(ergosta-4',6',22'-trienylidene) ergosta-4,6,8,22-tetraene (0.2 g.) m.p.245°, $[\alpha]_D$ +3°. (Found: C, 89.3; H, 11.0. $C_{56}H_{82}$ requires C, 89.2; H, 10.8%.). λ_{max} in chloroform 360 (ε = 41,500), 374 (ε = 52,400), and 389 mμ (ε = 47,600). ν_{max} 2900, 1450, 1370, 1160, 1020, 965, 805, and 775 cm^{-1}.

Electrolytic Reduction of $\Delta^{4,6}$ dehydrotigogenone.

A solution of $\Delta^{4,6}$ dehydrotigogenone (1.0 g.) in ethanol (750 c.c.) containing sodium acetate (12 g.) was electrolytically reduced at 15° for 3 hr.. The ethanol solution was poured into water (3 litres) and centrifuged. The supernatant liquid was decanted off and the solid was dissolved in benzene, dried (Na_2SO_4) and the solution concentrated. Some acetone was added and the solution was allowed to crystallise to give prisms of 3,3'-bi-(25D-3β-hydroxyspirosta-4,6-dienyl) (0.5 g.), m.p. 300°, $[\alpha]_D$ -215°. (Found: C, 78.8; H, 9.5. $C_{54}H_{78}O_6$ requires C, 78.7; H, 9.8%). λ_{max} in ethanol 208 (ε = 9,000) and 235 mμ (ε = 10,000). ν_{max} 3390, 2940, 1450, 1370, 1335, 1235, 1170, 1050, 1000, 975, 955, 895, and 865 cm^{-1}.

Dehydration of 3,3'-Bi(25D-3β-hydroxyspirost-4,6-dienyl). A solution of the pinacol (250 mg.) in chloroform (5 c.c.) and ethanol (2 c.c.) was treated with a drop of concentrated hydrochloric acid and heated on a steam bath for 30 min.. The solution was washed with sodium bicarbonate (2 x 10 c.c.), water (2 x 10 c.c.), and dried over anhydrous sodium sulphate. The chloroform was removed and the residue was recrystallised from petroleum ether (b.p. 40-60°), to give yellow prisms of 3,3'-(25D-spirosta-4',6'-dienylidene)-25D-spirosta-4,6,8-triene, (150 mg.) m.p. 276°, $[\alpha]_D$ -40.5°. (Found: C, 82.2; H, 9.4. $C_{54}H_{74}O_4$ requires C, 82.4; H, 9.4%). λ_{max} in chloroform 360 (ε = 45,200), 374 (ε 60,600), and 392 mμ (ε = 55,400). ν_{max} 2940, 1370, 1335, 1170, 1100, 970, 917, 900, 917, 900, and 865 cm^{-1}.

Electrolytic Reduction of Cholesta-1,4-dien-3-one. Cholesta-1,4-dien-3-one (0.8 g.) was dissolved in ethanol (750 c.c.) and sodium acetate (12 g.) was added. The solution was electrolytically reduced at 20° in the manner already described for 3 hr.. The ethanol solution was poured into water (3 litres) and the precipitated organic material was filtered off, dissolved in benzene, dried (Na_2SO_4), and crystallised by the addition of acetone to give prisms

of 3,3'-bi(3β-hydroxy cholesta-1,4-dienyl) (0.65 g.) m.p. 130° with decomposition, $[\alpha]_D$ +68.1°. (Found: C, 84.2; H, 11.4. $C_{54}H_{86}O_2$ requires C, 84.5; H, 11.2%.) λ_{max} in ethanol 206 mμ (ε = 17,400), ν_{max} 3450, 2940, 1460, 1380, 1205, 1135, 1105, 1010, 917, 860, 800, 765, and 675 cm^{-1}.

Dehydration of 3,3'-Bi(3β-hydroxycholesta-1,4-dienyl).

3,3'-Bi(3β-hydroxycholesta-1,4-dienyl) (0.3 g.) was dissolved in chloroform (10 c.c.) and methanol (10 c.c.) and concentrated hydrochloric acid (1.0 c.c.) was added. The solution was boiled for 5 minutes, washed with saturated potassium bicarbonate solution (3 x 20 c.c.), water (3 x 20 c.c.), and dried (Na_2SO_4). The solvent was removed and the product was recrystallised from petroleum ether (b.p. 40-60°), to give yellow prisms of the hydrocarbon, 3,3'(cholesta-4',6'-dienylidene)-cholesta-1,4,6-triene (0.25 g.), m.p. 196°, $[\alpha]_D$ +14.5°. (Found: C, 88.4; H, 11.4. $C_{54}H_{82}$ requires C, 88.7; H, 11.3%). λ_{max} in chloroform 342 (ε = 9,000), 360 (ε = 12,700), and 378 mμ (ε = 12,500). ν_{max} 2940, 1460, 1380, 1170, 1010, 966, 860, 830, 800, 750, and 735 cm^{-1}.

Electrolytic Reduction of $\Delta^{1,4}$ dehydrotigogenone.

A solution of $\Delta^{1,4}$ dehydrotigogenone (1.0 g.) in ethanol (750 c.c.) containing sodium acetate (12 g.) was electrolytically reduced in the manner previously described, for 3 hr. at 15°.

The product was isolated by pouring into water (3 litres) extracting with benzene, drying the extract (Na_2SO_4), concentrating and chromatographing on alumina (30 g.). Recrystallisation from benzene-acetone gave prisms of 3,3'-bi(25D-3β-hydroxyspirosta-1,4-dienyl) (0.7 g.) m.p. 250°, $[\alpha]_D$ -49.7°. (Found: C, 79.4; H, 9.4. $C_{54}H_{78}O_6$ requires C, 78.8; H, 9.5%). λ_{max} in ethanol 206 mμ (ε = 15,700). ν_{max} 3390, 2940, 1475, 1380, 1240, 1170, 1100, 1055, 980, 960, 917, and 895 cm^{-1}.

Dehydration of 3,3'-Bi(25D-3β-hydroxyspirosta-1,4-dienyl). A solution of the pinacol (0.3 g.) in chloroform (10 c.c.) and methanol (5 c.c.) was dehydrated by boiling for 5 min. with a drop of concentrated hydrochloric acid. The product was isolated by washing the solution with a saturated sodium bicarbonate solution (2 x 10 c.c.), water (2 x 10 c.c.) and drying. Removal of the solvent and recrystallisation of the product from chloroform-methanol gave yellow prisms of 3,3'(25D-spirosta-4',6'-dienylidene)-spirosta-1,4,6-triene, (250 mg.), m.p. above 360°, $[\alpha]_D$ -47.2°. (Found C, 82.1; H, 9.43. $C_{54}H_{74}O_4$ requires C, 82.4; H, 9.41%). λ_{max} in chloroform 340 (ε = 15,600, 360 (ε = 21,400), and 376 mμ (ε = 22,800). ν_{max} 2980, 1460, 1380, 1245, 1175, 1100, 970, 917, 900, 865, and 750 cm^{-1}.

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SUMMARY OF Ph.D. THESIS

An Experimental Investigation of the Photoproduction of π^+ Mesons from Hydrogen near Threshold

by

Erwin Gabathuler

An experimental investigation of the energy dependence of the differential cross-section near threshold for the reaction $\gamma + p \longrightarrow \pi^+ + n$ was undertaken by the author because of the disagreement which existed in current literature between the theoretical predictions given by single dispersion relations and the experimental data. Moreover, the extrapolation of the experimental data to threshold was inconsistent with the related information from pion scattering experiments, and therefore a comprehensive investigation of the π^+ photoproduction cross-section was of considerable interest.

The experiment was performed by irradiating a thin-walled liquid hydrogen target with the 250 MeV bremsstrahlung beam of the Glasgow electron synchrotron, and detecting the pions which emerged at an angle of 58° to the incident beam direction. The design of the proton target incorporated a pressure compensating device to provide a thin slice of liquid hydrogen of uniform thickness. The low energy pion detector consisted of a scintillation counter telescope, and utilised the characteristic rapid decay of the π^+ meson to identify the /

the pions, which were produced together with electrons, protons and gamma rays. In addition, pulse height selection methods were employed for unambiguous detection of the pions down to the lowest energy, which was 6 MeV.

The experimental information was analysed and the results provided conclusive evidence that the energy dependence of the pion photoproduction cross-section in the threshold region was in agreement with the theoretical predictions, in contradiction to the previous experimental data. Further, the threshold value of the π^+ cross-section obtained by extrapolating the results to zero pion energy was in accord with the most recent information obtained from pion scattering measurements.

Low energy π^+ mesons were also detected using a time of flight technique to separate the pions from electrons and protons. Additional information was provided by displaying the $\pi^+ \rightarrow \mu^+$ decay, and the results showed that it was possible to separate the pions by this method.

THE THERMAL DECOMPOSITION OF ESTERS, POLYESTERS, AND RELATED SUBSTANCES.

A summary of a thesis submitted to the University of Glasgow in accordance with the regulations governing the award of the degree of Doctor of Philosophy.

by

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November, 1960.

SUMMARY.

In the first section of the thesis, a study was made of the vapour-phase decomposition of the ester cyclohexyl benzoate. The ester was pyrolysed in a flow reactor system at temperatures between 300° and 500°. Thermal breakdown of the ester was also studied in a static system by an empirical method in which the breakdown rate was followed by measuring pressure changes in a system containing the vapourised ester with a quantity of liquid reflux. From the study using the flow reactor system it was found that the ester decomposed by an exclusive alkyl-oxygen scission to give benzoic acid and cyclohexene only, over the range of temperatures employed. In the presence of small amounts of metal catalysts, breakdown of the ester was more complex and several competitive scissions were detected. From the static reactor system it was found that the exclusive alkyl-oxygen scission of the ester was a homogeneous reaction.

In the second part of the thesis, the thermal decomposition routes of three esters were studied using a flow system at 500°. The first ester, vinyl benzoate, was investigated

as/

as part of a study of the decomposition of the polyester 'Terylene'. The main pyrolysis route was re-examined in greater detail and a new minor competitive scission established, by which the ester produced keten and benzaldehyde.

Two other related enol carboxylates, isopropenyl benzoate, and acetophenone enol benzoate, were pyrolysed and the products examined. Decomposition of each ester took place by several competitive scissions including thermal rearrangement to a β-diketone, previously reported to be the exclusive breakdown product for this group of esters.

STUDIES IN THE PYRAZOLIDINE FIELD AND DIMERISATION OF STEROIDS.

Summary of Ph.D. Thesis, October 1961.

James Redpath.

PART ONE.

"Studies in the Pyrazolidine Field" describes the syntheses of early pyrazolidine derivatives and the discovery that 2,3-dimethyl-1-phenyl-5-pyrazolone, or antipyrine, possessed pharmacological properties. Other important drugs followed, such as Pyramidon and Phenylbutazone, and the syntheses of these are described briefly. The discovery of certain dyestuffs containing the pyrazoline ring system, such as Tartrazine and Xylene Light Yellow, maintained interest in this field. More recent work has been carried out on derivatives of Phenylbutazone, or 4-n-butyl-3,5-dioxo-1,2-diphenylpyrazolidine, in an attempt to reduce the toxicity of this drug, but this aim has not been achieved.

Of the many derivatives of Phenylbutazone described in the literature, none has been reported in which one of the ketone groups in the system has been replaced by an imino group, although some imino-oxo-pyrazolidines are known. 3-Imino-5-oxo-1,2-diphenyl-pyrazolidine was prepared by the condensation of cyanoacetyl chloride with hydrazobenzene, but attempts to substitute a 4-alkyl group in the molecule were unsuccessful. An alternative synthesis, using ethyl cyanoacetate and hydrazobenzene proved disappointing, but a more successful synthesis was carried out by treating chloroacetyl hydrazobenzene with potassium cyanide. This was also adapted to give

the 4-methyl pyrazolidine by using chloropropionyl hydrazobenzene, but was not successful with higher homologues. 3-Imino-5-oxo-1,2-diphenylpyrazolidine and its 4-methyl derivative reacted readily with cyclohexanone, benzaldehyde, butyraldehyde, phosphorus pentachloride, bromine, and acetic anhydride, to give various derivatives which are fully described.

PART TWO.

"Dimerisation of Steroids" describes several of the reactions which occur when unsaturated compounds are exposed to sunlight or ultraviolet light. Dimers are formed from anthracene, 3-methylcyclohexenone, thymoquinone, coumarin, cinnammic acid and other unsaturated compounds, giving generally a cyclobutane derivative. Cholest-4-en-3-one and testosterone propionate dimerise similarly, but other steroid dimerisations are known which involve oxidation and photodimerisation simultaneously. Ergosterol, ergosteryl acetate, 22,23-dihydroergosterol, and 7-dehydrocholesterol undergo this oxidative dimerisation to give the corresponding "pinacols".

The irradiation of cholesta-4,6-dien-3-one by ultraviolet light gives a compound shown to be a dimer, but formulated wrongly in 1944 by two Russian Chemists, Ushakov and Kosheleva. Ergosta-4,6,22-trien-3-one, and 4,6-dehydrotigogenone dimerise similarly. Ultraviolet and infrared absorption evidence, and a variety of reductions of the dimer using lithium borohydride and Raney nickel,

finally established a structural formula for the compound in which the two halves of the molecule are joined by a 5-membered ring system. Nuclear magnetic resonance spectra and optical rotatory dispersion curves confirm the structure.

Many non-photolytic reductive dimerisations of steroids are known in which the reducing agent is sodium amalgam or zinc and ethanol. These give pinacols which undergo dehydration on treatment with acid. A study of this reaction was carried out by electrolytically reducing cholesta-4,6-dien-3-one, cholesta-1,4-dien-3-one, ergosta-4,7,22-trien-3-one, ergosta-4,6,22-trien-3-one, 4-dehydrotigogenone, 4,6-dehydrotigogenone and 1,4-dehydrotigogenone. Dehydration of the pinacols was done with hydrochloric acid and the products were examined by ultraviolet and infrared spectroscopy.