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The Hydroxylamino Derivatives of Santonin

THE HYDROXYLAMINO DERIVATIVES OF SANTONIN.

by

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PREFACE

All the compounds that have a direct bearing on the arguments expressed in this work are represented on a single chart on p. 137. The overall scheme can be more readily followed if constant reference is made to this chart, which can conveniently be left folded out as the text is read. Arabic numerals are given only to the compounds included on this chart, and these are underlined to avoid confusion with reference numbers. Other compounds, and some of the reaction intermediates, are given Roman numerals.

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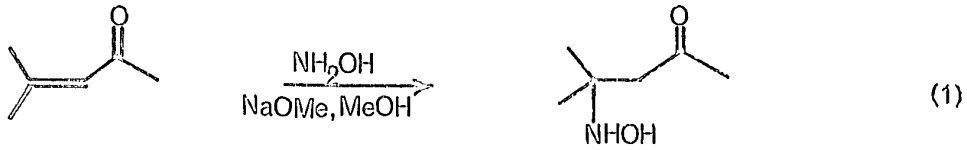
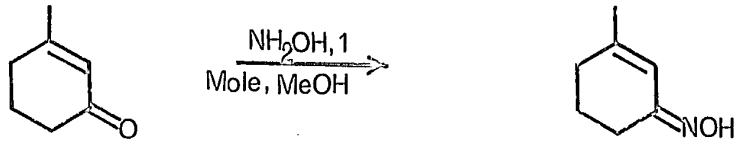
THE HYDROXYLAMINO DERIVATIVES OF SANTONIN

A. Introduction.

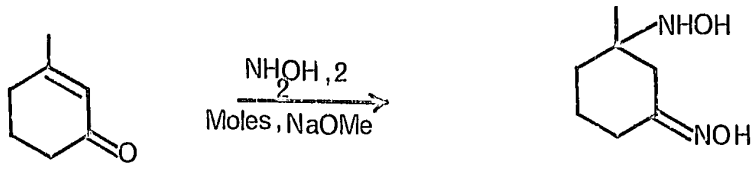
$\alpha\beta$-Unsaturated ketones generally react with hydroxylamine to give the oxime, but sometimes give a β-hydroxylamino-ketone or a β-hydroxylamino-oxime (1,2). Some examples are given in equations 1-5.



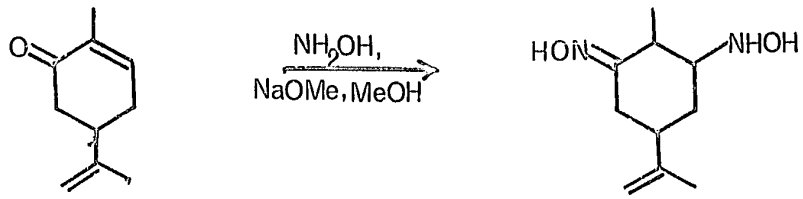
(1)



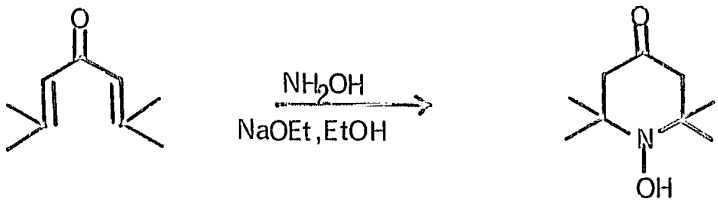
(2)



(3)



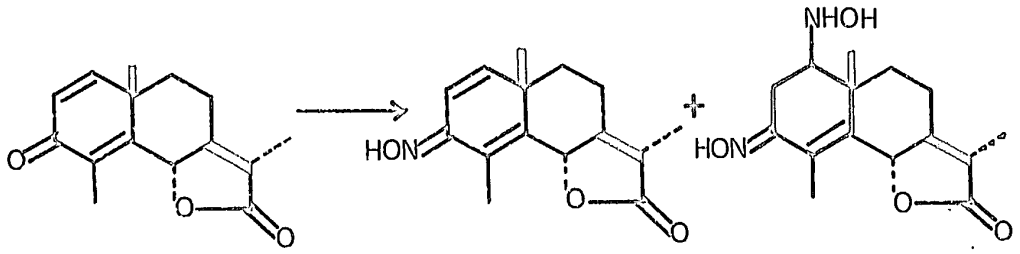
(4)



(5)

Francesconi and Cusmano (3) noted that (-)α-santonin (1), an $\alpha\beta, \alpha'\beta'$-di-unsaturated ketone, gave the oxime (2) and two isomeric hydroxylaminosantonin oximes. The correct carbon skeleton of santonin itself was not known to these early workers.

Later, when the structure of santonin was known, Sir John Simonsen and D. H. R. Barton (4) assigned the structure I to the two hydroxylamino-oximes, without specifying the stereochemistry of either the oxime or

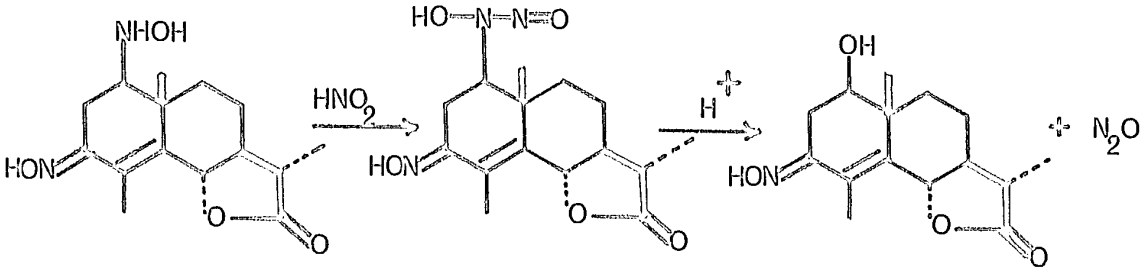


1 2 I

hydroxylamino groups. The correct stereochemistry of santonin itself was later established (5-8) to be as shown in formula 1.

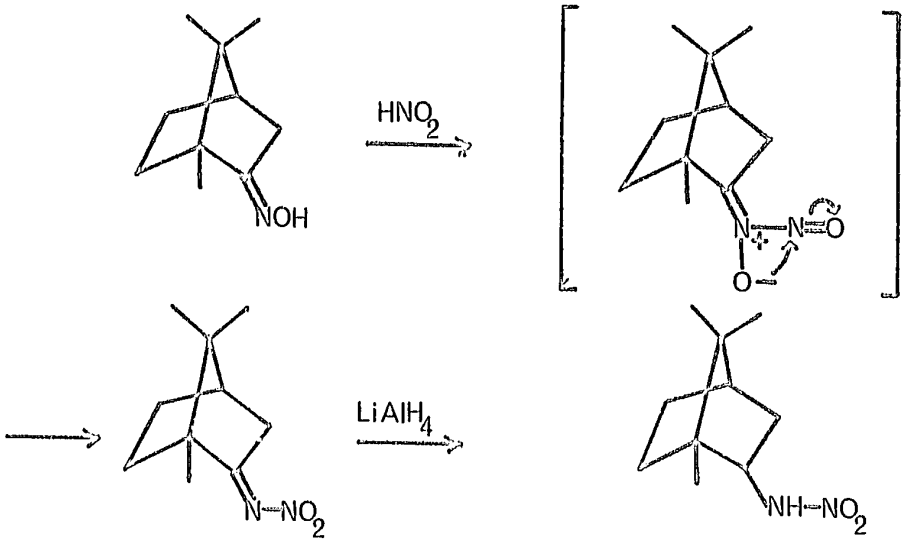
On treatment with nitrous acid, the two hydroxylaminosantonin oximes (I) gave two nitroso compounds (II) which in turn, when heated with 50% acetic acid, gave nitrous oxide and two isomeric products, formulated as

the hydroxy compounds (III).



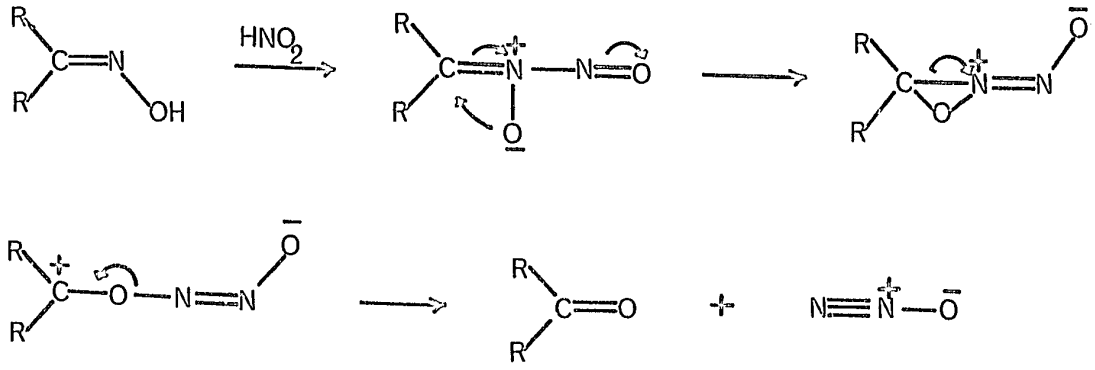
I II III

The possibility of the nitrous acid attacking the oxime group must also be considered. It is well known (9-15) that oximes can react with nitrous acid, and from certain oximes, stable "pernitroso" derivatives can be isolated. The structure of these "pernitroso" derivatives has recently been reviewed by Freeman (13,14) and by Wieland and Grimm (15). Freeman has shown that oximes with



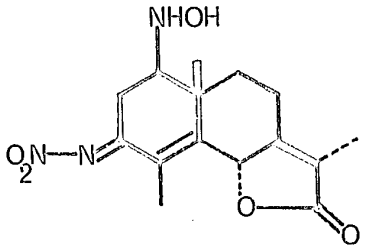
neighbouring tertiary alkyl groups give stable compounds proved by their infra-red and U.V. spectra and by reduction to nitro-amines to have the nitrimmine structure.

Earlier workers (9-12) had noted that oximes of 1,2-diketones or α-keto esters and of most simple unbranched alkyl ketones with electron attracting groups adjacent to the oxime also react with nitrous acid but stabilise themselves by splitting off N_2O in the presence of acid. A possible mechanism is:

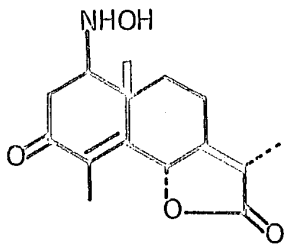


Wieland and Grimm (15) have furnished evidence for this mechanism by using O^{18} labelled oximes, and analysing the N_2O gas in a mass-spectrometer. All the O^{18} went into the ketone product and none into the N_2O.

If the hydroxylaminosantonin oximes reacted in this way the products would be either a nitrimmine (IV) or an unsaturated ketone (V).



IV

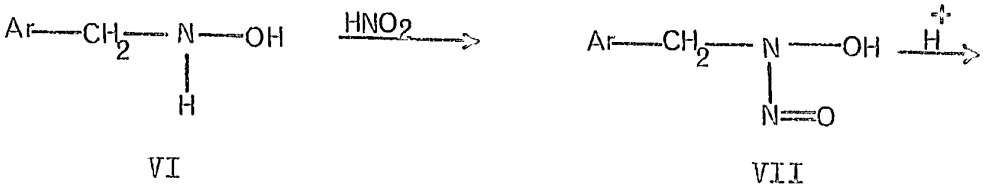


V

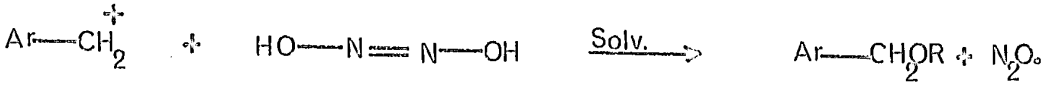
In fact, no nitrimmines or ketonic products were reported to be formed in this reaction. This is to be expected, as equimolar amounts of hydroxylaminosantonin oxime and sodium nitrite were used, and attack evidently takes place preferentially on the more nucleophilic hydroxylamino nitrogen and not at all on the nitrogen of the oxime grouping.

The reactions of other N-nitroso-N-alkyl hydroxylamines have been investigated in some detail (16,17), and probably involve the intermediacy of carbonium ions. This is illustrated by the reaction of N-benzylhydroxylamine (VI) with nitrous acid.

The nitroso compound (VII) may be solvolysed in the presence of acid:

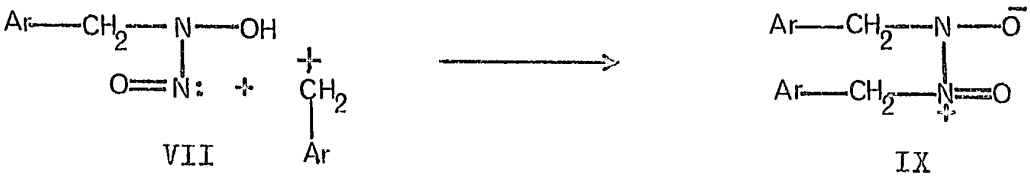


VI VII



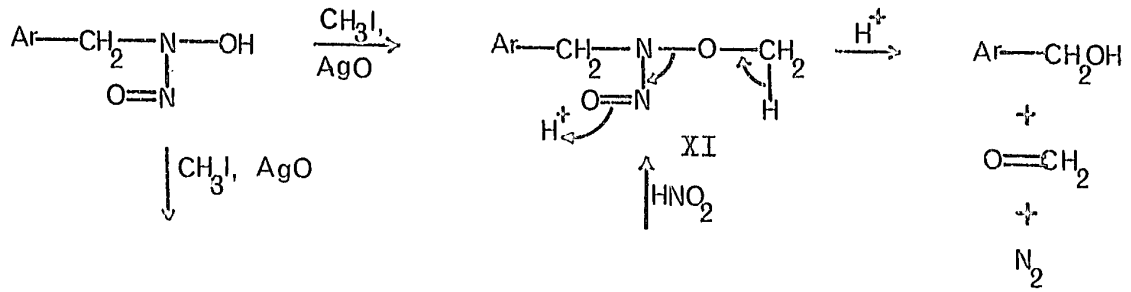
VIII

The alcohol (VIII) or the nitroso dimer (IX) may be isolated according to conditions. The nitrosohydroxylamine (VII) on treatment with methyl iodide in the presence



VII IX

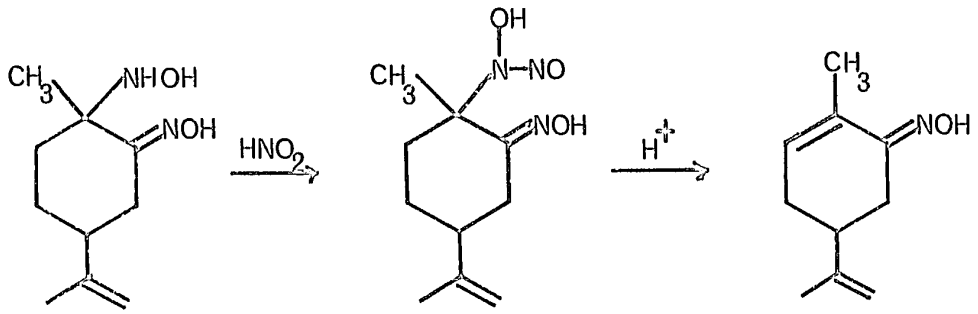
of silver oxide affords the nitrone (X) in about 90% yield, and the O,N-disubstituted nitrosohydroxylamine (XI) (10% yield).



X XII

The latter, which is the same compound that is formed by direct nitrosation of O,N-disubstituted hydroxylamines (XII), eliminates nitrogen and not nitrous oxide when treated with acid. An alcohol and an aldehyde are the final products (18).*

The intermediate carbonium ions may also stabilise themselves by elimination of a proton to give olefins, as shown below for the hydroxylamine XIII derived from limonene (20,21).

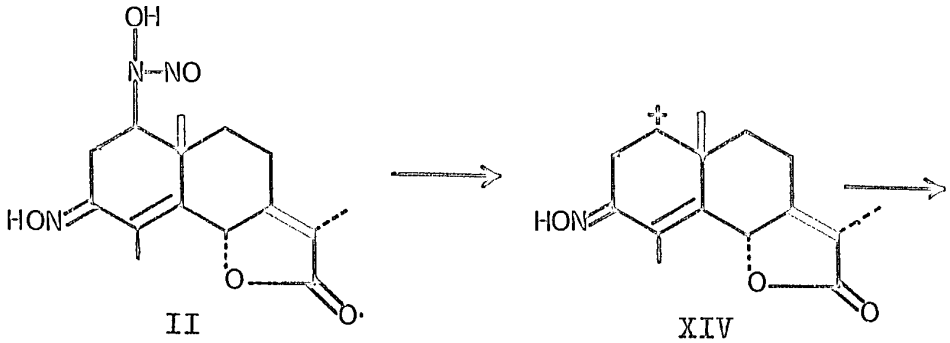


XIII

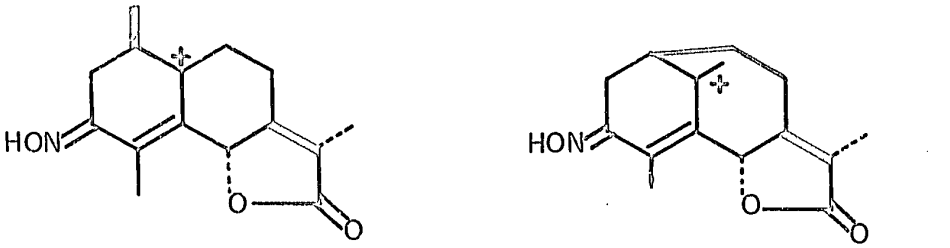
The secondary carbonium ions (XIV) which would be derived by elimination of nitrous oxide from the nitroso-hydroxylaminosantonin oximes (II) are ideally constituted for rearrangement involving either the angular methyl group

*O-alkyl hydroxylamines, on treatment with nitrous acid give an alcohol and nitrous oxide (19). The intermediates are not isolated.

or one of the other neighbouring carbon-carbon bonds, depending on the stereochemistry of the departing group, to give more stable tertiary carbonium ions (e.g., XV or XVI), and thence a rearranged alcohol.



II XIV



XV XVI

Francesconi and Cusmano (3) noted that dehydration of either of the isomeric hydroxysantonin oximes III gave a product ($C_{15}H_{19}NO_3$) isomeric with santonin oxime (2) but not identical to it. This may be considered evidence against Simonsen and Barton's structure III, which would be expected to lose water to give santonin oxime (2).

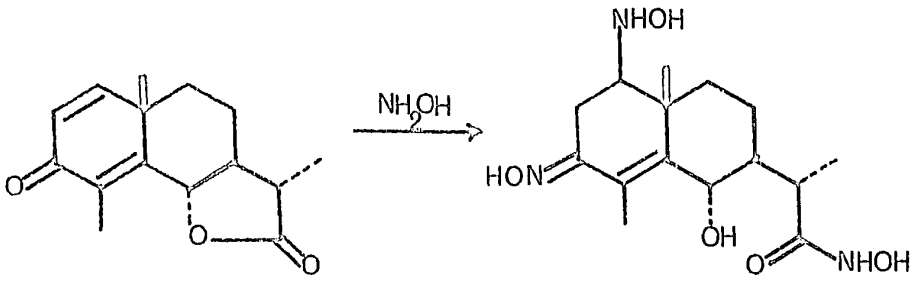
Because of the uncertainty surrounding the

structures of the various compounds, we have undertaken to study them further, using physical techniques (e.g., I.R. and n.m.r. spectroscopy and thin layer chromatography) not available to the earlier workers.

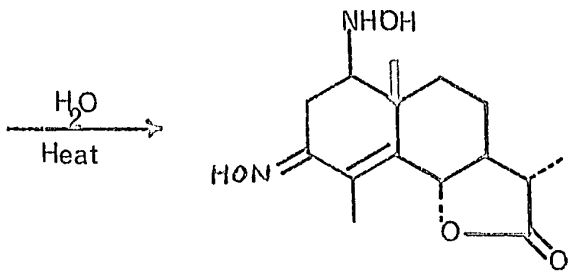
B. Discussion.

1. Hydroxylaminosantonin Oximes -α and -β.

Francesconi and Cusmano (3) found that hydroxylaminosantonin oxime-α (I) is formed when santonin reacts with hydroxylamine in the presence of an excess of sodium methoxide; when it reacts with hydroxylamine in the presence of excess hydroxylamine hydrochloride, a hydroxamic acid (XVII) is formed. The latter cyclises in boiling water with evolution of hydroxylamine to give the isomeric hydroxylaminosantonin oxime-β (I).



1 XVII



I

The formation of hydroxylamino-oximes from

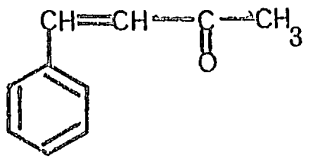
santonin and other $\alpha\beta$-unsaturated ketones is evidently the result of two competing reactions: formation of the oxime; and attack of hydroxylamine on the double bond to give the hydroxylamino-ketone, followed by reaction of the carbonyl group to give the hydroxylamino-oxime. The faster the rate of oxime formation, the lower will be the ratio of hydroxylamino-oxime to simple oxime in the product.

2. Factors Affecting Addition of Hydroxylamine to Unsaturated Ketones.

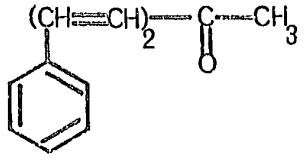
Two effects may be operating to influence the ratio of hydroxylamino-oxime to simple oxime.

(a) The Effect of Ketone Structure.

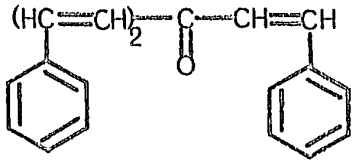
For the series of ketones XVIII to XX the relative rates of formation of the simple oximes in the



XVIII



XIX



XX

presence of one mole each of hydroxylamine hydrochloride

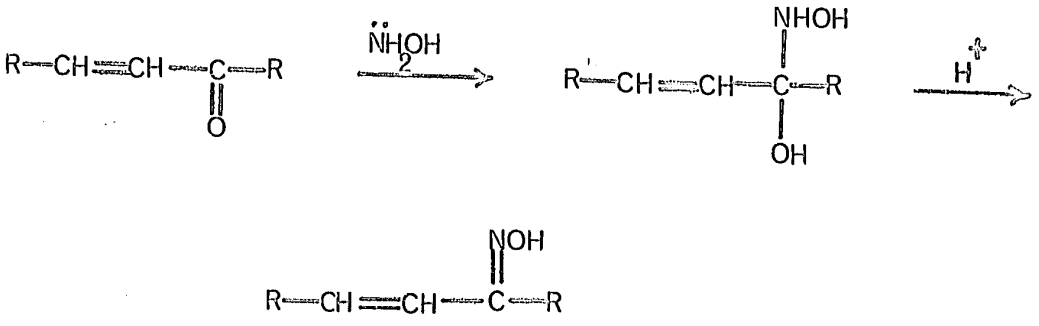
and sodium acetate, are:

XVIII > XIX > XX

The opposite order is observed for the ratios of addition product to simple oximes, favoured by the presence of excess hydroxylamine and sodium methoxide. Addition takes place only to the unsaturated ketone: the oxime of XX, when refluxed with excess hydroxylamine, undergoes no further change.

(b) The Effect of pH.

The initial addition of hydroxylamine to the carbonyl group takes place most rapidly in neutral or basic solution (22), and this step becomes rate determining only if the solution is strongly acidic.



The rate determining step in basic solution is

therefore the dehydration of the initially formed carbinolamine. (The rates and relative importance of these two steps are reversed in strongly acid solution). For the same reasons, the formation of the hydroxylamino-oximes would also be expected to be faster in basic solution.

It then becomes obvious that at higher pH, the rate of oxime formation relative to the rate of attack at the double bond will be slower, because of the slowness of dehydration of the intermediate carbinolamine.

We have found that this applies also to the santonin case, the yield of hydroxylamino-oxime being very low under the slightly acid conditions of ordinary oxime formation, and zero when santonin oxime was used as the starting material. The best yield was obtained in the preparation of the α-isomer (see experimental) where excess sodium methoxide was used: the yield of the β-isomer, in which excess hydroxylamine hydrochloride was used, was always lower.

3. Preparation of the Hydroxylaminosantonin Oximes and their Derivatives.

(a) Hydroxylaminosantonin Oxime-α.*

Santonin (1) was refluxed with four molar equivalents of hydroxylamine in methanol solution to which had been added a 0.4 molar excess of sodium methoxide. The product was 75% santonin oxime (2) and 25% hydroxylaminosantonin oxime-α.

The latter had the physical properties quoted by Francesconi and Cusmano (3); m.p. 230°, $[\alpha]_D^{25}$ + 46.5° (lit. m.p. 229-230°, $[\alpha]_D^{12}$ + 47.44°). However, from the spectral data described below it was immediately obvious that structure I could not be correct.

First, a compound of structure I should have a strong absorption peak in the ultraviolet spectrum near 235 mμ. Our compound did not have any absorption peak above 200 mμ.

The infra-red spectrum of hydroxylaminosantonin oxime-α (Fig. 1) was also incompatible with structure I. It showed only one sharp band near 1640 cm^{-1}, whereas

*For an explanation of the nomenclature used throughout this work, see p.143

Figure 1.

The infra-red spectrum of hydroxylamino-santonin oxime-α (3).

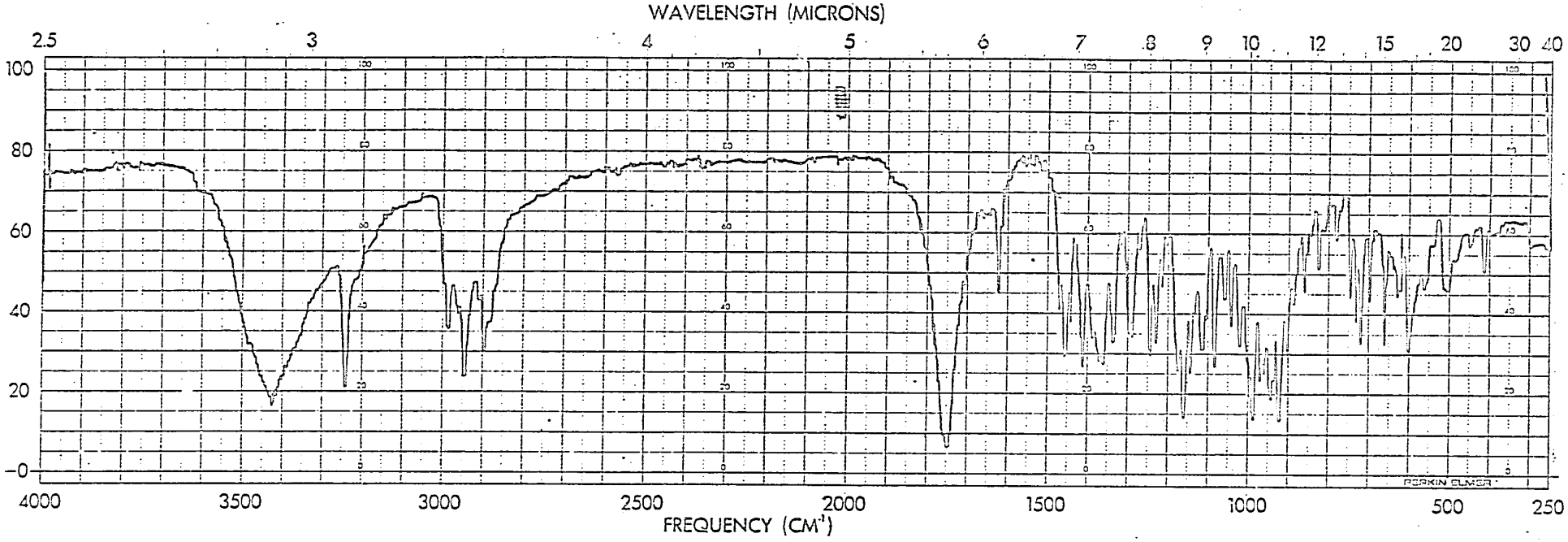
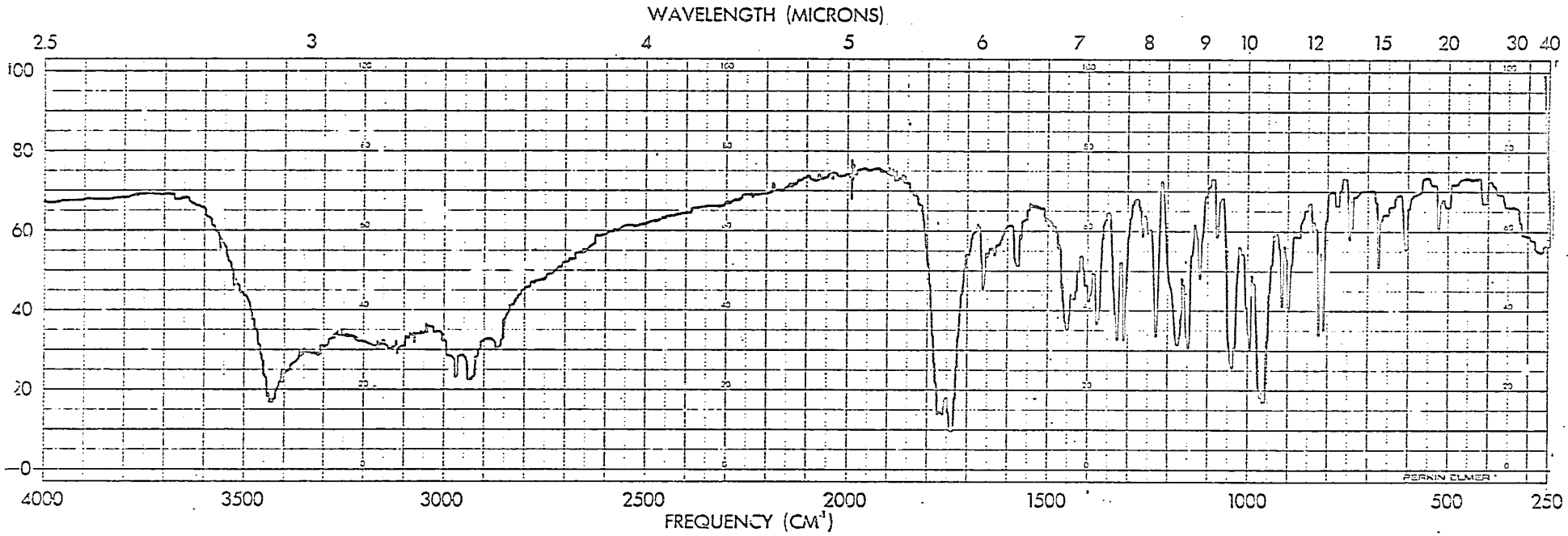

WAVELENGTH (MICRONS)
2.5
3
4
5
6
7
8
9
10
12
15
20
30
40
100
80
60
40
20
0
4000
3500
3000
2500
2000
1500
1000
500
250
FREQUENCY (CM-1)
PERKIN ELMER

Figure 2.

The infra-red spectrum of santonin oxime (2).


WAVELENGTH (MICRONS)
2.5
3
4
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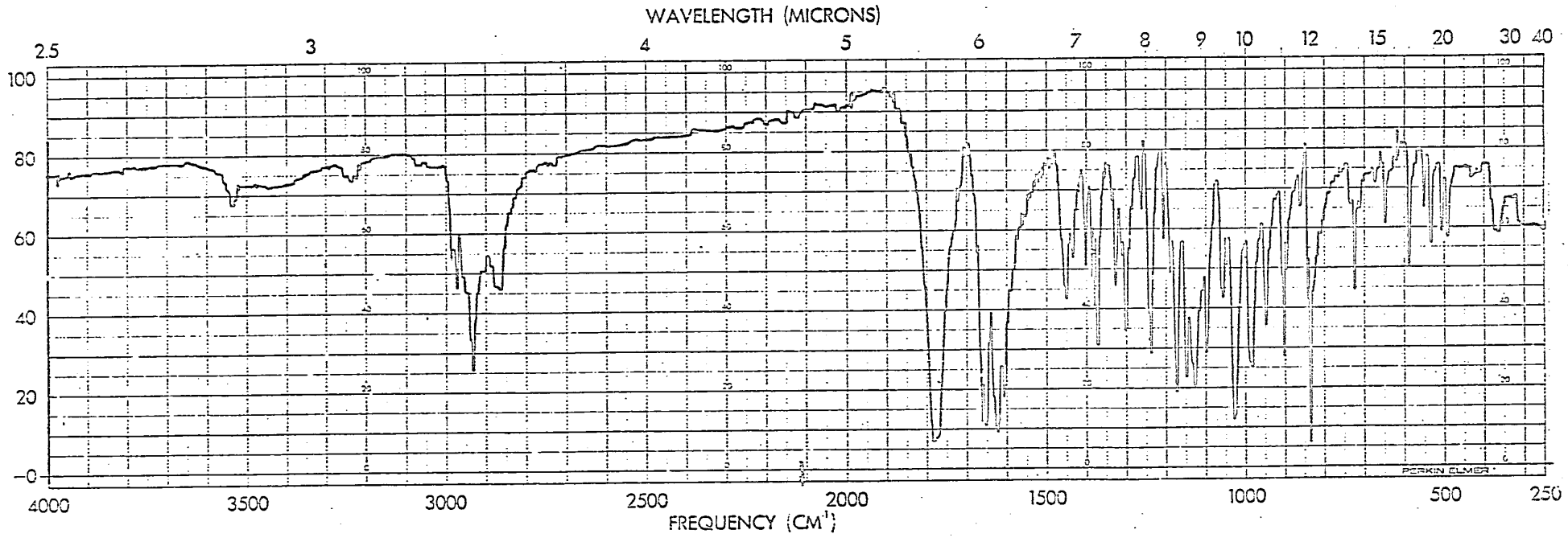
6
7
8
9
10
12
15
20
30
40
100
80
60
40
20
0
4000
3500
3000
2500
2000
1500
1000
500
250
FREQUENCY (CM-1)
PERKIN ELMER

Figure 3.

The infra-red spectrum of santonin (1).


WAVELENGTH (MICRONS)
2.5
3
4
5
6
7
8
9
10
12
15
20
30
40
100
80
60
40
20
0
4000
3500
3000
2500
2000
1500
1000
500
250
FREQUENCY (CM-1)
PERKIN ELMER

santonin oxime (2) has three bands in the region 1580-1660 cm^{-1}, (Fig. 2), where they are associated with the C=N and two C=C stretching vibrations. Santonin also has two C=C stretching vibrations in this region (Fig. 3). The single peak at 1640 cm^{-1} in the product is assigned to the C=N stretching vibration of the oxime, and the absence of any other bands in this region is evidence for the absence of double bonds in conjugation with the oxime group.

Finally, the n.m.r. spectrum (Fig. 4 and table 1) was in disagreement with Simonsen and Barton's structure I. Two of the three methyl groups of santonin and santonin oxime give rise to sharp singlet peaks, and the third (C-11 methyl) gives rise to a well defined doublet (Figs. 5 and 6, and table 1). The spectrum of I would show similar peaks. However, the spectrum of hydroxylaminosantonin oxime-α has two methyl peaks as doublets and only one as a singlet. The C-4 methyl group, which gives rise to a singlet peak at 2.13 p.p.m. in santonin (1) and at 2.16 p.p.m. in santonin oxime (2) was a doublet (J= 7 c.p.s.) at 1.23 p.p.m. Further, the doublet at 4.88 p.p.m. in 1 and 4.80 p.p.m. in 2, assigned to the proton at C-6, was shifted upfield to 4.10 p.p.m. in hydroxylaminosantonin oxime-α. The double bond at C-4 has evidently disappeared, with the consequent upfield shifts of the C-4 methyl group and C-6 hydrogen.

Figure 4.

The n.m.r. spectrum of hydroxylaminosantonin oxime-α (3).

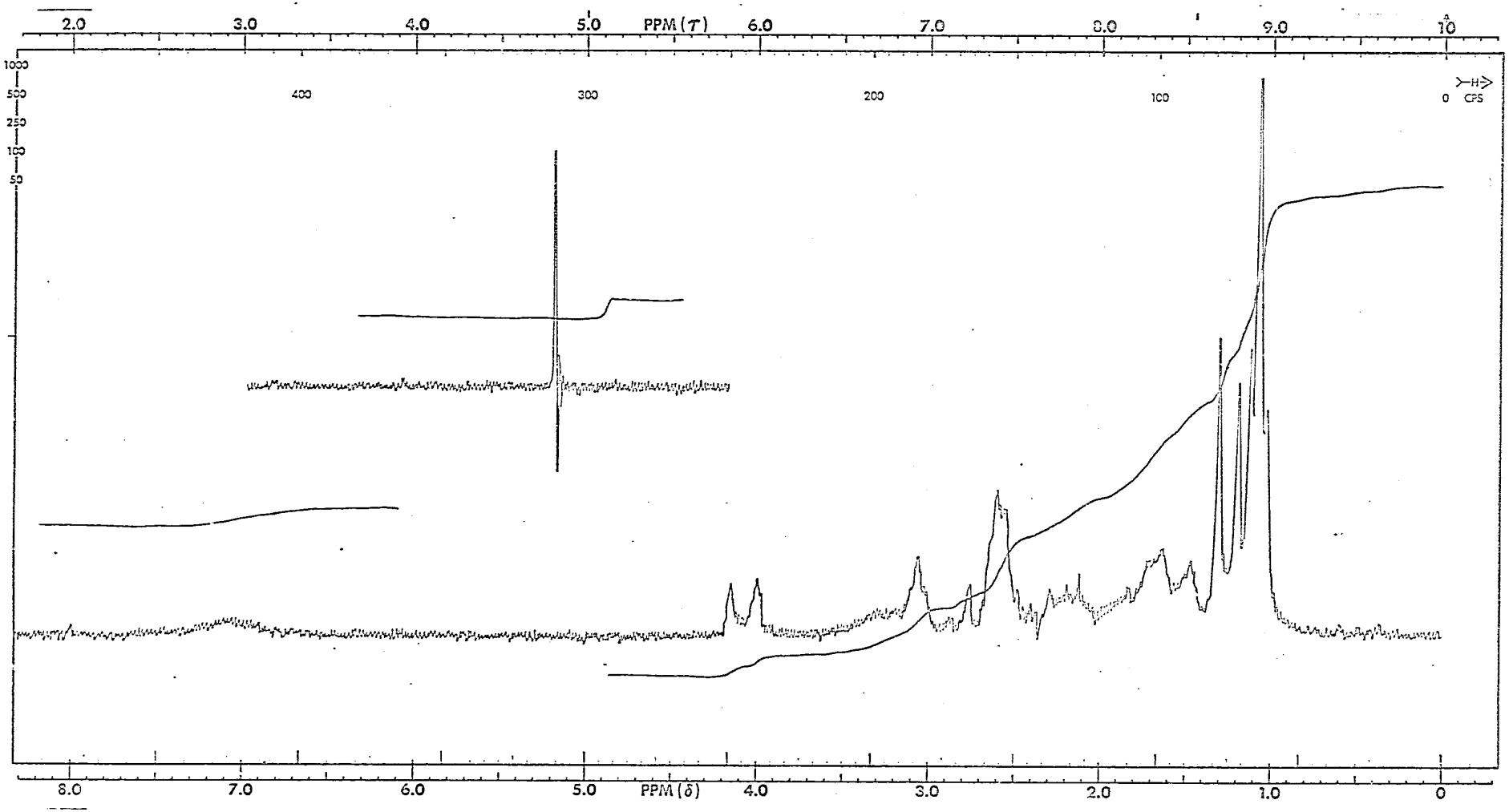
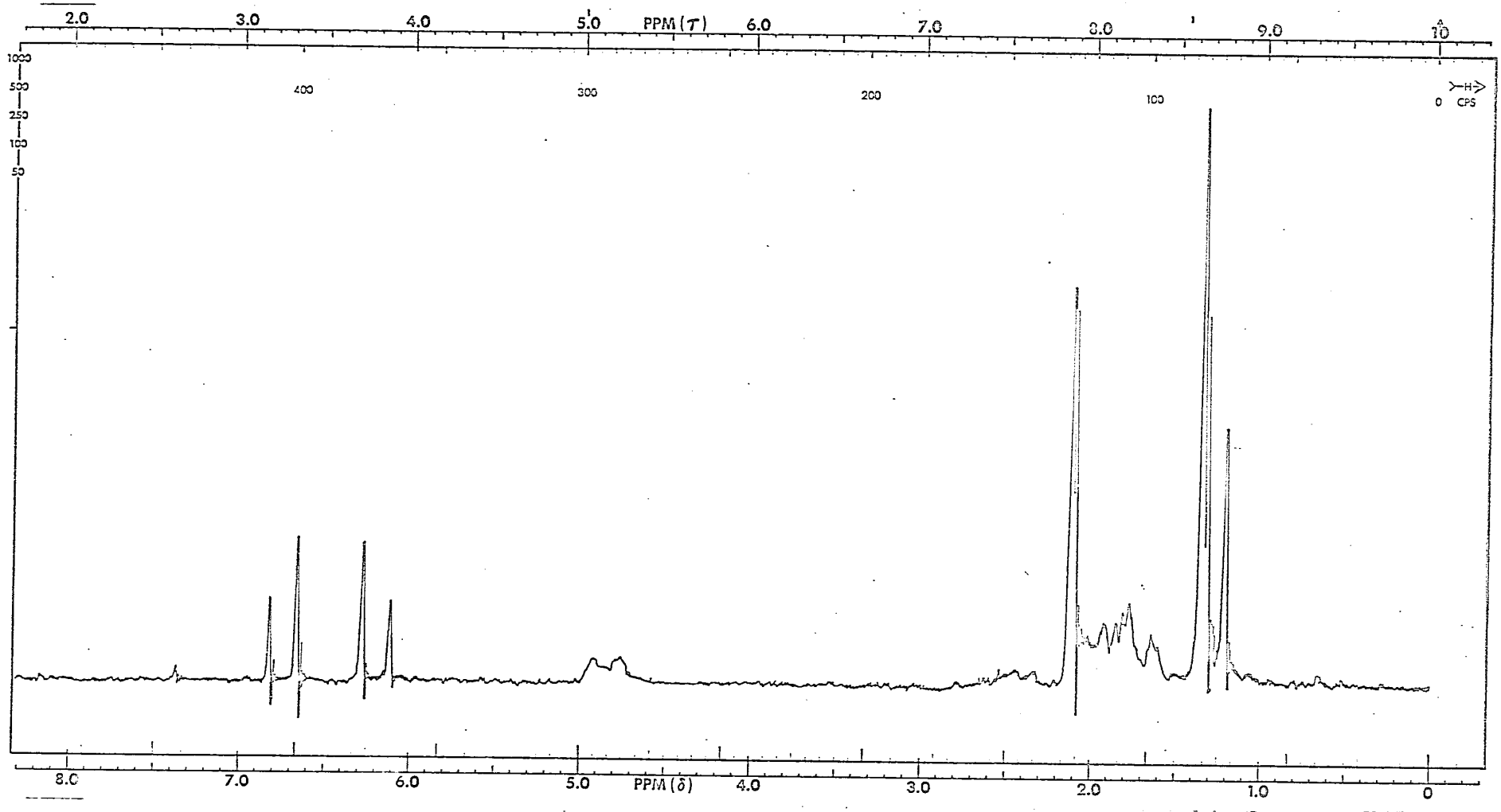

2.0
3.0
4.0
5.0
PPM (τ)
6.0
7.0
8.0
9.0
10
1000
500
250
100
50
400
300
200
100
0
CPS
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

Figure 5.

The n.m.r. spectrum of santonin (1).


2.0
3.0
4.0
5.0
PPM (τ)
6.0
7.0
8.0
9.0
10
1000
500
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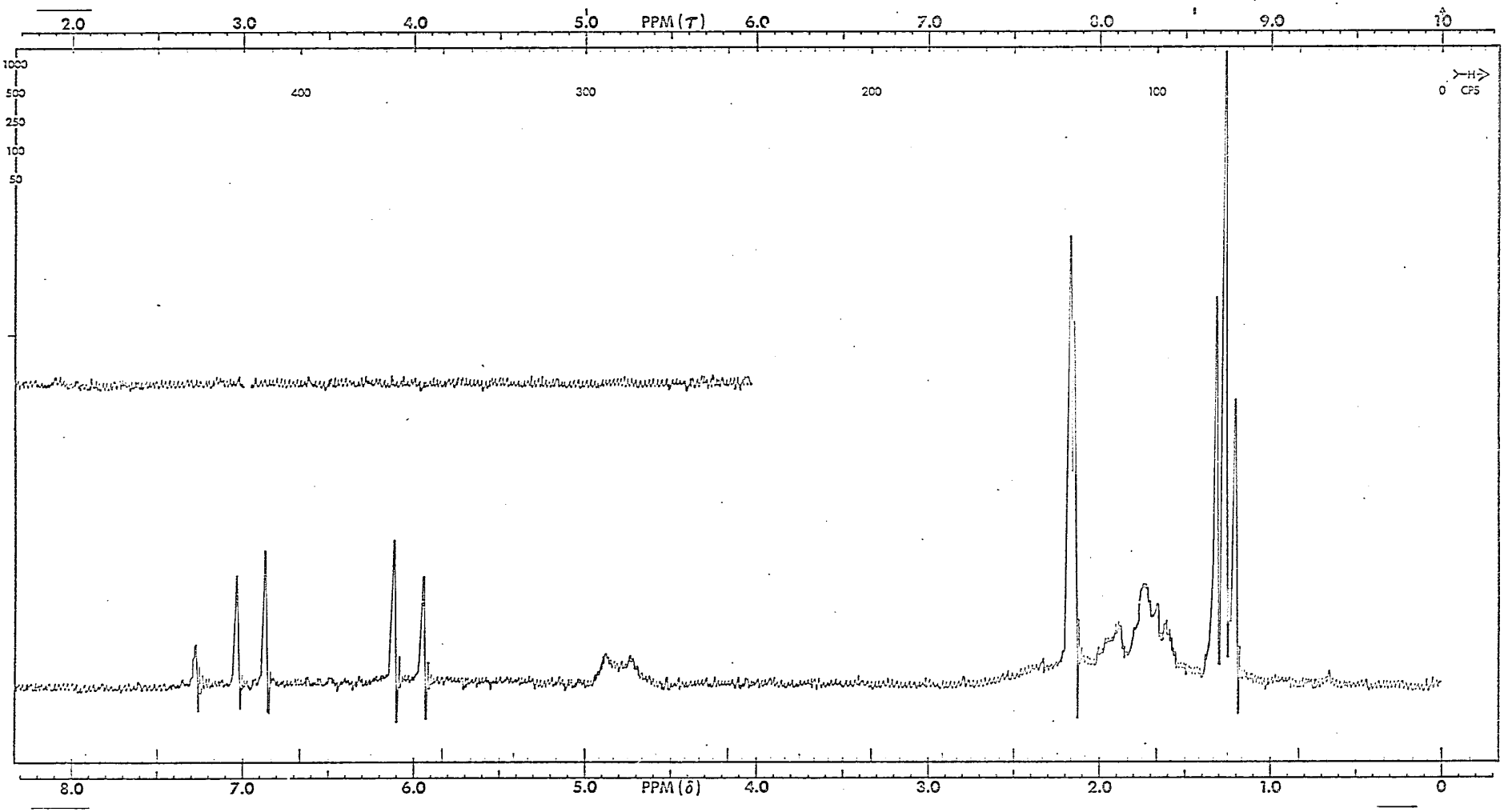
100
50
400
300
200
100
0 CPS
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

Figure 6.

The n.m.r. spectrum of santonin oxime (2).


2.0
3.0
4.0
5.0
PPM (τ)
6.0
7.0
8.0
9.0
10
1000
500
250
100
50
400
300
200
100
0 CPS
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

The double bond at C-1 has also disappeared, as the AB system due to the pair of olefinic protons in 1 and 2 in the low-field region of the spectrum is absent from the spectrum of hydroxylaminosantonin oxime-α.

Further evidence against structure I came from studies of exchangeable hydrogen atoms in the compound. In the presence of D_2O, only two protons exchanged, whereas the structure I would have three exchangeable protons. The exchanges were shown by the disappearance of (a) a sharp singlet at 10.42 p.p.m. assigned as in 2 to the oxime proton, and (b) a broad peak at 7.07 p.p.m. assigned to an NH proton.

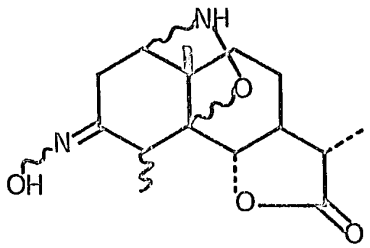
(b) O,N-Dibenzoyl Derivative of Hydroxylamino-santonin Oxime-α.

The two exchangeable hydrogens of hydroxylamino-santonin oxime-α were replaced by benzoyl groups in the formation of a dibenzoyl derivative by reaction with benzoyl chloride in pyridine. The oily product from the reaction resisted all attempts to crystallise it from ethanol and methanol-water mixtures. However, minute crystals were obtained in about 10% yield from ether solution after several weeks in the refrigerator, m.p. 175-178°.

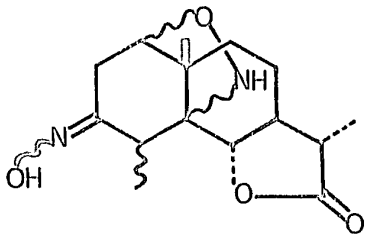
This dibenzoyl compound had no exchangeable protons in its n.m.r. spectrum (Fig. 7, and table 1). Further, its infra-red spectrum showed no OH or NH stretching bands, but instead had an O-benzoyl carbonyl band at 1750 cm^{-1} and an N-benzoyl (amide-I) band at 1640 cm^{-1}.

It is evident that apart from its oxime proton, hydroxylaminosantonin oxime-α contains only one active hydrogen, and that this hydrogen is attached to nitrogen and not to oxygen. Hence the hydroxylamino group must be O,N-disubstituted.

The presence of an —NH—O— (epoxyimino) group in, and the absence of the two original olefinic double bonds from, hydroxylaminosantonin oxime-α is evidence for the structure XXI or XXII for the compound.



XXI



XXII

Each of these structures corresponds to eight

Figure 7.

The n.m.r. spectrum of O,N-dibenzoylhydroxyl-aminosantonin oxime-α (4).

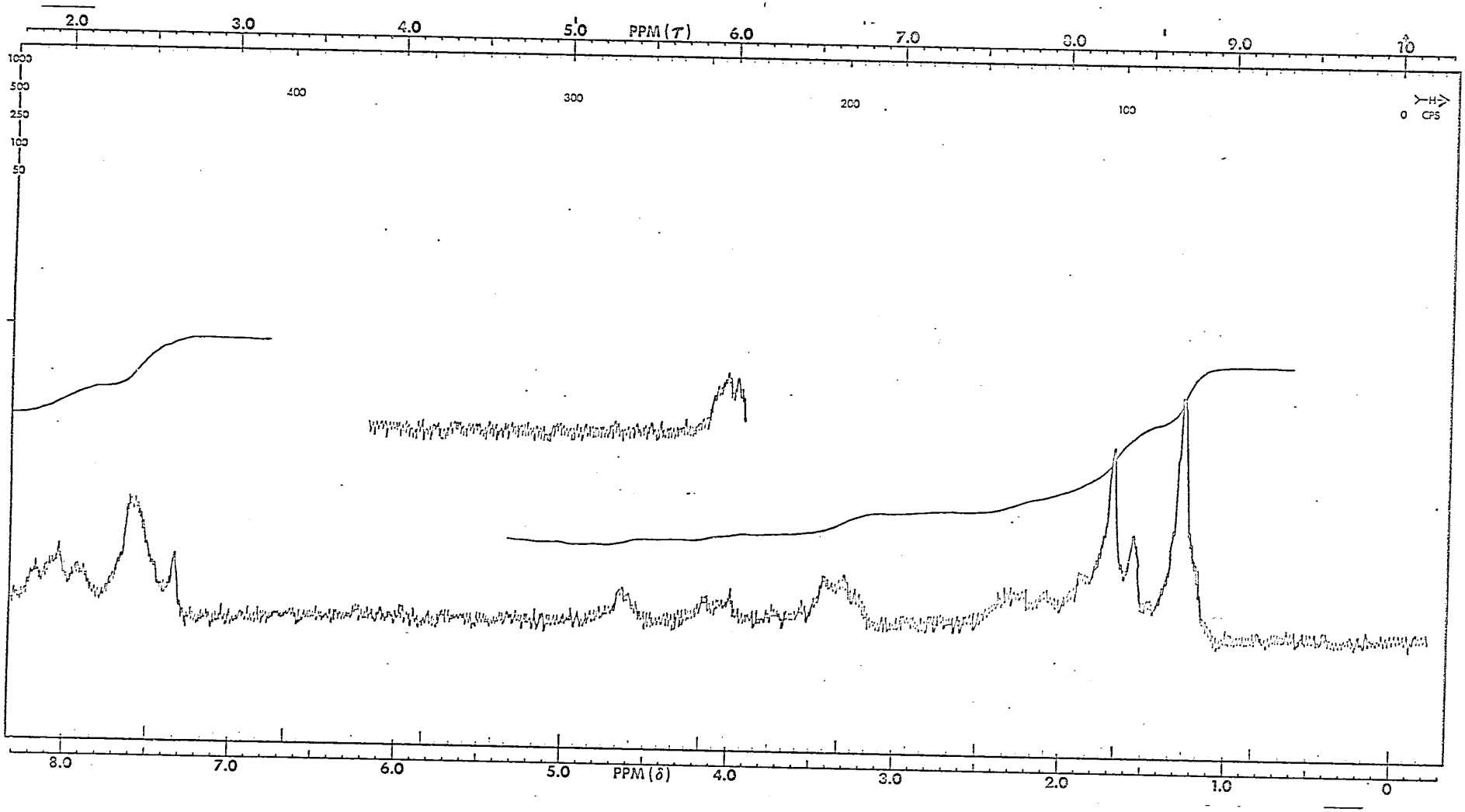
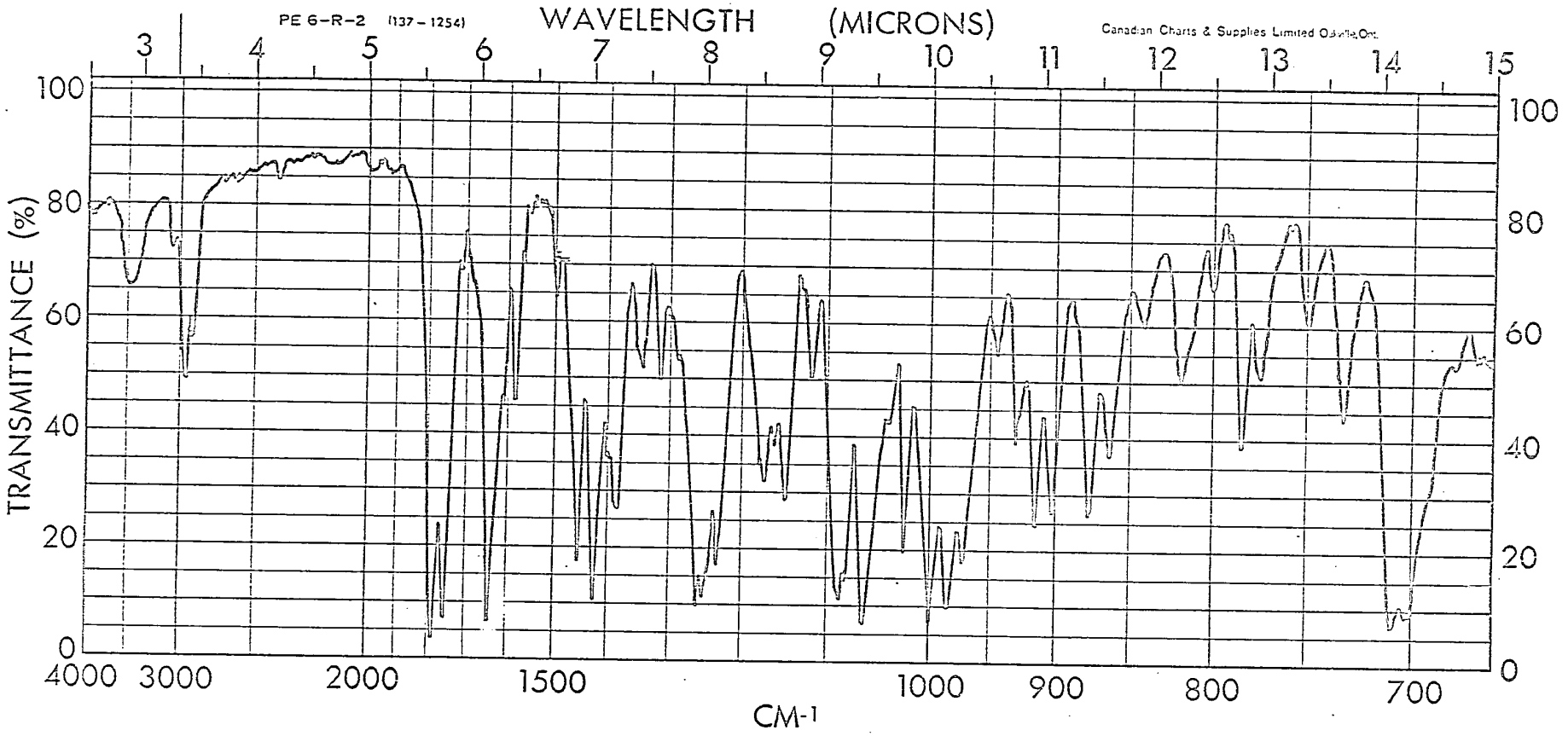

2.0
3.0
4.0
5.0
PPM (τ)
6.0
7.0
8.0
9.0
10
1000
500
250
100
50
400
300
200
100
0 CPS
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

Figure 8.

The infra-red spectrum of O,N-dibenzoyl-hydroxylaminosantonin oxime-α (4).


PE 6-R-2 (137-1254)
WAVELENGTH (MICRONS)
Canadian Charts & Supplies Limited Oakville, Ont.
3
4
5
6
7
8
9
10
11
12
13
14
15
100
80
60
40
20
0
TRANSMITTANCE (%)
4000
3000
2000
1500
1000
900
800
700
CM-1

possible isomers. It is shown in the sequel that in fact, hydroxylaminosantonin oxime-α is represented by 3 (chart 1), one of the isomers of XXI.

(c) Hydroxylaminosantonin Oxime-β.

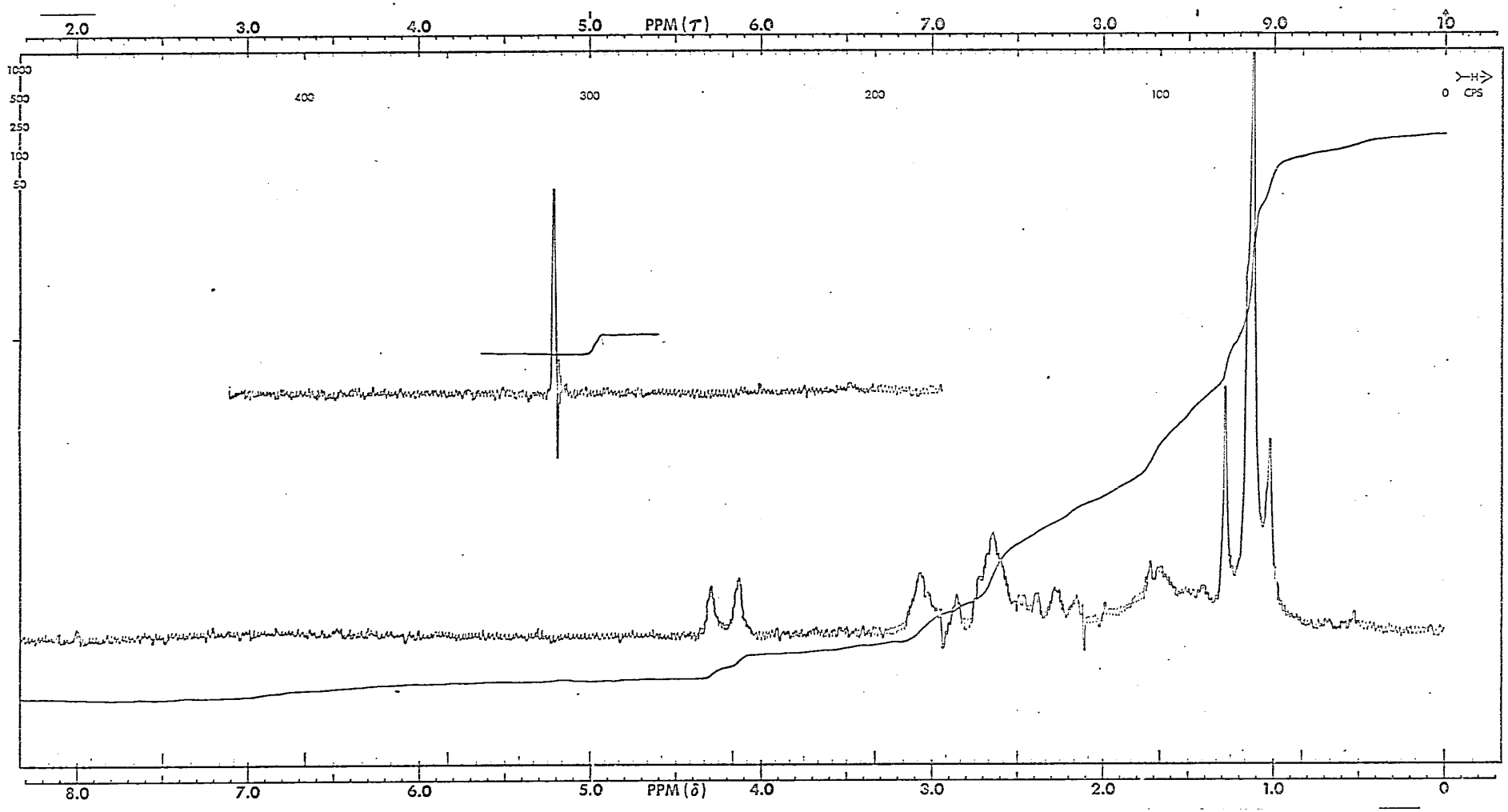
Hydroxylaminosantonin oxime-β was prepared by reaction of santonin with four molar equivalents of hydroxylamine in methanol to which was added a 0.4 molar excess of hydroxylamine hydrochloride, according to the method of Francesconi and Cusmano (3).

The product was obtained as colourless needles m.p. 232-233°, $[\alpha]_D^{25}$ 0.00, (lit. m.p. 232-233°, $[\alpha]_D^{12}$ - 3.0°). A procedure giving better yields is described in the experimental.

The ultraviolet absorption spectrum of this compound showed that, like the α-isomer, it had no double bonds in conjugation with the oxime grouping. The n.m.r. spectrum (Fig. 9 and table 1) was also very similar to that of the α-isomer, and showed the presence of two exchangeable protons. This was confirmed by examination of the dibenzoyl derivative (14) reported by Francesconi and Cusmano (3), which had no exchangeable protons in its n.m.r.

Figure 9.

The n.m.r. spectrum of hydroxylaminosantonin oxime-β (13).


2.0
3.0
4.0
5.0
PPM (τ)
6.0
7.0
8.0
9.0
10
1000
500
250
100
50
400
300
200
100
0 CPS
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

spectrum (Fig. 10 and table 1).

The infra-red spectrum (Fig. 11) also was very similar to that of the α-isomer, except that the OH stretching region was much more complex, indicating possibly a mixture of syn- and anti- oximes in this case, and a single geometrical isomer in the case of the α-isomer.

T.l.c. studies of the two compounds also indicated that the α-isomer was homogeneous and that the β-isomer was a mixture of two compounds, possibly geometrical isomers. Thus the α-isomer gave a single spot (R_f (b) 0.50) while the β-isomer gave two overlapping spots centered at the same point (R_f (b) 0.50) as the α-isomer.

These results indicate that the β-isomer, like the α-isomer, may have the structures XXI or XXII. In the sequel it is shown that it is the C-4 epimer 13 of the α-compound 3 (chart 1).

4. De-oximation of Hydroxylaminosantonin Oximes-α and -β.

(a) Levulinic Acid Treatment of Hydroxylaminosantonin Oximes-α and -β.

The isomerism of the hydroxylaminosantonin oximes-α

Figure 10.

The n.m.r. spectrum of O,N-dibenzoylhydroxylaminosantonin oxime-β (14).

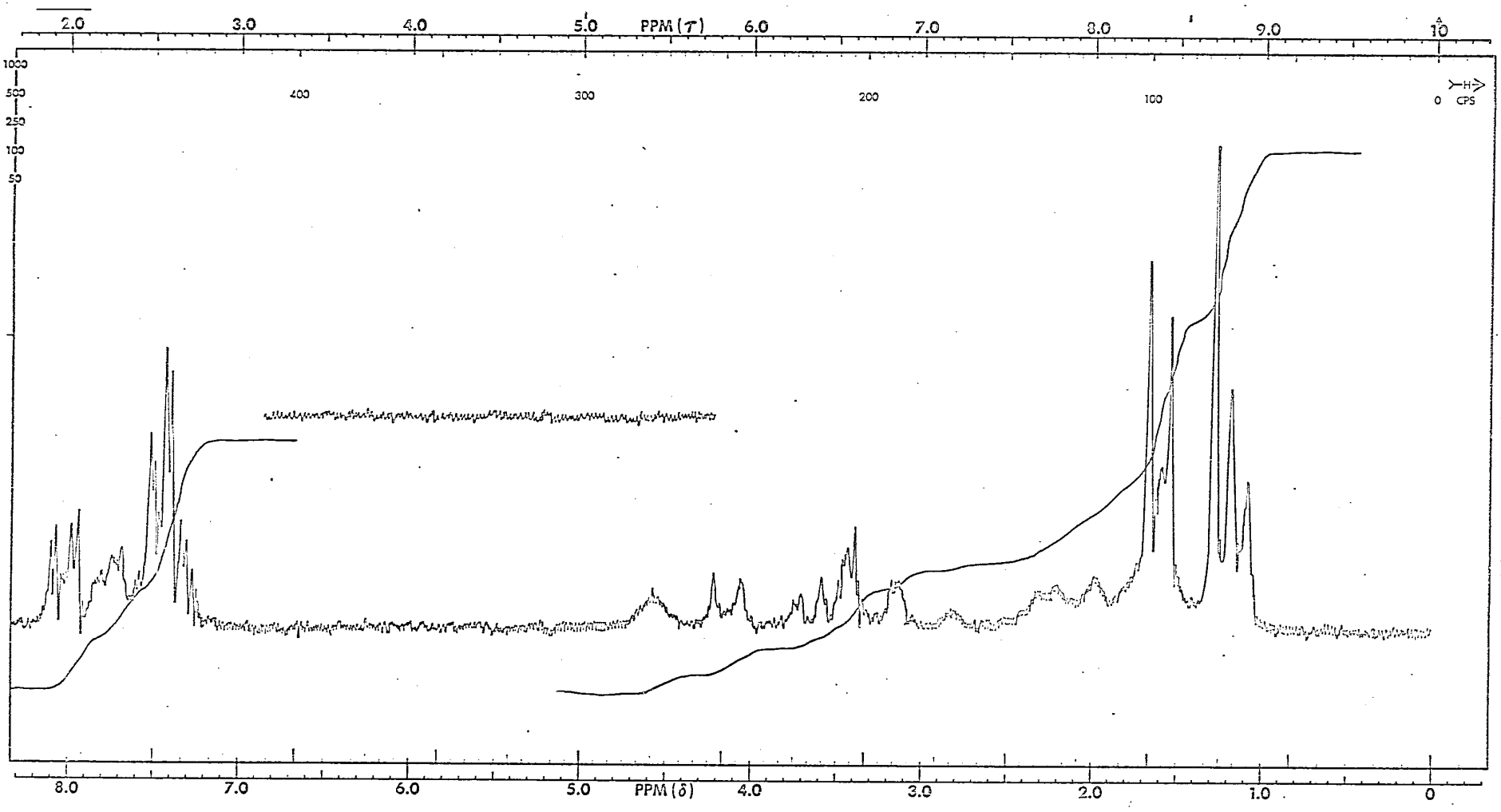

2.0
3.0
4.0
5.0
PPM (τ)
6.0
7.0
8.0
9.0
10
1000
500
250
100
50
400
300
200
100
0 CPS
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

Figure 11.

The infra-red spectrum of hydroxyl-aminosantonin oxime-β (13).

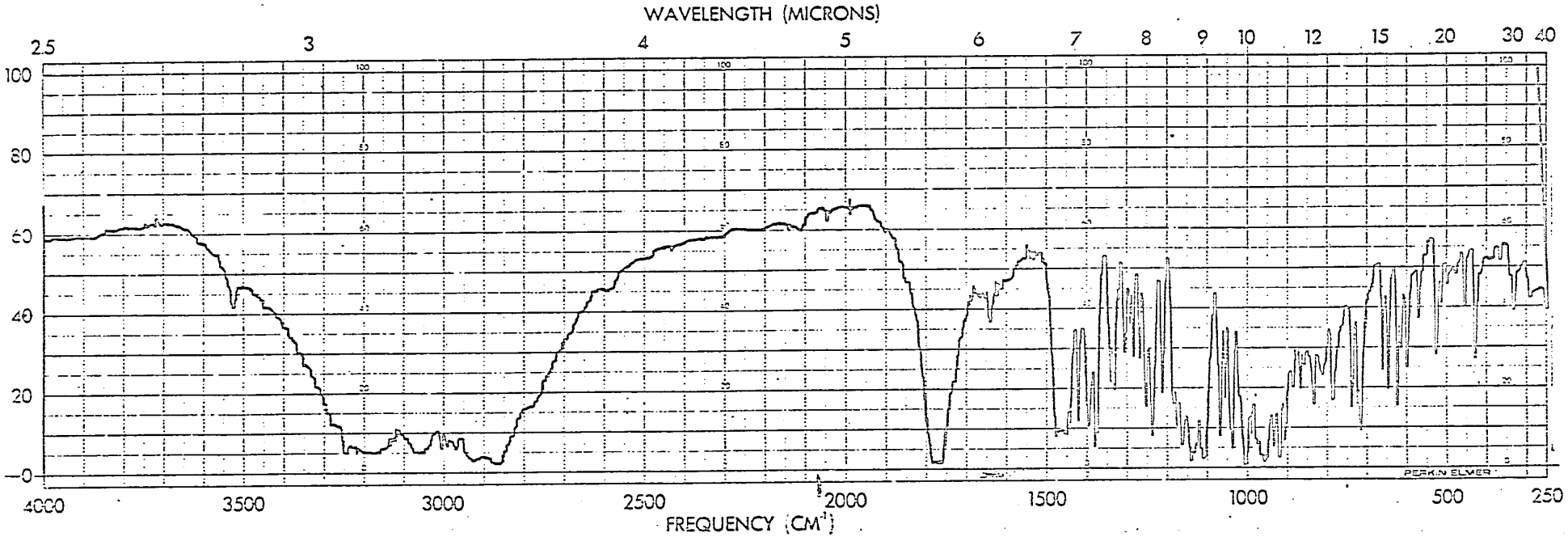
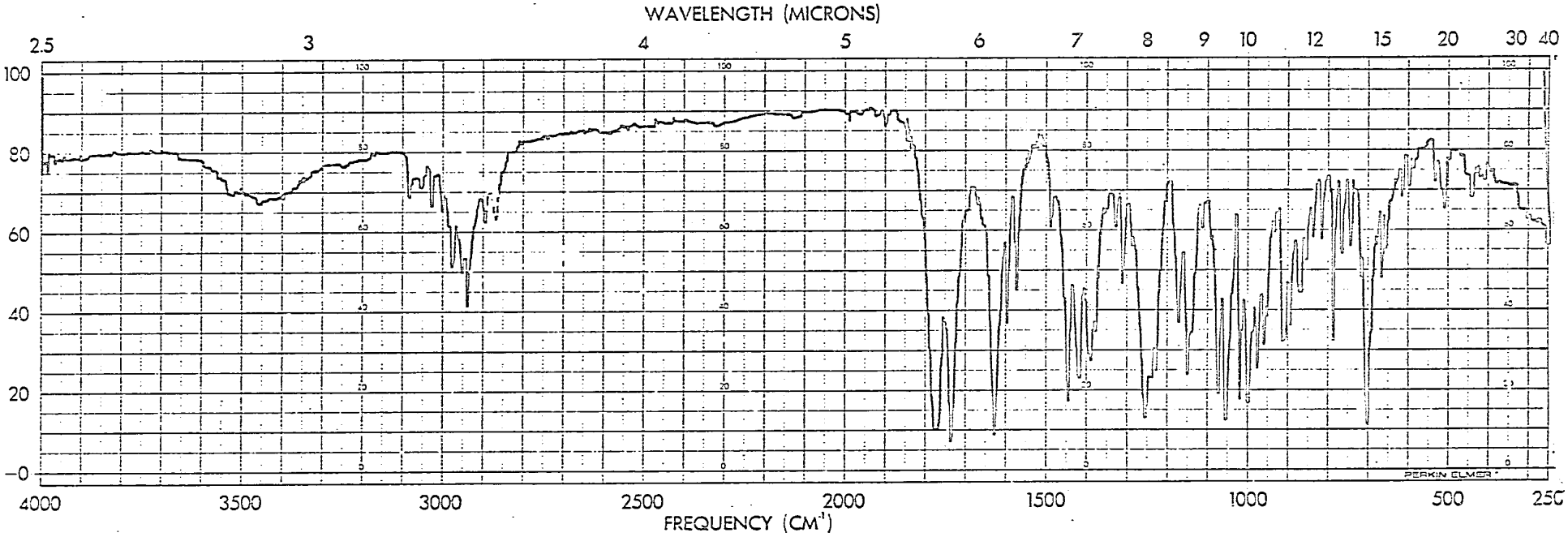

WAVELENGTH (MICRONS)
2.5
3
4
5
6
7
8
9
10
12
15
20
30
40
100
80
60
40
20
0
4000
3500
3000
2500
2000
1500
1000
500
250
FREQUENCY (CM⁻¹)
PERKIN ELMER

Figure 12.

The infra-red spectrum of O,N-dibenzoyl-hydroxylaminosantonin oxime-β (14).


WAVELENGTH (MICRONS)
2.5
3
4
5
6
7
8
9
10
12
15
20
30
40
100
80
60
40
20
0
4000
3500
3000
2500
2000
1500
1000
500
250
FREQUENCY (CM-1)
PERKIN ELMER

and -β could conceivably be due only to different configurations of the oxime grouping. Consequently, attempts were made to remove this grouping under conditions mild enough not to affect the rest of the molecule. The levulinic acid reagent (90% levulinic acid and 10% 1 N hydrochloric acid) of de Puy and Ponder (23) was first tried. However, this caused the loss of the epoxyimino group and the formation of santonin oxime (2) from both the α- and β-isomers. The mechanism of this reaction is not known but it is not simply an acid-catalysed elimination, since the hydroxylamino compounds are stable in hydrochloric acid alone.

(b) Sodium Bisulphite De-oximation of Hydroxylaminosantonin Oximes-α and -β.

De-oximation with sodium bisulphite (3½ molar equivalents) in aqueous ethanol (24,25) followed by decomposition of the intermediate bisulphite complex with excess dilute hydrochloric acid was next tried. Reaction of the α-isomer was rapid, and t.l.c. analysis showed the disappearance of the starting material and the appearance of small amounts of santonin (1) R_f (a) 0.70, and two new compounds R_f (a) 0.24, and R_f (a) 0.00.

Chloroform extraction of the acidified reaction

mixture gave only santonin, indicating that the epoxyimino group is, in fact, eliminated to a small extent, and that de-oximation is taking place. Any ketones with the epoxy-imino bridge that are produced (e.g. 6, 15) would dissolve in dilute hydrochloric acid and therefore would not be extractable with chloroform. The acidified reaction mixture in fact showed two spots on t.l.c. analysis, one, R_f (a) 0.70 due to santonin, and the other, R_f (a) 0.00, due to the hydrochloride salt of 6.

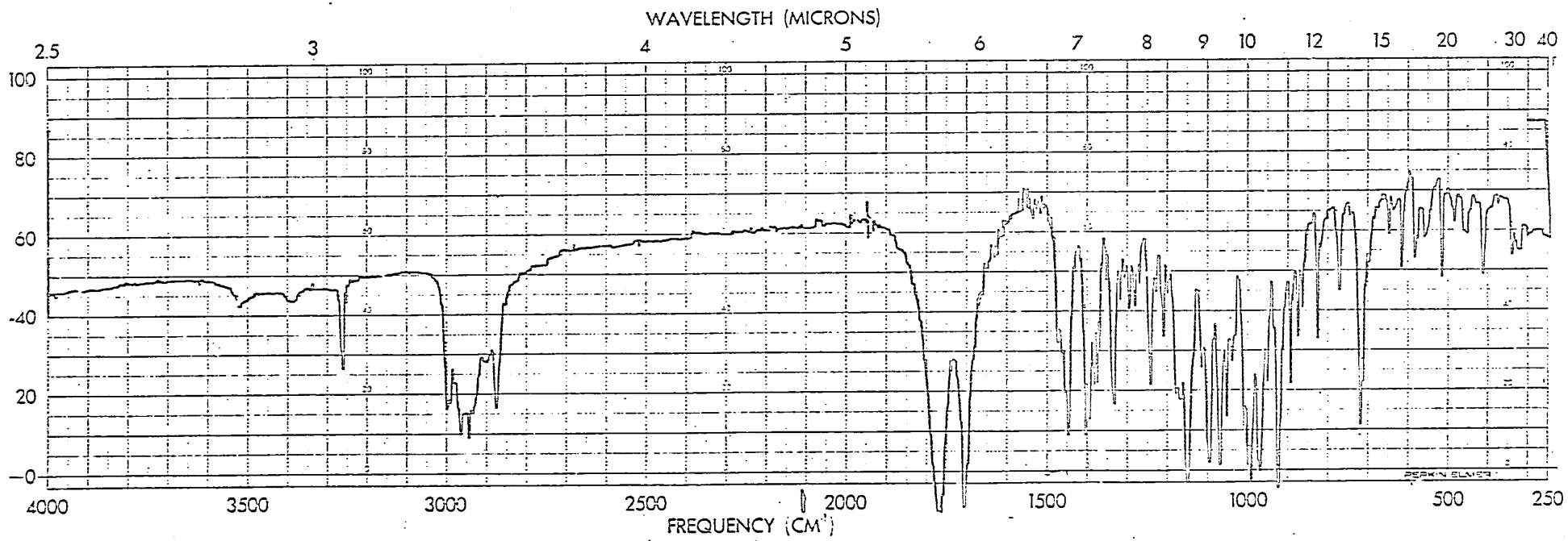
Neutralisation of the acidified reaction mixture with bicarbonate liberated a ketone $C_{15}H_{21}NO_3$ which was extracted with chloroform and crystallised from 96% ethanol, m.p. 190°, $[\alpha]_D^{25}$ + 13.9°.

The infra-red spectrum (Fig. 13) of this ketone showed two carbonyl stretching bands, at 1775 cm^{-1} due to the lactone, and 1710 cm^{-1}, typical of a saturated six-membered cyclic ketone, and a sharp NH stretching band at 3260 cm^{-1}, but showed no OH stretching band. This shows that the nitrogen ($C_{15}H_{21}NO_3$) comes from the epoxyimino and not from the oxime group of the starting material.

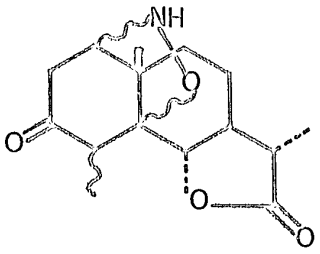
The ultraviolet absorption spectrum had λ_{max} 294 $m\mu$, ϵ_{max} 17, assigned to the n—π^* transition of the carbonyl

Figure 13.

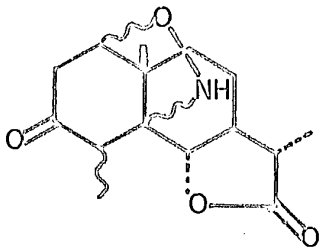
The infra-red spectrum of
5,1-(α-epoxyimino)-4α-tetrahydrosantonin (6).


WAVELENGTH (MICRONS)
2.5
3
4
5
6
7
8
9
10
12
15
20
30
40
100
80
60
40
20
0
4000
3500
3000
2500
2000
1500
1000
500
250
FREQUENCY (CM⁻¹)
PERKIN ELMER

group. This spectrum confirms the observation made above from the I.R. data, that the carbonyl group is unconjugated. The data show that $C_{15}H_{21}NO_3$ has the structure XXIII or XXIV, resulting from the deoximation of XXI or XXII. The



XXIII



XXIV

results in the sequel show that in fact the compound has the structure 6 (chart 1). The n.m.r. data which serve to confirm the stereochemistry shown in 6, are discussed later on p.91

(c) Sodium Bisulphite De-oximation of Hydroxylaminosantonin Oxime-β.

Reaction of hydroxylaminosantonin oxime-β with aqueous ethanolic sodium bisulphite gave initially a more complex reaction mixture. T.l.c. analysis showed starting material (R_f (a) 0.35), santonin (R_f (a) 0.70), and three other spots (R_f (a) 0.00; 0.24; and 0.55). The last spot

was not given by the reaction products of the α-isomer. The reaction was complete in three hours. The major product obtained on working up as described above proved to be the same epoxyimino ketone (6) as was obtained from the α-isomer.

T.l.c. analysis of the mother liquors from the crystallisation of (6) showed that the new compound R_f (a) 0.55, constituted about 15% of the mixture. However, addition of a small amount of sodium methoxide to the mother liquors resulted in the complete disappearance of the spot R_f (a) 0.55 from the t.l.c. analysis of the mixture, though the R_f values of the other spots remained unchanged. This method of analysis was not sufficiently sensitive to detect any change in intensity of the spot (R_f (a) 0.24) due to the major component (6).

The conversion of both the α- and β-isomers to the same epoxyimino ketone XXIII or XXIV by removal of the oxime group indicated that they both had the epoxyimino bridge attached to the same positions of the santonin skeleton, XXI or XXII, and that they both had the same configuration at the bridgeheads. The formation of santonin identified by comparison with an authentic specimen, in the de-oximation reaction of both the α- and β-isomers indicated that no

changes had taken place in the stereochemistry of the lactone ring during their formation from santonin and hydroxylamine.

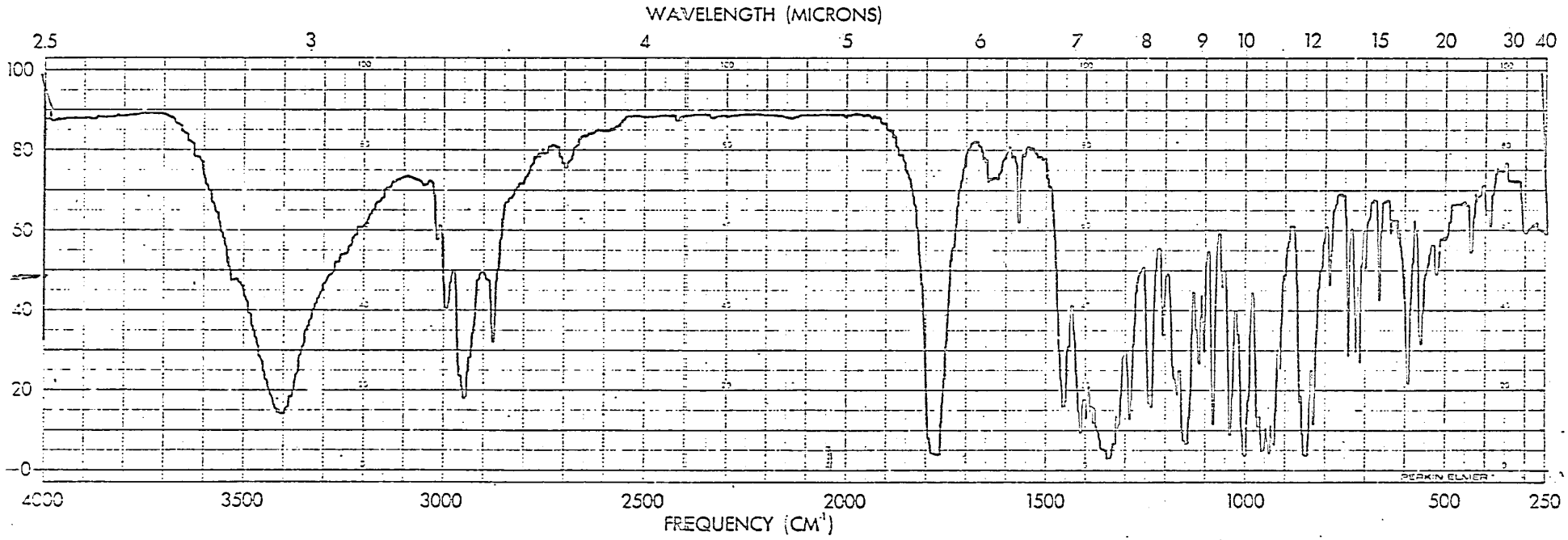
The difference between them must therefore reside either in the configuration at C-4 or in the configuration (syn or anti) of the oxime grouping (or both): the latter difference is removed by de-oximation, and the C-4 methyl group is capable of easy epimerisation. The results show that this methyl group is in the less stable configuration in hydroxylaminosantonin oxime-β, whose structure is shown to be 13 in the sequel. (The ketone (15) initially formed on de-oximation of the β-isomer gives rise to the spot of R_f (a) 0.55; this ketone (15) is obviously less stable than its epimer (6) so that the spot disappears when the solution is made alkaline).

5. Nitroso Derivative of Hydroxylaminosantonin Oxime-α.

Hydroxylaminosantonin oxime-α (3), treated with one equivalent of nitrous acid in the cold as described by Francesconi and Cusmano (3) gave a nitroso compound in good yield as minute faintly yellow needles, $C_{15}H_{21}N_3O_5$ m.p. 164-165°, $[\alpha]_D^{25}$ - 112.9°, which gave a single spot on t.l.c. analysis. (This compound was shown eventually to have the structure 7).

Figure 14.

The infra-red spectrum of the nitroso derivative of hydroxylaminosantonin oxime-α, (7).


WAVELENGTH (MICRONS)
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60
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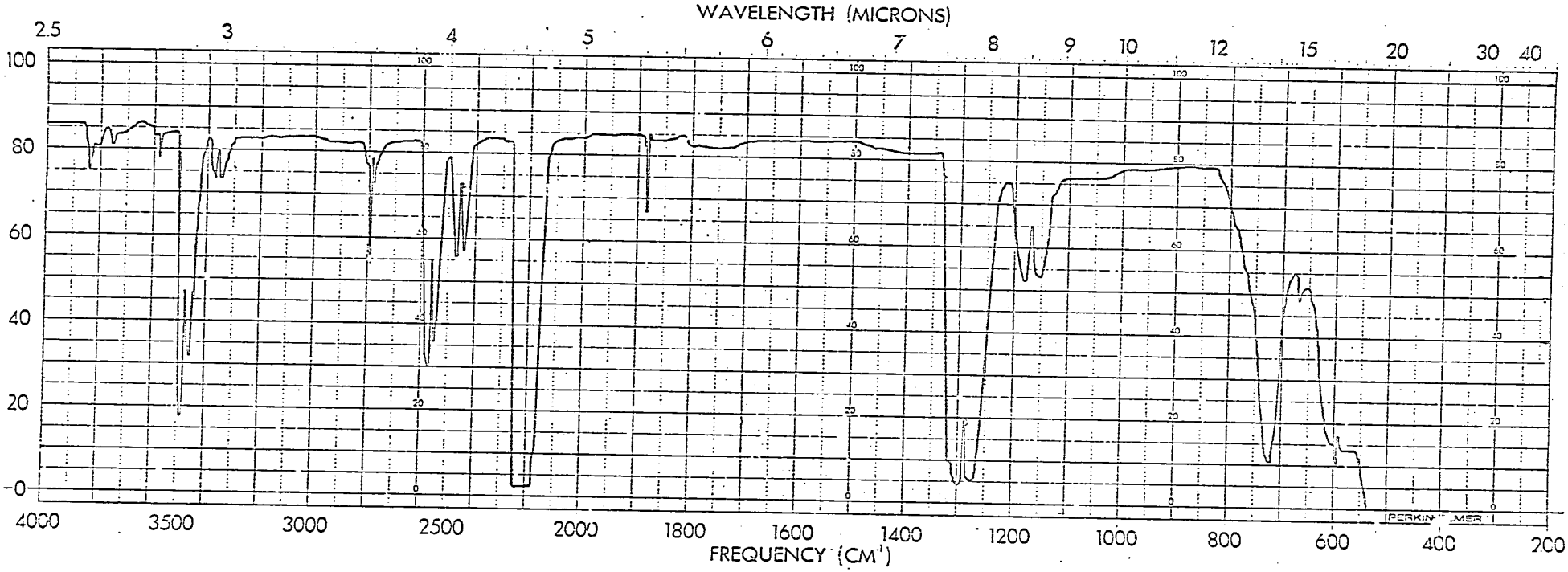
4000
3500
3000
2500
2000
1500
1000
500
250
FREQUENCY (CM-1)
PERKIN ELMER

The infra-red spectrum (Fig. 14) of this compound showed that the nitrous acid had reacted with the NH of the epoxyimino group, and not with the oxime grouping (to give a nitrimmine (13, 14)). It showed strong OH absorption at 3525 cm^{-1}, a single sharp carbonyl band at 1775 cm^{-1}, a strong band at 1350 cm^{-1} assigned to the N=O stretching vibration, and a weak band at 1630 cm^{-1} assigned to the C=N stretching mode of the oxime group. The origin of the weak band at 1570 cm^{-1} is not known. Apparently it is not an artefact as it occurred in the spectra of different batches of the nitroso compound crystallised from a variety of solvents and occurs also in the spectrum of the nitroso derivative of the β-isomer described below. There were no NH stretching bands.

That the reaction —O—NH— ⟶ —O—N—N=O had taken place was further indicated by the ultraviolet absorption spectrum. The compound had λ_{max} 246 mμ, ϵ_{max} 7,650 (cf. dimethylnitrosamine, λ_{max} 232 mμ, ϵ_{max} 5,900 (26)). If the oxime group had reacted to give a nitrimmine, a strong absorption at 270 mμ would be expected (13,14).

Figure 15.

The infra-red spectrum of the gas evolved (N_2O) in the decomposition of the nitroso derivative (7) of hydroxylaminosantonin oxime-α.


WAVELENGTH (MICRONS)
2.5
3
4
5
6
7
8
9
10
12
15
20
30
40
100
80
60
40
20
0
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
400
200
FREQUENCY (CM⁻¹)
PERKIN ELMER

(a) Decomposition of Nitroso Derivative of Hydroxylaminosantonin Oxime-α (7): Formation of 3-anti-Oximino-5,10-(α-epoxy)-1β,4α-hexahydrohyposantonin (8).

The nitroso compound (7) when heated with 50% acetic acid for ten minutes, slowly evolved a colourless gas which was collected in a trap at -190°. The I.R. spectrum (Fig. 15) of the gas was identical to that of an authentic sample of N_2O, in the literature (27). The reaction mixture, on addition of water, deposited fine white crystals. These were recrystallised from aqueous methanol, giving a 70% yield of colourless prisms, $C_{15}H_{21}NO_4$, m.p. 199-201°, $[\alpha]_D^{25}$ + 220°, agreeing in its properties with the compound isolated by Francesconi and Cusmano (3) for which Simonsen and Barton (4) have proposed structure III (p. 4).

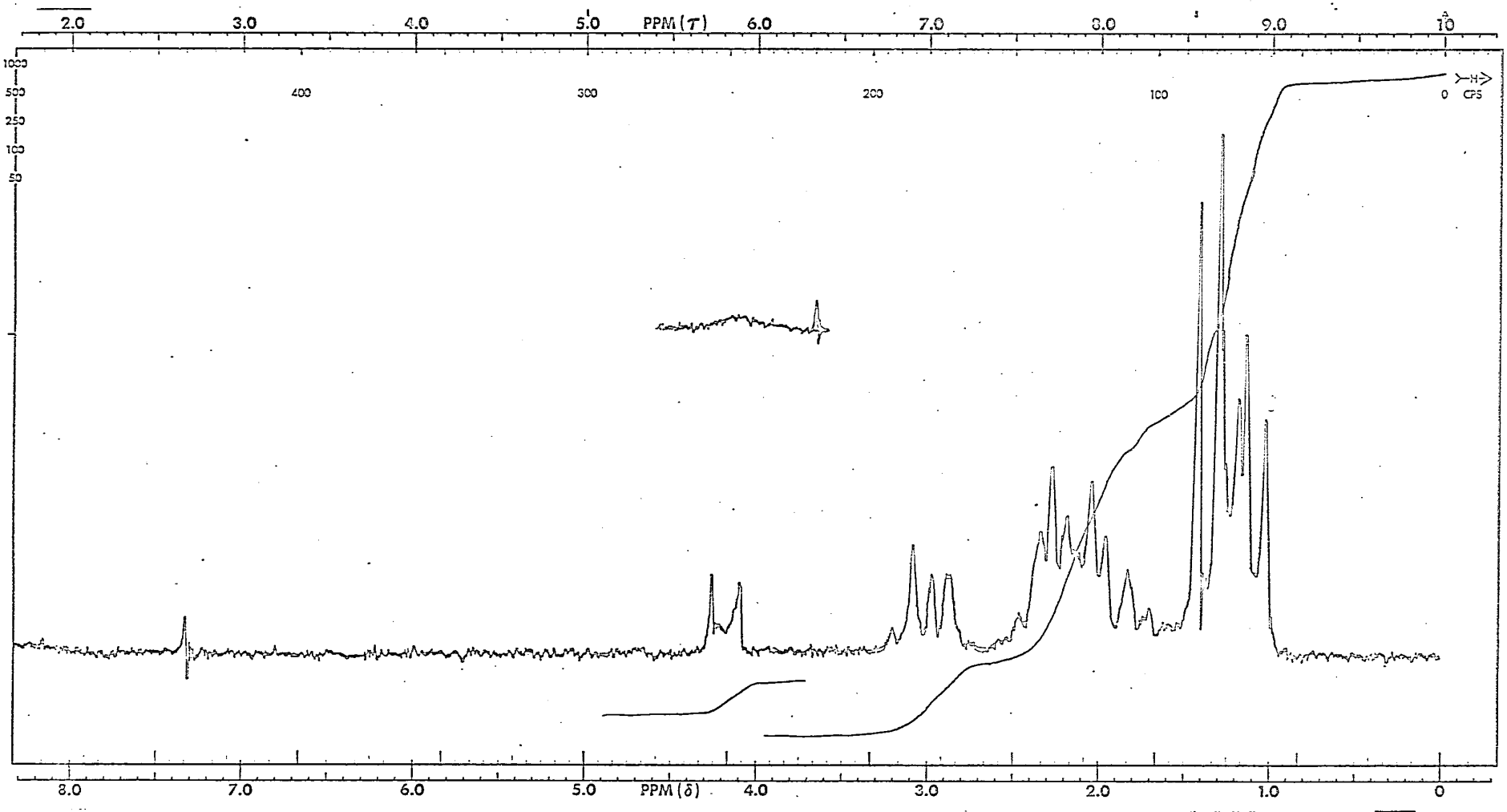
This structure can be eliminated, since the ultraviolet absorption spectrum showed no peak above 200 mμ. The n.m.r. spectrum (Fig. 16 and table 2) was most informative. It showed all three methyl groups as doublets at 1.35 p.p.m., (J = 7 c.p.s.), 1.23 p.p.m., (J = 6.0 c.p.s.), and 1.09 p.p.m., (J = 6.5 c.p.s.). This is possible only if the angular methyl group has migrated from the 10-

Figure 16.

The n.m.r. spectrum of 3-anti-oximino-5,10-(α-epoxy)-1β,4α-hexahydrohyposantonin (8).

(a) Deuterochloroform.

(b) Benzene.


2.0
3.0
4.0
5.0
PPM (τ)
6.0
7.0
8.0
9.0
10
1000
500
250
100
50
400
300
200
100
0 CPS
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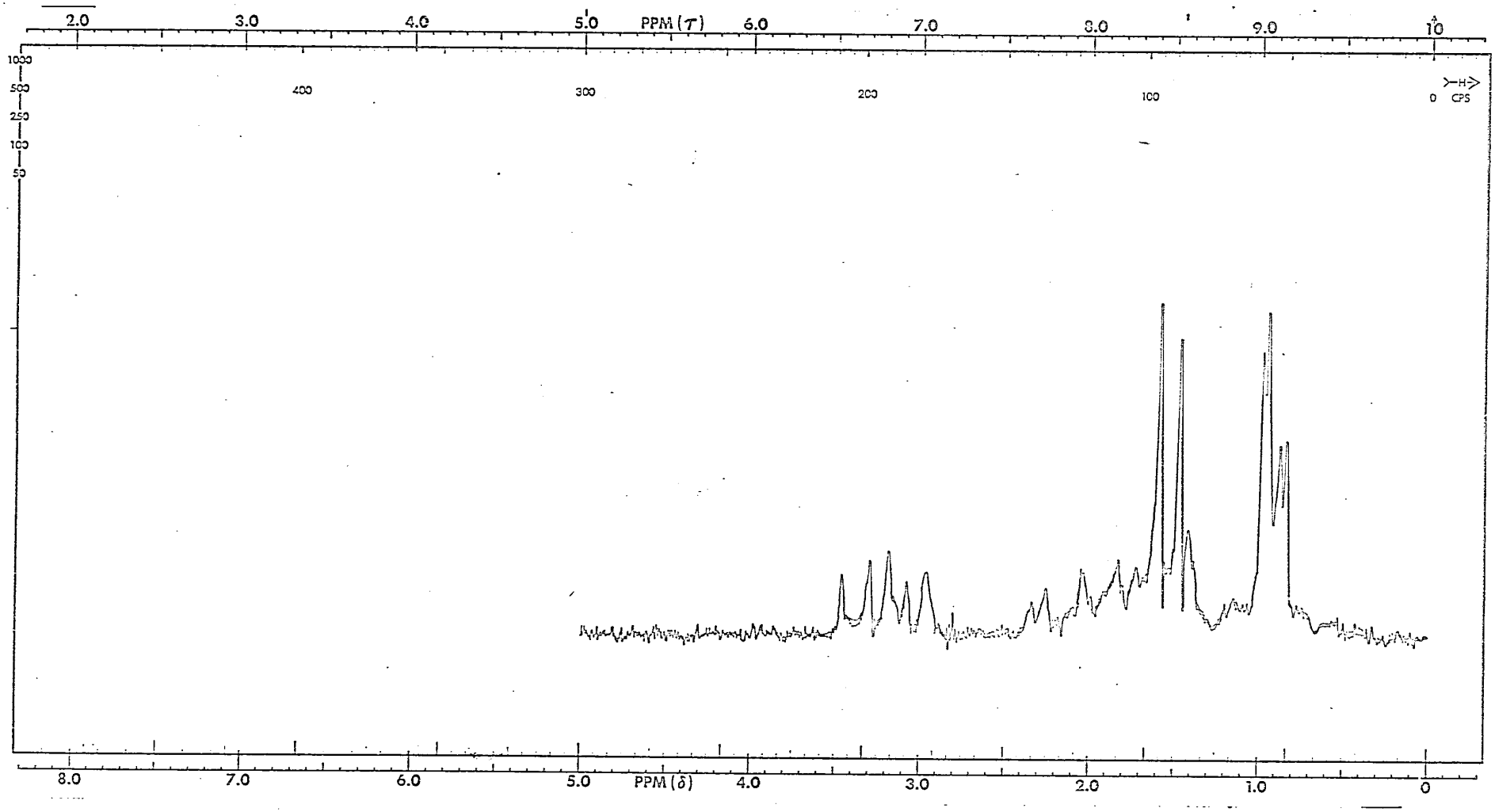
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0


2.0
3.0
4.0
5.0
PPM (τ)
6.0
7.0
8.0
9.0
10
1000
500
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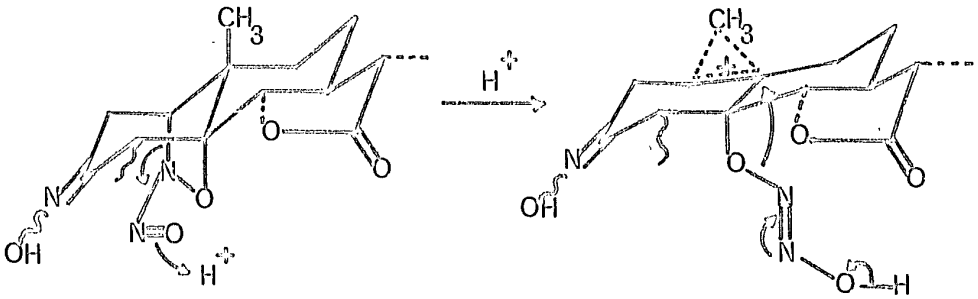
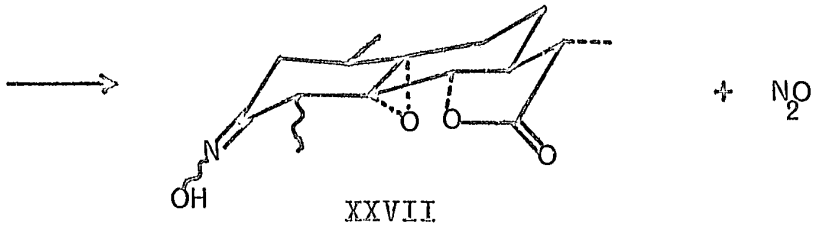
100
50
400
300
200
100
0 CPS
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

position to the 1- position. This in turn suggests the formula XXV for the nitroso compound in which the nitrosamine group is axial and trans to the C-10 methyl group;



XXV XXVI



XXVII

only this arrangement permits an easy migration of the methyl group from the 10- to the 1- position, by the mechanism shown (XXV-XXVII). The position of the methyl group on carbon atom 1 is confirmed by further reactions (7 → 8 → 11 → 12) of the denitrosated product, discussed later.

This rearrangement precludes all formulae based

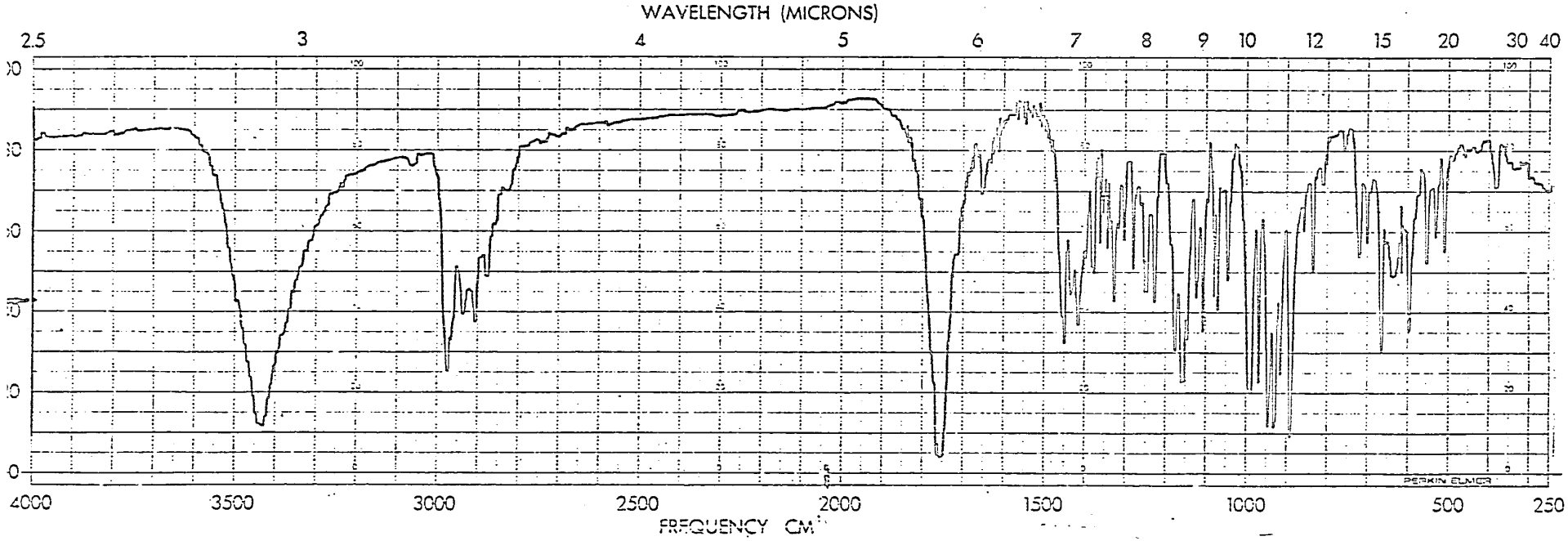
on structures XXII, or on structure XXI having the epoxyimino bridge β- to the original tricyclic system. Hydroxylaminosantonin oxime-α therefore has the 5,1-(α-epoxyimino) grouping. (As the α- and β-isomers of hydroxylaminosantonin oxime have been converted to the same epoxyimino-ketone (6) it follows that the epoxyimino grouping in the β-isomer is also 5,1- linked and α- to the original tricyclic system. This was confirmed by a study of the β-nitroso compound discussed later).

The second respect in which Barton and Simonsen's formula requires revision concerns the nature of the function containing the fourth oxygen atom of the denitrosated product $C_{15}H_{21}NO_4$, (XXVII). The n.m.r. spectrum shows that apart from the C-6 proton (4.18 p.p.m.) and the oxime proton (8.75 p.p.m.) there are no other protons resonating below 3.5 p.p.m., and that the oxime proton is the only one exchangeable with D_2O. The spectrum thus indicates that only one of the four oxygen atoms is a free hydroxyl group, i.e. the oxime hydroxyl. The fourth oxygen atom must therefore form part of a heterocyclic ring.

The infra-red spectrum of the compound (Fig. 17) showed OH absorption from the oxime grouping at 3440 cm^{-1} of about the same intensity as that of the nitroso compound

Figure 17.

The infra-red spectrum of 3-anti-oximino-5,10-(α-epoxy)-1β,4α-hexahydrohyposantonin (8).


WAVELENGTH (MICRONS)
2.5
3
4
5
6
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8
9
10
12
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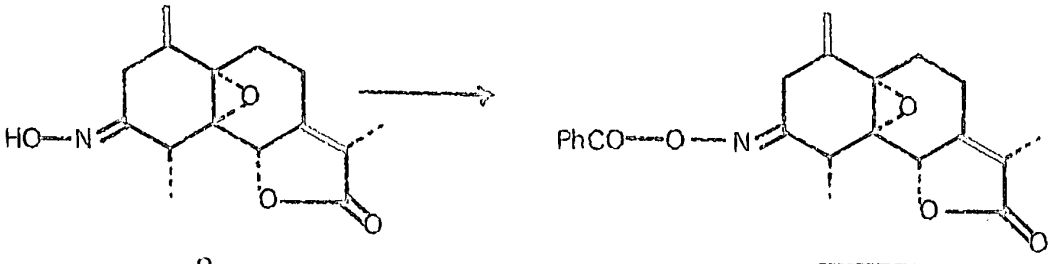
20
30
40
4000
3500
3000
2500
2000
1500
1000
500
250
FREQUENCY CM⁻¹
PERKIN ELMER

(7), a lactone carbonyl at 1760 cm^{-1} and a weak band at 1653 cm^{-1} assigned to the C=N stretching vibration of a saturated oxime. This also would be inconsistant with the presence of two hydroxyl groups in the molecule.

(b) 3-anti-Benzoyloximino-5,10-(α-epoxy)-1β, 4α-hexahydrohyposantonin (XXVIII).

The same conclusions as above came from studies of the infra-red and n.m.r. spectra of the monobenzoate of the rearranged product 8, prepared in the usual way.

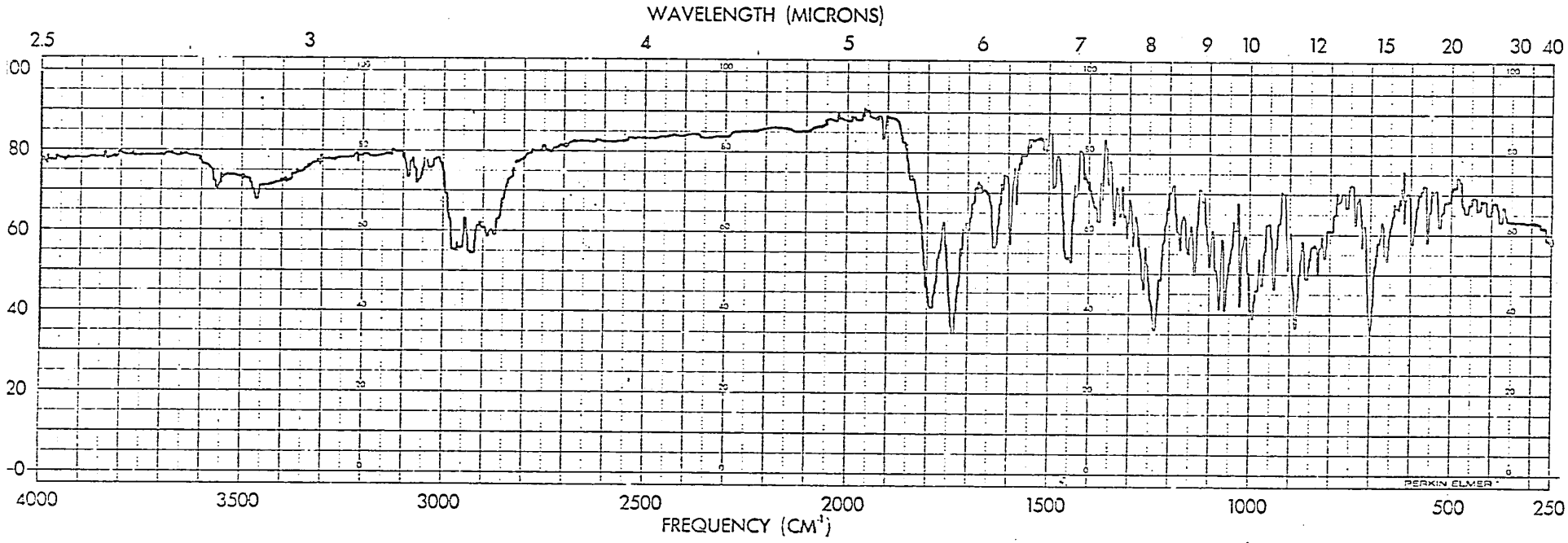


8 XXVIII

This benzoate (XXVIII), m.p. 134-138°, gave a single spot (R_f (a) 0.75) on t.l.c. analysis. Its I.R. spectrum (Fig. 18) showed no OH absorption, but had carbonyl absorption at 1775 (s) and 1738 (s) cm^{-1}, assigned to the lactone and oxime benzoate carbonyl groups. A band at 1620 cm^{-1} was assigned to the C=N stretching mode, shifted 33 cm^{-1} to longer wavelength from the same

Figure 18.

The infra-red spectrum of 3-anti-benzoyloximino-5.10-(α-epoxy)-1β,4α-hexahydrohyposantonin (XXVIII).


WAVELENGTH (MICRONS)
2.5
3
4
5
6
7
8
9
10
12
15
20
30
40
00
80
60
40
20
-0
4000
3500
3000
2500
2000
1500
1000
500
250
FREQUENCY (CM-1)
PERKIN ELMER

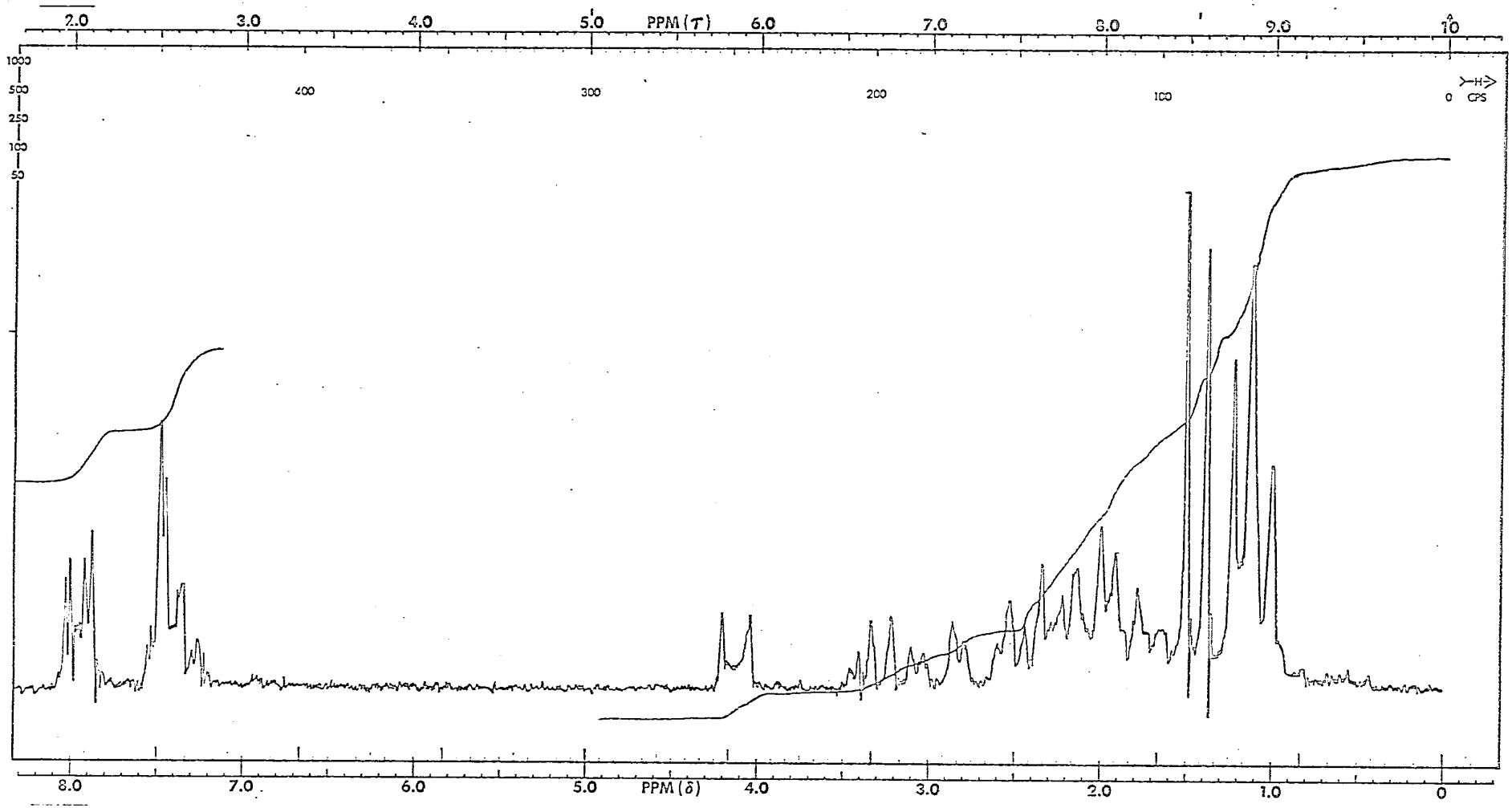
band in the unsubstituted oxime.

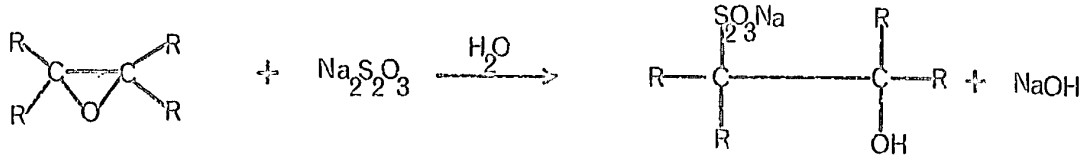
The n.m.r. spectrum (Fig. 19) was similar to that of the parent oxime 8, except that it had no exchangeable protons. A second hydroxyl group and an olefinic double bond being excluded by the spectral data, the analysis permits only a cyclic ether function for the fourth oxygen atom of the de-nitrosated product. The only plausible formulation with such a function is an epoxide, as in XXVII. The mechanism shown (XXV —> XXVI —> XXVII) also accomodates the formation of nitrous oxide as a second reaction product. Decomposition of other N-nitroso-O,N-dialkylhydroxylamines have so far been found to give nitrogen and not nitrous oxide (see p. 7) with the formation of alcohols and aldehydes, but proceed by mechanisms impossible with the present compounds.

Four stereoisomeric formulae (8, 9, 19, 20, chart 1) are possible for an epoxide formula of structure XXVII, and the reactions described below for the denitrosated product show it to have the formula 8. However, an attempt to prove the presence of the epoxy group by reaction with sodium thiosulphate (28, 29) was fruitless. This reaction serves for the quantitative estimation of epoxide oxygen content.

Figure 19.

The n.m.r. spectrum of 3-anti-benzoyloximino-5,10-(α-epoxy)-1β,4α-hexahydrohyposantonin (XXVIII).


2.0
3.0
4.0
5.0
PPM (τ)
6.0
7.0
8.0
9.0
10
1000
500
250
100
50
400
300
200
100
0 CPS
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

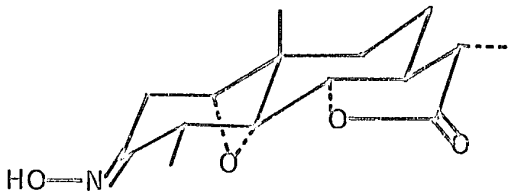


It is carried out in aqueous acetone with phenolphthalein present. As the reaction proceeds, the alkali that is formed is continuously titrated with 0.1N acetic acid, (1 ml of 0.1N acid = 1 milliequivalent of epoxide oxygen). The reaction is reportedly complete after 25 minutes at 100°, for epoxides that have hydrogen attached to the epoxide carbons, but no figures are quoted, as far as we are aware, for fully substituted epoxides.

When this reaction was attempted using the denitrosated compound 8, no reaction occurred, even after several hours heating.

S. Searles (30) has shown that trimethylene oxides react with sodium thiosulphate in the same way, but ten times more slowly. If such a structure were present in the oxime as in structure XXIX, thiosulphate ion might

be expected to attack at C-1. Since no reaction takes place, we may discount this possibility which in any case



XXIX

would run counter to the n.m.r. evidence for a methyl group shifted to C-1.

6. Treatment of 3-anti-Oximino-5,10-(α-epoxy)-1β, 4α-hexahydrohyposantonin (8) with Levulinic Acid.

(a) At Room Temperature.

Treatment of the presumed epoxy-oxime (8) with levulinic acid reagent was carried out in the hope of obtaining an epoxy-ketone suitable for n.m.r. studies. A crystalline product was obtained which showed two spots on t.l.c. analysis. One had R_f (a) 0.50 identical to that of the starting material, the other one had R_f (a) 0.60. Preparative thin layer chromatography of the mixture gave two fractions.

The first fraction (R_f (a) 0.50) crystallised as colourless prisms m.p. 187-190°, mixture melting point with the starting material (8), 173°. Its elemental analysis showed it to be isomeric with the starting material and its spectral properties indicated that it was a stereoisomer of (8). Thus the ultraviolet spectrum showed no absorption peak above 200 mμ.

The infra-red spectrum (Fig. 20) showed OH stretching at 3450 cm^{-1}, lactone carbonyl absorption at 1750 cm^{-1} similar to 8, but a sharp peak at 1636 cm^{-1} assigned to the C=N stretching mode of an oxime (cf. 1653 cm^{-1} in 8). There were distinct differences in the "fingerprint" region.

The n.m.r. spectrum (Fig. 21 and table 2) showed three methyl groups as doublets very close to their positions in the epoxy-oxime (8). Other peaks in the n.m.r. spectrum (which is discussed in detail on p.88) show the compound to be the syn-isomer (9) of the parent epoxy-oxime (8).

The second fraction (R_f (a) 0.60) crystallised from cold ether as colourless platelets $C_{15}H_{21}O_4Cl$, m.p. 130° (decomp.). This compound was unstable and turned

Figure 20.

The infra-red spectrum of 3-syn-oximino-5,10-(α-epoxy)-1β,4α-hexahydrohyposantonin (9).

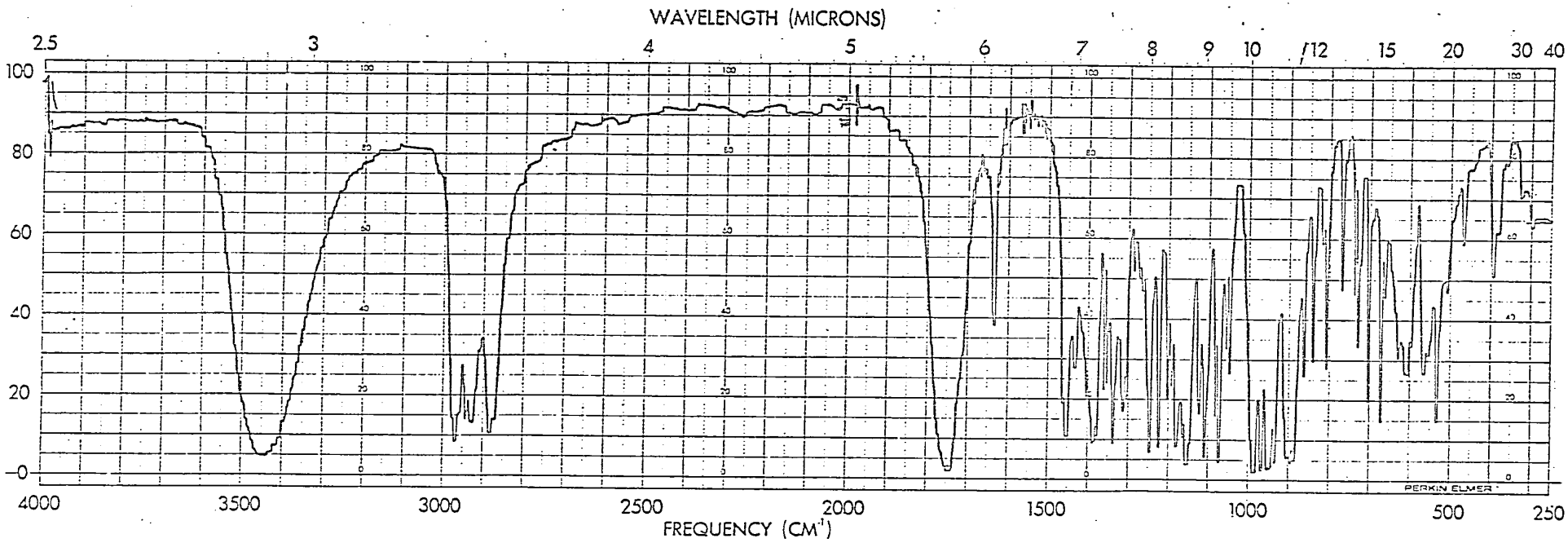
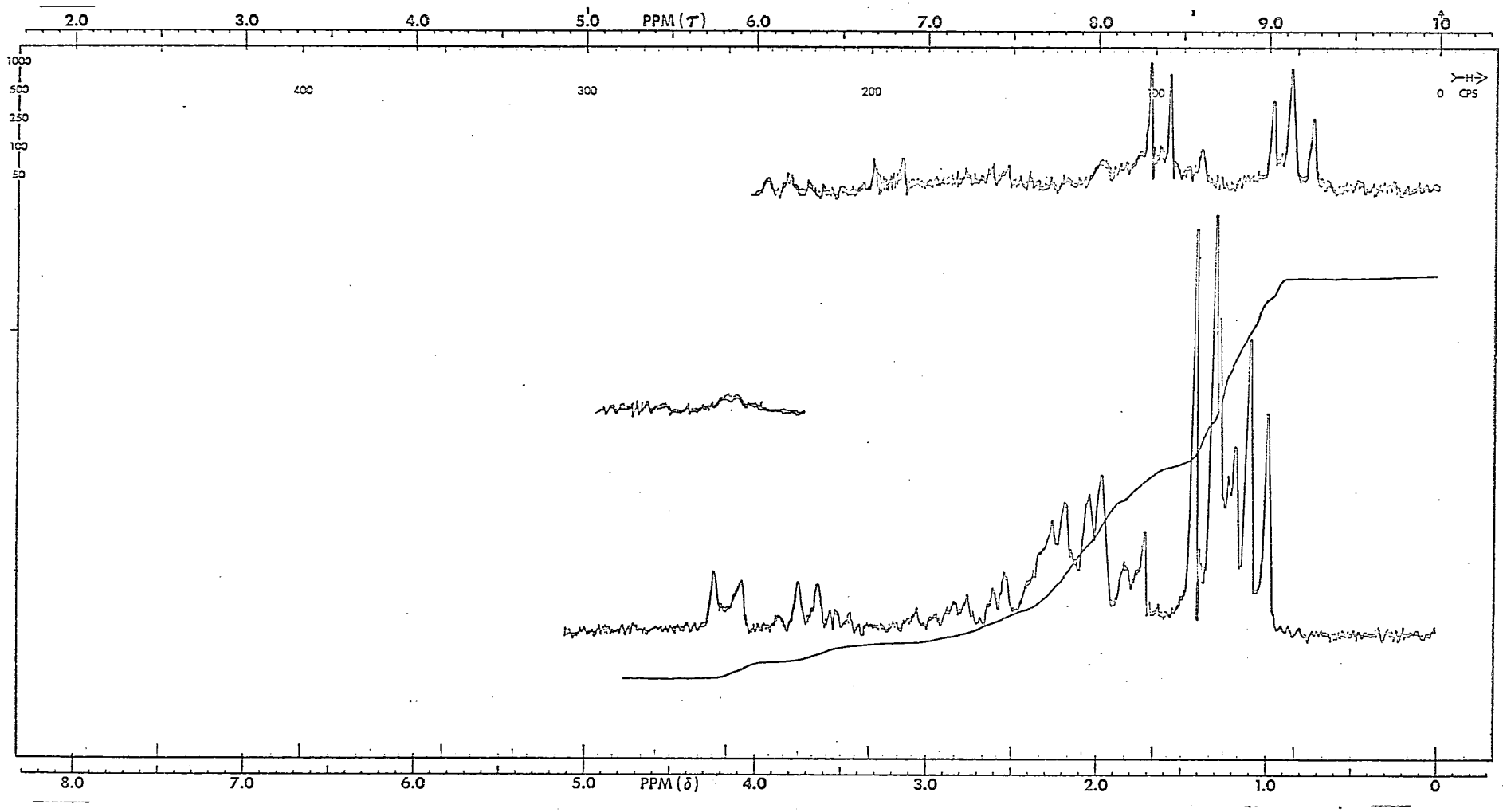

WAVELENGTH (MICRONS)
2.5
3
4
5
6
7
8
9
10
12
15
20
30
40
100
80
60
40
20
0
4000
3500
3000
2500
2000
1500
1000
500
250
FREQUENCY (CM-1)
PERKIN ELMER

Figure 21.

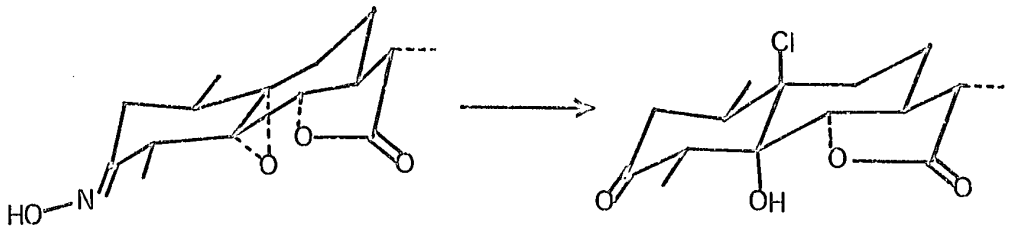
The n.m.r. spectrum of 3-syn-oximino-5,10-(α-epoxy)-1β,4α-hexahydrohypo-santonin (9).


2.0
3.0
4.0
5.0
PPM (τ)
6.0
7.0
8.0
9.0
10
1000
500
250
100
50
400
300
200
100
0 CPS
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

brown on standing. The infra-red spectrum (Fig. 22) had a strong OH absorption band at 3430 cm^{-1}, and two carbonyl bands at 1763 cm^{-1} (lactone) and 1705 cm^{-1}, (saturated cyclohexanone). There was also a band at 682 cm^{-1}, assigned to the C—Cl stretching mode.

The n.m.r. spectrum (Fig. 23 and table 2) showed two coincident methyl groups as doublets at 1.12 p.p.m., and a methyl group doublet at 0.99 p.p.m., a complex multiplet integrating to 3 protons at 3.25 p.p.m., assigned to the protons at C-2 and C-4, α- to the carbonyl group. The ultraviolet spectrum showed no absorption peak above 200 mμ, confirming the absence of any double bonds α- to the carbonyl group.

De-oximation has apparently occurred with concurrent cleavage of the epoxide ring to give the chlorohydrin (10). This product was not studied further,

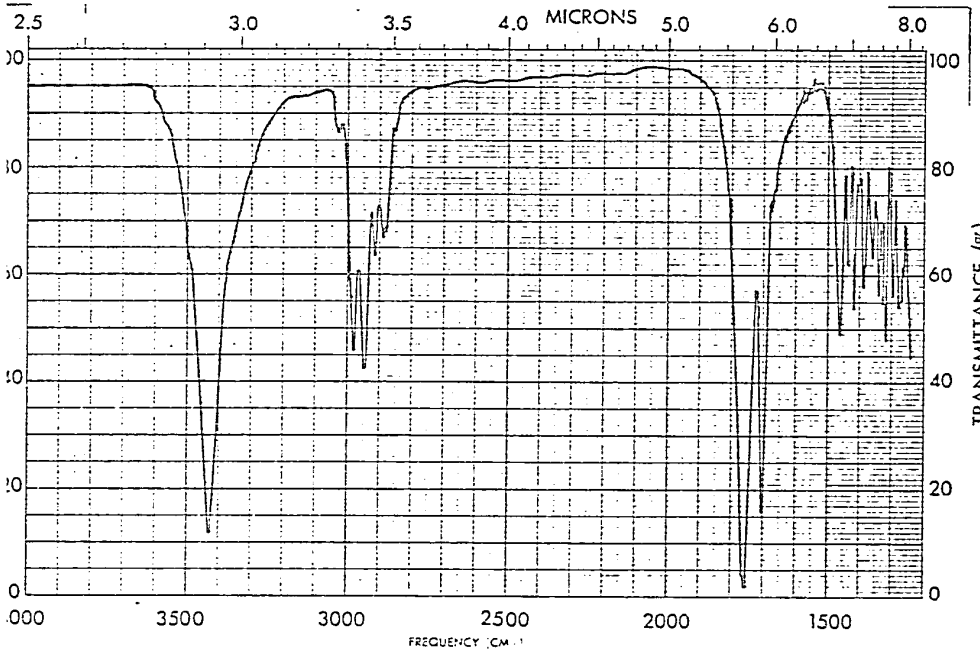


8 10

due to a shortage of material caused by its decomposition.

Figure 22.

The infra-red spectrum of the chlorohydrin (10).


2.5
3.0
3.5
4.0
MICRONS
5.0
6.0
8.0
100
80
60
40
20
0
3500
3000
2500
2000
1500
FREQUENCY (CM⁻¹)

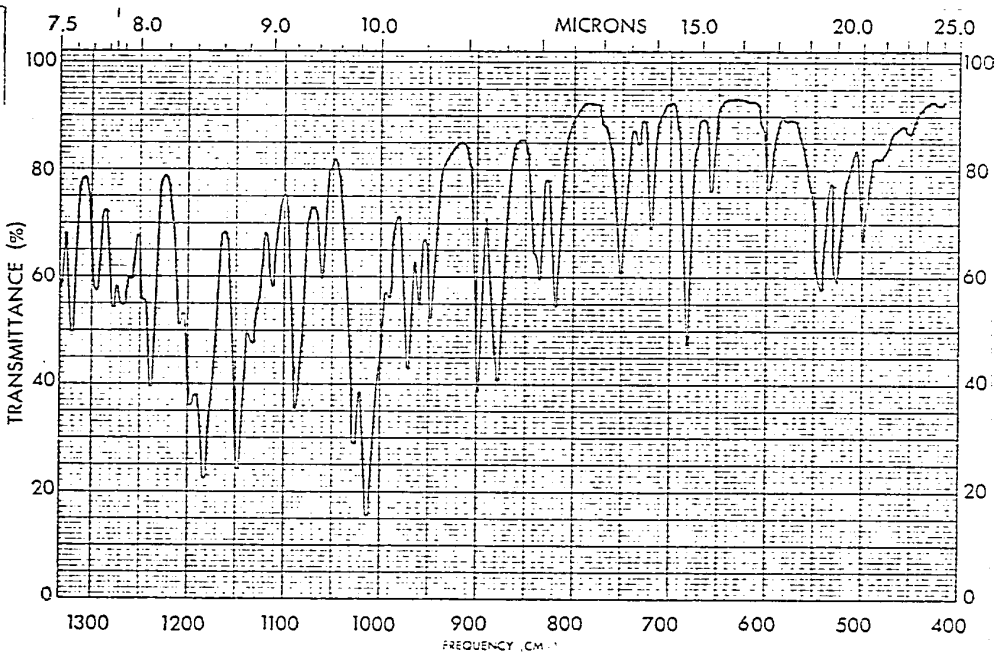
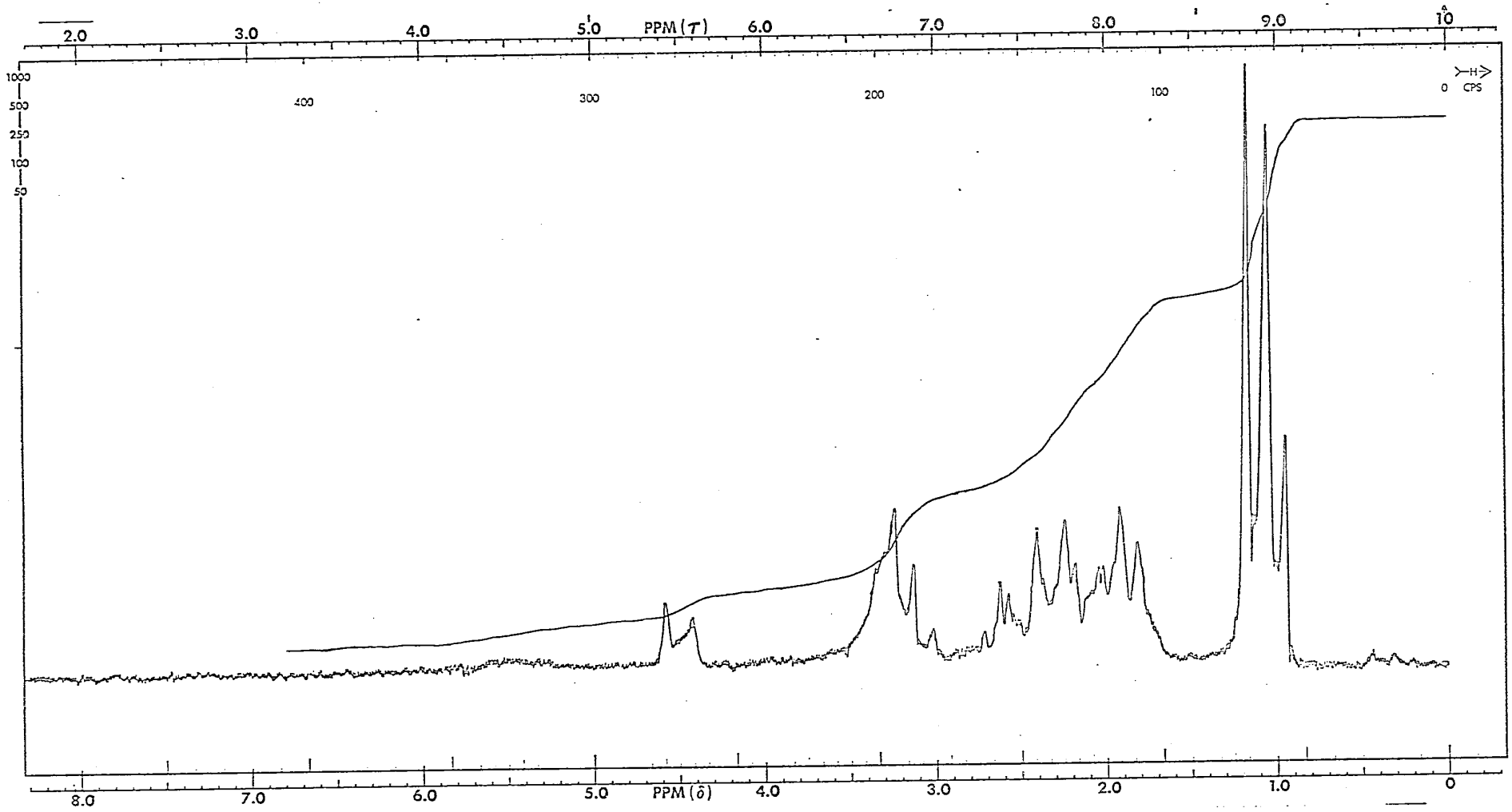

7.5
8.0
9.0
10.0
MICRONS
15.0
20.0
25.0
TRANSMITTANCE (%)
100
80
60
40
20
0
1300
1200
1100
1000
900
800
700
600
500
400
FREQUENCY (CM⁻¹)

Figure 23.

The n.m.r. spectrum of the chlorohydrin (10).


2.0
3.0
4.0
5.0
PPM (τ)
6.0
7.0
8.0
9.0
10
1000
500
250
100
50
400
300
200
100
0 CPS
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

(b) At 100° for 4 hours.

When the epoxy oxime (8) was refluxed for four hours with levulinic acid reagent, a different crystalline compound $C_{15}H_{18}O_3$ was obtained, m.p. 108-109°, which gave a single spot on t.l.c. analysis (R_f (a) 0.75).

The ultraviolet spectrum showed two peaks (λ_{max} 232.5 mμ, ϵ_{max} 3,800, and λ_{max} 288 mμ, ϵ_{max} 11,100) strongly indicating a di-unsaturated ketone for which the structure 11 is proposed. This was also indicated by the infra-red spectrum (Fig. 24) which showed two carbonyl bands, one at 1780 cm^{-1} (lactone) and a second at 1660 cm^{-1}, assigned to an unsaturated ketone. A medium intensity band at 1620 cm^{-1} is assigned to a C=C stretching vibration.

The n.m.r. spectrum (Fig. 25) showed one olefinic proton as a broad peak at 5.32 p.p.m., one methyl group as a sharp singlet at 1.94 p.p.m., and two methyl groups as doublets at 1.15 p.p.m., (J = 6.00 c.p.s.), and 1.02 p.p.m., (J = 6.50 c.p.s.).

The value of λ_{max} in the ultraviolet spectrum calculated from Woodward's rules (31), for a compound of formula 11 would be 303 mμ, in fair agreement with the

Figure 24.

The infra-red spectrum of 3-oxo-$\Delta^{4,9}$-1β-dihydrohyposantonin (11).

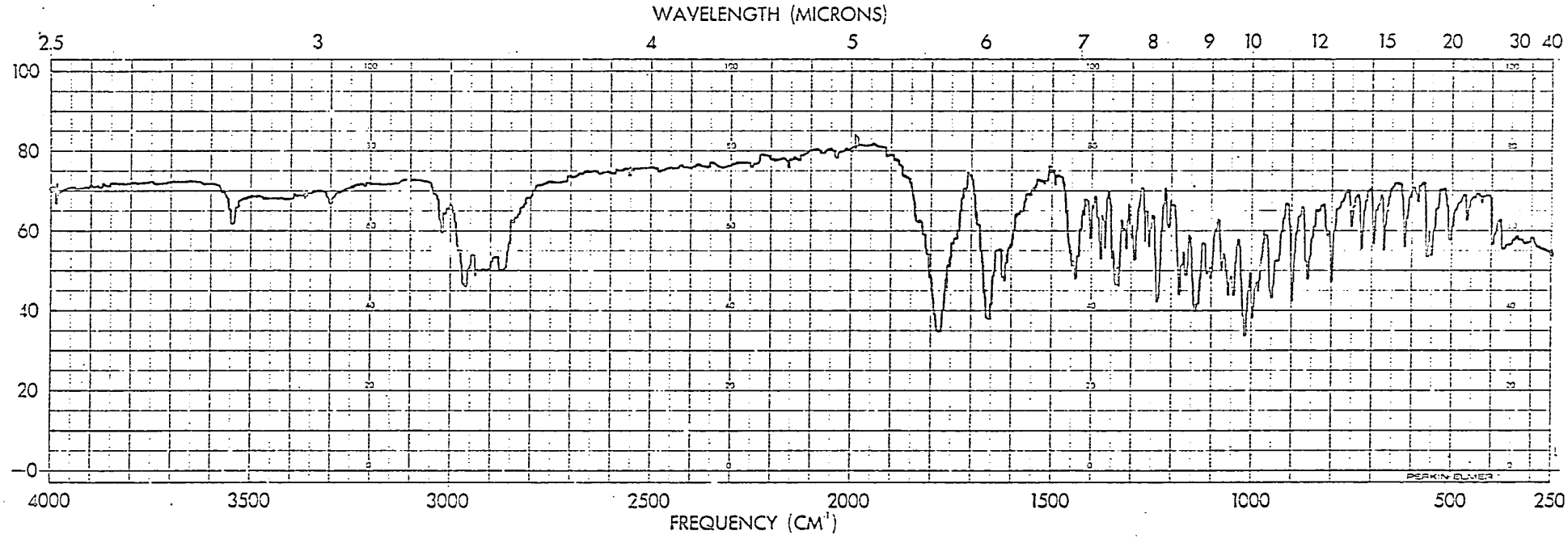
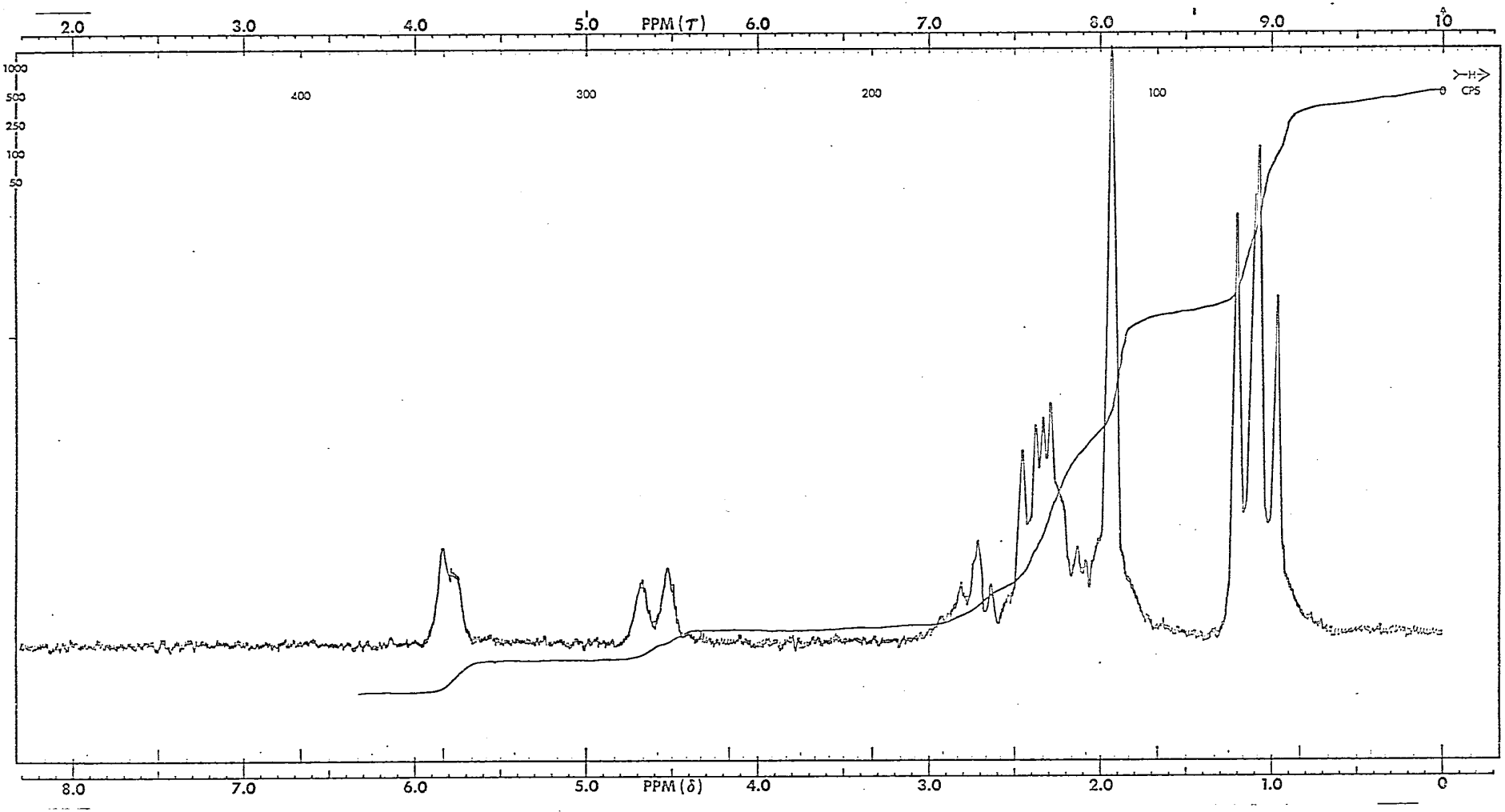

WAVELENGTH (MICRONS)
2.5
3
4
5
6
7
8
9
10
12
15
20
30
40
100
80
60
40
20
0
4000
3500
3000
2500
2000
1500
1000
500
250
FREQUENCY (CM-1)
PERKIN ELMER

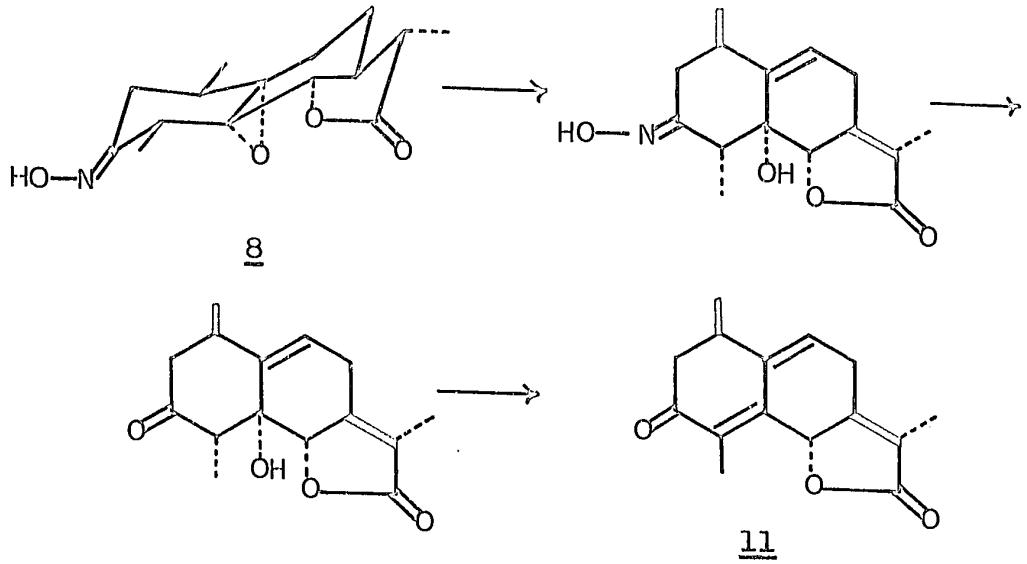
Figure 25.

The n.m.r. spectrum of 3-oxo-$\Delta^{4,9}$-1β-dihydrohyposantonin (11).


2.0
3.0
4.0
5.0
PPM (τ)
6.0
7.0
8.0
9.0
10
1000
500
250
100
50
400
300
200
100
0
CPS
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

value found (288 mμ). The discrepancy may be due to the presence of the lactone ring, as Woodward's rules are based on studies of typically hydrocarbon models.

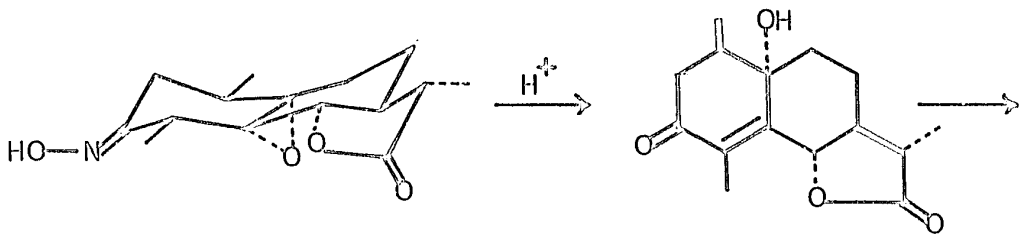
The reaction probably proceeds by initial cleavage of the epoxide ring, followed by de-oximation and β-elimination of water as shown below.



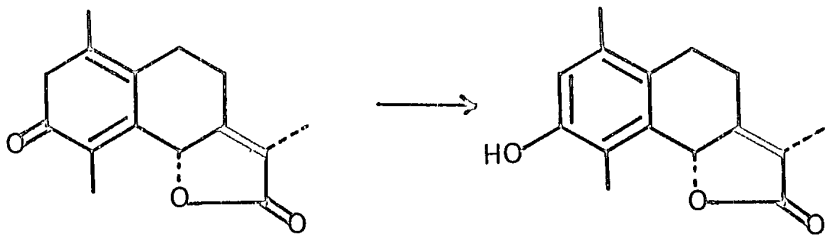
8 11

If de-oximation had taken place first, then β-elimination of the epoxide would be expected as shown, followed by the energetically more favourable dehydration in ring A to give the compound XXX, in which ring A is aromatic. In fact, no phenolic products were detected under these conditions, though the closely related

desmotroposantonin was formed under more drastic conditions



8



XXX

as described in the next section. (The compound XXX decomposes readily to give (-)α-desmotroposantonin (12), and has only been isolated as its acetate (32)).

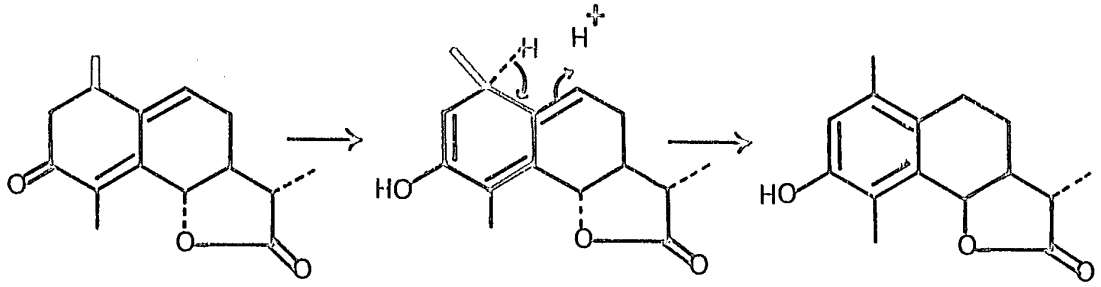
(c) At 100° for 15 hours.

More prolonged treatment of the epoxy-oxime (8) with levulinic acid reagent, for 15 hours at 100° gave a different crystalline compound, appearing as a single spot

(R_f (a) 0.65) on t.l.c. analysis.

Recrystallisation gave a 50% yield of white needles, m.p. 194°, identified as (-)α-desmotroposantonin (lit. m.p. 194° (33)) by mixture melting point, and ultraviolet spectrum (λ_{max} 289 mμ, ϵ_{max} 3,800) and infra-red spectrum (OH absorption at 3,400 cm^{-1}, sharp aromatic bands at 1600 and 1492 cm^{-1}; Fig. 26). The optical rotation ($[\alpha]_D^{25}$ - 140°) and n.m.r. spectrum were also identical to those of an authentic specimen.*

The reaction probably proceeds via the unsaturated ketone (11) discussed above:



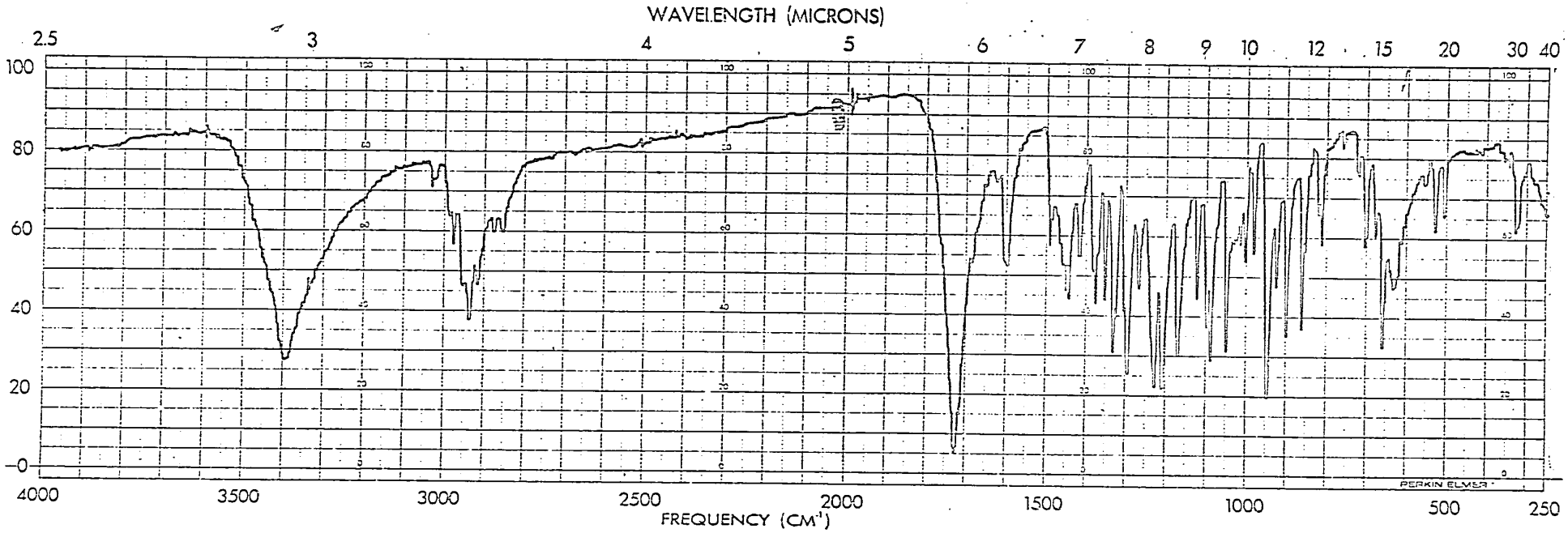
11 12

(-)α-Desmotroposantonin has the same stereochemistry at C-11 as santonin, so that epimerisation at this centre has

*Kindly supplied by Mr H. Alper, of these laboratories.

Figure 26.

The infra-red spectrum of (-)α-desmotroposantonin (12).


WAVELENGTH (MICRONS)
2.5
3
4
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6
7
8
9
10
12
15
20
30
40
100
80
60
40
20
0
4000
3500
3000
2500
2000
1500
1000
500
250
FREQUENCY (CM-1)
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not taken place at any stage in the reaction sequence 1 → 3 → 7 → 8 → 11 → 12.

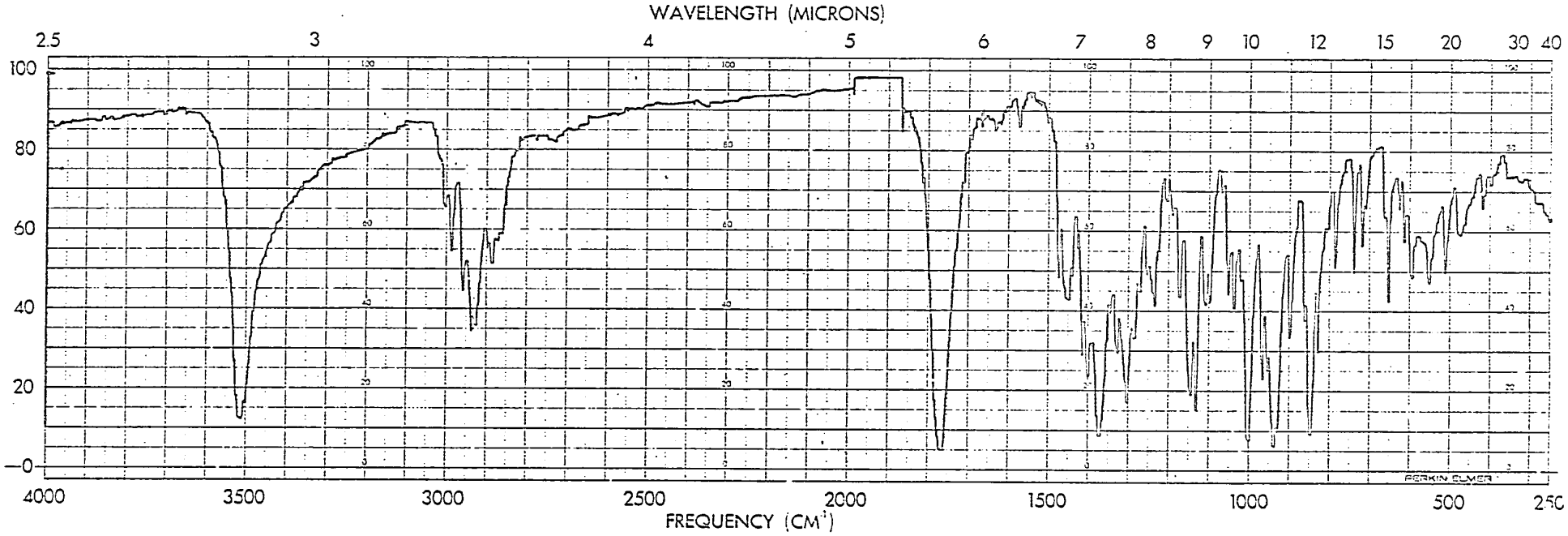
7. Nitroso Derivative of Hydroxylaminosantonin Oxime-β (18).

Hydroxylaminosantonin oxime-β (13) was treated with nitrous acid as described above for the preparation of the 4α-isomer, except that glacial acetic acid was used as the solvent. The product was obtained from the reaction mixture as a yellow precipitate, giving large bright yellow needles on recrystallisation. These, even on repeated crystallisation gave a double spot on t.l.c. analysis (R_f (b) 0.30; 0.40), and melted unsharply over the range 168-172°. On standing the product decomposed slowly, a new spot appearing (R_f (b) 0.70) on t.l.c. analysis. The new spot had the same R_f value as the products 19 and 20 described in the next section.

The infra-red spectrum (Fig. 27) of the nitroso compound was very similar to that of the 4α-isomer 7 though the N=O stretching band was at shorter wavelength (1375 cm^{-1}). The ultraviolet spectrum (λ_{max} 246, ϵ_{max} 7,300) was also similar to that of the α-isomer.

Figure 27.

The infra-red spectrum of the nitroso derivative of hydroxylaminosantonin oxime-β (18).


WAVELENGTH (MICRONS)
2.5
3
4
5
6
7
8
9
10
12
15
20
30
40
100
80
60
40
20
0
4000
3500
3000
2500
2000
1500
1000
500
FREQUENCY (CM-1)
PERKIN ELMER

(a) 3-Oximino-1β-$\Delta^{4,9}$-dihydrohyposantonin (21).

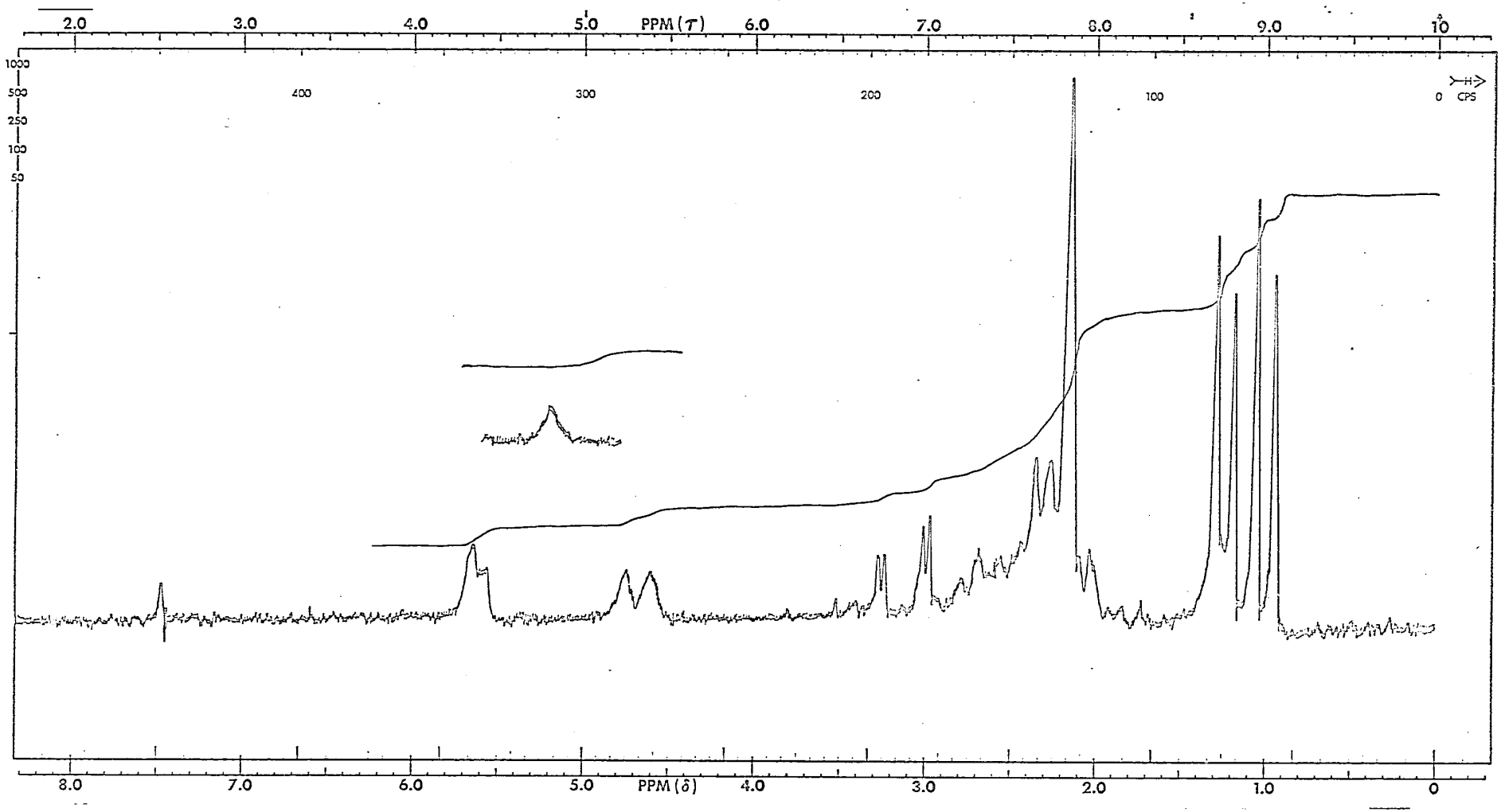
When the nitroso compound (18) was heated in 50% acetic acid on the steam bath for ten minutes, nitrous oxide (identified by its infra-red spectrum) was evolved. On cooling the reaction mixture to room temperature, two crops of crystals were obtained.

The first crop consisted of three compounds as shown by t.l.c. analysis (R_f (a) 0.50; 0.58; and 0.80). The second crop had R_f (a) 0.80 and was almost pure. This compound was much more soluble in common solvents than the other two. Two crystallisations from methanol gave the unsaturated oxime (21) as colourless prisms, m.p. 255° (decomp.).

The formula 21 (chart 1) of this compound follows from the ultraviolet spectrum (λ_{max} 276 mμ, ϵ_{max} 24,870) which indicated an extended system of conjugated double bonds, and the n.m.r. spectrum (Fig. 28 and table 2) which showed a broad peak (1 proton) at 5.65 p.p.m. that can be assigned to the olefinic proton at C-9. In this and other respects, the n.m.r. spectrum showed marked similarities to that of the corresponding ketone (11). A singlet

Figure 28.

The n.m.r. spectrum of 3-oximino-$\Delta^{4,9}$-1β-dihydrohyposantonin (21).


2.0
3.0
4.0
5.0
PPM (τ)
6.0
7.0
8.0
9.0
10
1000
500
250
100
50
400
300
200
100
0 CPS
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

(3 protons) at 2.17 p.p.m. may be assigned by virtue of its chemical shift and multiplicity to the C-4 methyl group attached to the double bond, and doublets at 1.23 and 1.01 p.p.m. are assigned to the C-1 and C-11 methyl groups. There was one proton exchangeable with D_2O, assigned to the oxime OH group.

The infra-red spectrum (Fig. 29) had OH absorption at 3400 cm^{-1}, olefinic hydrogen stretching absorption at 3035 cm^{-1}, and two weak bands at 1602 and 1590 cm^{-1} assigned to C=C and C=N stretching vibrations.

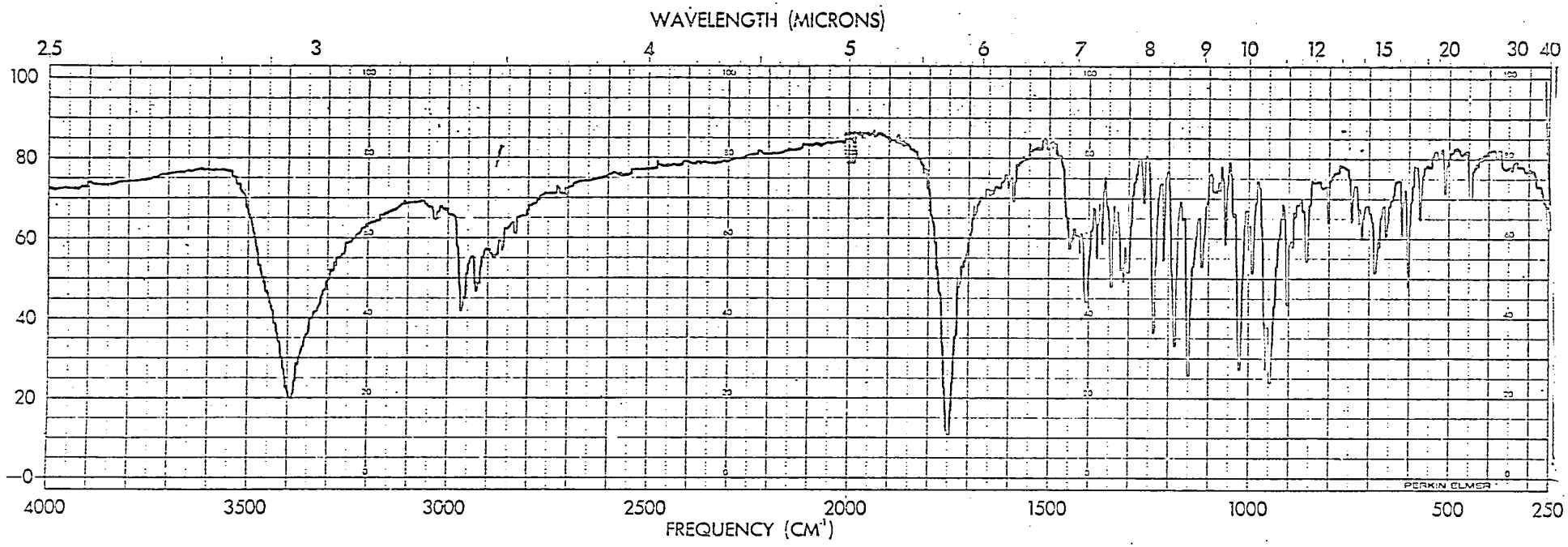
This oxime (21) on treatment with aqueous ethanolic sodium bisulphite (as described for the de-oximation experiments on p.33) gave a quantitative yield of the di-unsaturated ketone (11), identified by its infra-red spectrum.

(b) 3-syn-Oximino-5,10-(α-epoxy)-1β,4β-hexahydro-hyposantonin (19).

The other two compounds in the reaction mixture had very close R_f values in solvent (a), (0.50, and 0.58). and were coincident on a plate eluted with solvent (b), (R_f (b) 0.70). They were partially separated on a long silica gel column and finally purified on silica gel plates (solvent (a)).

Figure 29.

The infra-red spectrum of 3-oximino-$\Delta^{4,9}$-1β-dihydrohyposantonin (21).


WAVELENGTH (MICRONS)
2.5
3
4
5
6
7
8
9
10
12
15
20
30
40
100
80
60
40
20
0
4000
3500
3000
2500
2000
1500
1000
500
250
FREQUENCY (CM-1)
PERKIN ELMER

The more polar one (R_f (a) 0.50) crystallised from aqueous ethanol as needles $C_{15}H_{21}NO_4$ m.p. 186.5°, isomeric with 8 and 9. There was no absorption peak above 200 mμ in the ultraviolet spectrum.

The infra-red spectrum (Fig. 30) was very similar to that of 8, having sharp OH absorption at 3560, and a peak centered at 3200 cm^{-1}, indicating strong hydrogen bonding. The band at 1660 cm^{-1} is assigned to the C=N stretching vibration. There were distinct differences in the "fingerprint" region between 8 and 9, and the new compound (19).

The n.m.r. spectrum (Fig. 31 and table 2) showed three doublets at 1.54 p.p.m. (J = 7 c.p.s.), 1.10 p.p.m. (J = 6 c.p.s.), and 1.07 p.p.m. (J = 6.5 c.p.s.), assigned to the methyl groups at C-4, C-1, and C-11 respectively. There was one proton exchangeable with D_2O at 9.87 p.p.m., assigned to the oxime OH group. The spectrum was similar in many respects to that of 8 and 9 and is considered in detail later (p.88).

(c) 3-anti-Oximino-5,10-(α-epoxy)-1β,4β-hexahydrohyposantonin (20).

The remaining compound R_f (a) 0.58, obtained by

Figure 30.

The infra-red spectrum of 3-syn-oximino-5,10-(α-epoxy)-1β,4β-hexahydrohypo-santonin (19).

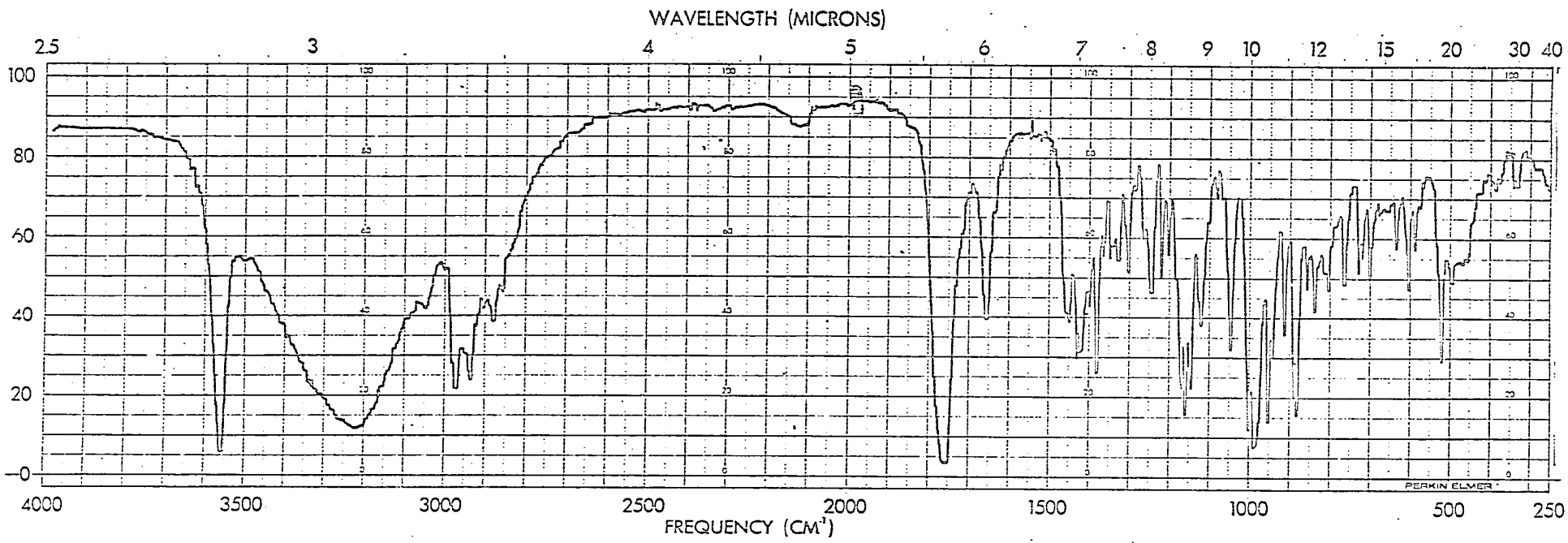
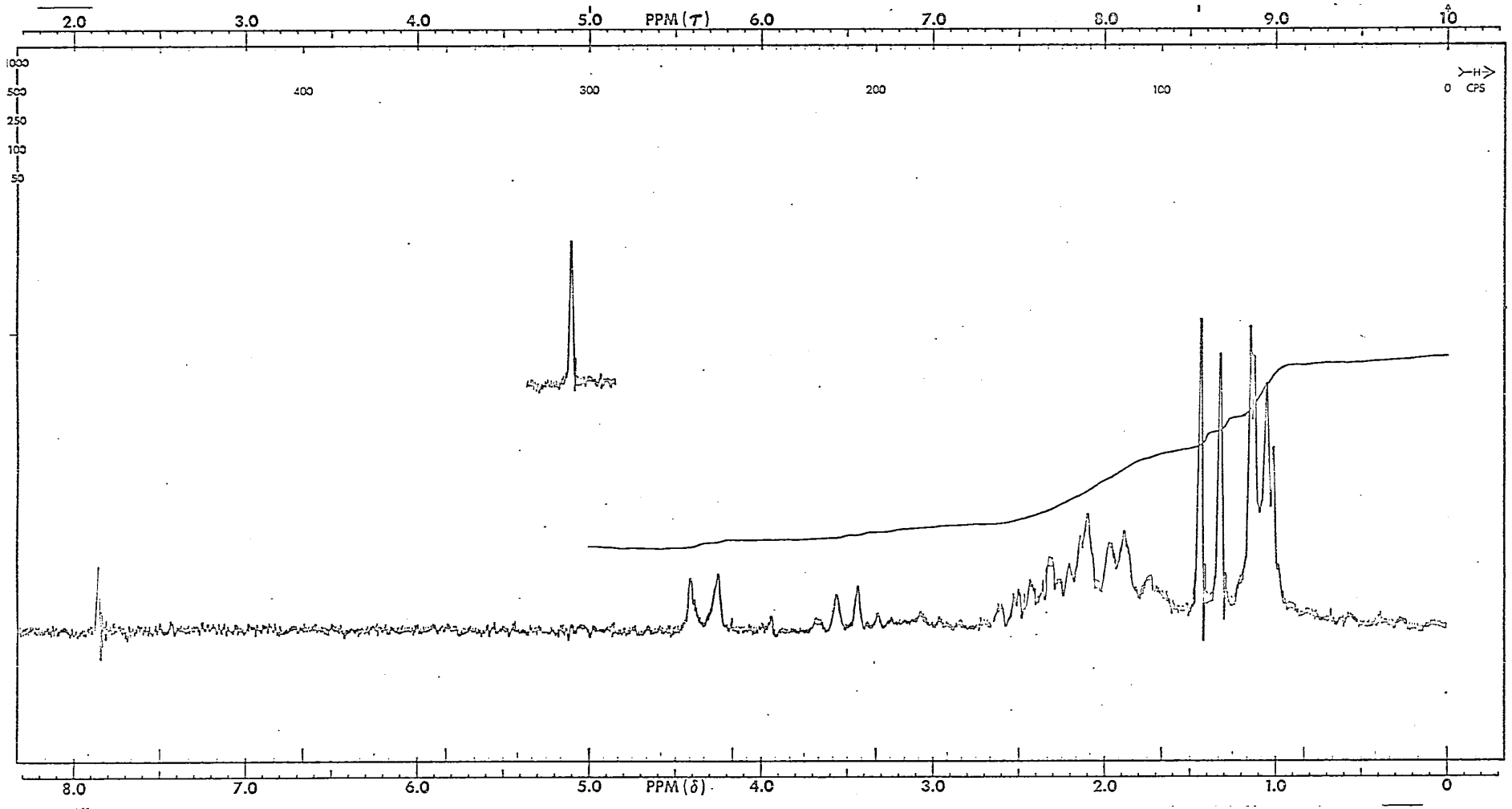

WAVELENGTH (MICRONS)
2.5
3
4
5
6
7
8
9
10
12
15
20
30
40
100
80
60
40
20
0
4000
3500
3000
2500
2000
1500
1000
500
250
FREQUENCY (CM-1)
PERKIN ELMER

Figure 31.

The n.m.r. spectrum of 3-*syn*-oximino-5,10-(α-epoxy)-1β,4β-hexahydrohypo-santonin (19).


2.0
3.0
4.0
5.0
PPM (τ)
6.0
7.0
8.0
9.0
10
1000
500
250
100
50
400
300
200
100
0 CPS
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

chromatography of the de-nitrosation reaction products as described above was crystallised from aqueous ethanol as white platelets, $C_{15}H_{21}NO_4$, m.p. 196.5° and appeared to be the fourth stereoisomer (20).

Thus, its ultraviolet spectrum had no absorption peak above 200 mμ. Its infra-red spectrum (Fig. 32) showed OH stretching at 3460 cm^{-1}, but with less broadening of the peak due to hydrogen bonding than in (19), a lactone carbonyl band at 1760 cm^{-1}, and a weak band at 1630 cm^{-1}, assigned to C=N stretching. The n.m.r. spectrum (Fig. 33), had doublets at 1.45 p.p.m. (J = 7.0 c.p.s.), 1.20 p.p.m. (J = 6.0 c.p.s.), and 1.12 p.p.m. (J = 6.5 c.p.s.) assigned to the C-4, C-1, and C-11 methyl groups respectively.

The presence of three compounds in the reaction mixture, instead of one, as Francesconi and Cusmano believed, explains the wide melting point range reported (3) for their product. We have found that the readily available mixture of 19 and 20, when refluxed with 50% acetic acid for one hour, was converted in 60% yield to the di-unsaturated oxime (21).

(d) Decomposition of Nitroso Derivative of Hydroxylaminosantonin Oxime-β in Levulinic Acid.

When the nitroso compound (18) was heated with

Figure 32.

The infra-red spectrum of 3-anti-oximino-5,10-(α-epoxy)-1β,4β-hexahydrohypo-santonin (20).

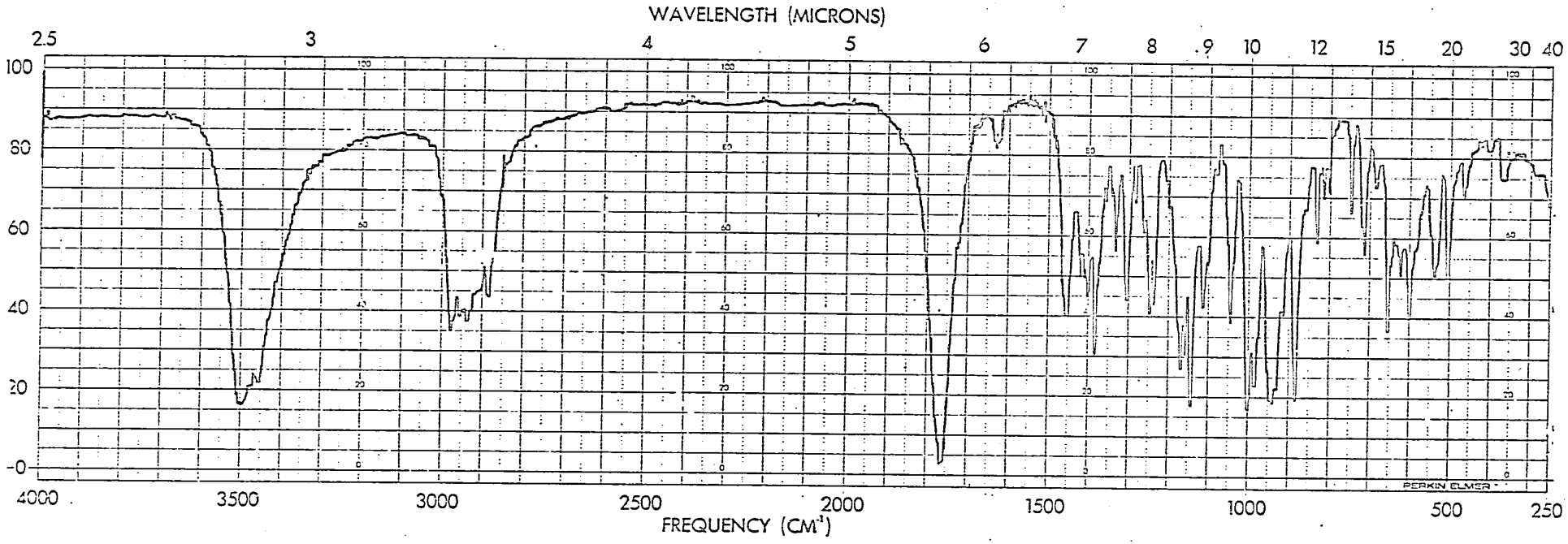
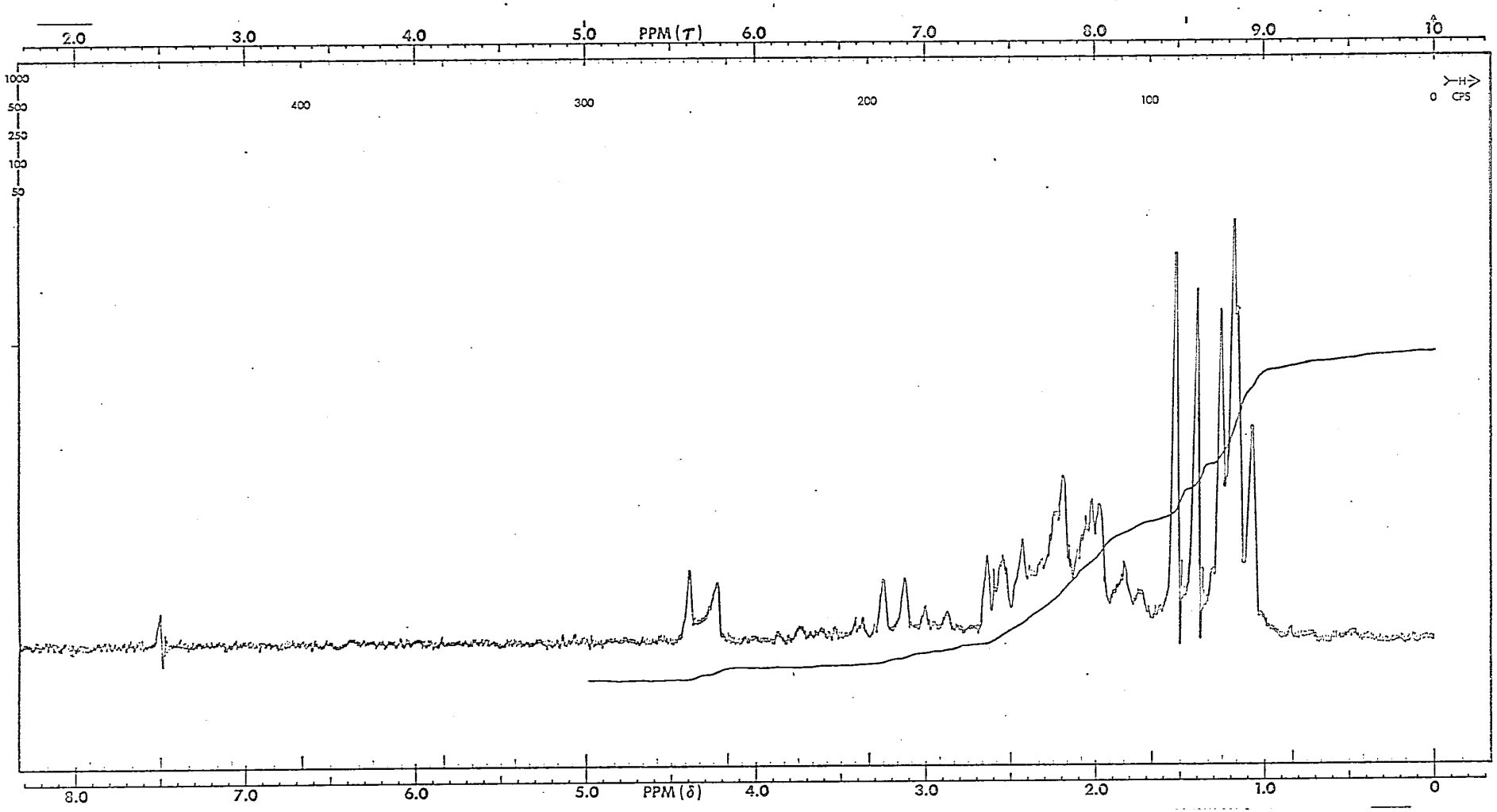

WAVELENGTH (MICRONS)
2.5
3
4
5
6
7
8
9
10
12
15
20
30
40
100
80
60
40
20
0
4000
3500
3000
2500
2000
1500
1000
500
250
FREQUENCY (CM-1)
PERKIN ELMER

Figure 33.

The n.m.r. spectrum of 3-anti-oximino-5,10-(α-epoxy)-1β,4β-hexahydrohypo-santonin (20).


2.0
3.0
4.0
5.0
PPM (τ)
6.0
7.0
8.0
9.0
10
1000
500
250
100
50
400
300
200
100
0 CPS
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

levulinic acid reagent on the steam bath for six hours, it afforded a complex mixture of products. Extraction with ether removed a yellow syrup which on standing, deposited santonin as colourless crystals. It was identified by its melting point (171°) and ultraviolet spectrum (λ_{max} 240 mμ, ϵ_{max} 13,400, and λ_{max} 260 mμ, ϵ_{max} 10,650).

Other spots detected on a t.l.c. plate R_f (a) 0.65, and R_f (a) 0.80) indicated the presence of (-)α-desmotroposantonin (12) and the di-unsaturated oxime (21).

8. The Stereochemistry of the Oxime Function and Methyl Group at C-4.

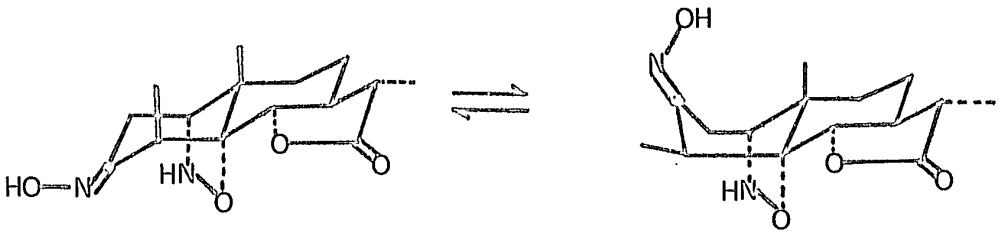
(a) Hydroxylaminosantonin Oximes and Their Derivatives.

The U.V., I.R. and n.m.r. spectra of the α- and β-hydroxylaminosantonin oximes are so similar that no stereochemical conclusions can be drawn. However, on t.l.c. analysis the α-isomer (3) behaves as a single pure compound, while the β-isomer gives a double spot and so is probably a mixture of syn- and anti- oximes (13).

The de-oximation studies (p.33) indicated that

hydroxylaminosantonin oxime-α (3) had the more stable C-4 methyl configuration, and gave a stable ketone (6) on deoximation, while the hydroxylaminosantonin oxime-β (13) had the less stable methyl configuration and gave a ketone (15) that isomerised rapidly in basic solution to give (6). It follows from this that the configuration of the C-4 methyl group is α in the α-series of compounds, and β in the β-series.*

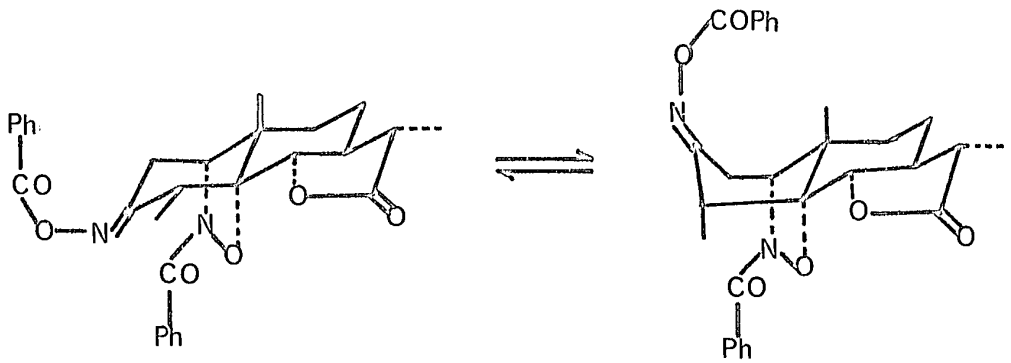
Both the α- and β-isomers can exist in either the chair or boat conformations. The boat conformation may be particularly favoured by the α-isomer as this relieves the considerable 1:3 diaxial interaction between the two methyl groups at C-4 and C-10 (34) as shown below.



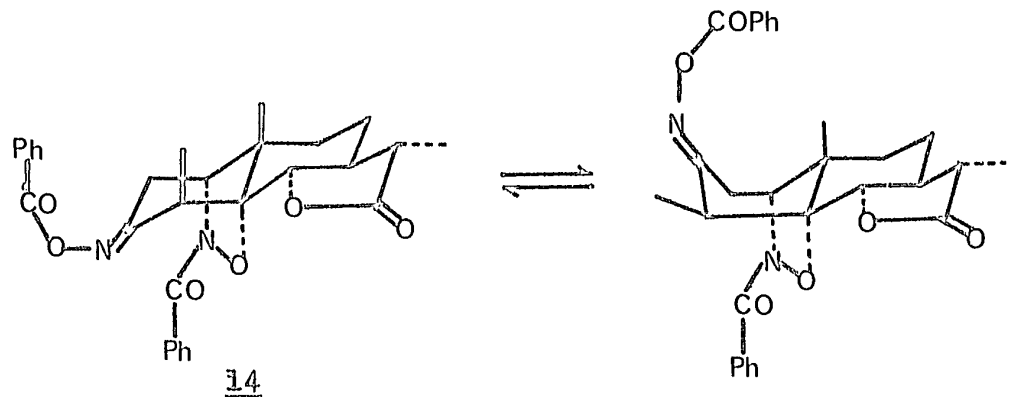
13

*The symbols α and β have two different meanings in this sentence. The isomeric hydroxylaminosantonin oximes were differentiated as α and β on a purely arbitrary basis by Francesconi and Cusmano (3). By chance it happens that these correctly describe the methyl configuration at C-4 of the two compounds, following the convention developed by Fieser for indicating conformations of substituents in steroids.

The dibenzoyl derivatives (4) and (14) both give rise to a single spot on a t.l.c. plate and are evidently single geometrical isomers of the oxime grouping, even though the starting material in the case of the β-isomer was a mixture of syn- and anti- isomers (13). The dibenzoyl compounds, having the bulky benzoyloximino group might be expected to have the more stable anti- configuration as shown below. The boat conformation would be particularly favoured



4



14

by the derivative (14) of the β-series, for the same reasons described above for the parent hydroxylaminosantonin oxime-β

Table 1.

The n.m.r. spectra of compounds having a C-10 methyl group.

COMPOUND	SOLVENT	C-4 CH_3	C-4 H	OXIME H	C-2 methylene		C-10 CH_3	C-11 CH_3	C-6 H	OTHER	
1.	$CDCl_3$	2.13					1.34	1.27	4.88	6.22;	6.75
2.	"	2.16		9.60			1.27	1.27	4.80	6.04;	6.87
3.	$(CD_3)_2SO$	1.22		10.42			1.07	1.07	4.10	7.07	
4.	$CDCl_3$	1.62	3.35		3.35;	4.60	1.31	1.15	4.17	3.25	
5.	"	1.42	3.11	9.43	2.05;	2.19	1.23	1.23	4.12		
6.	"	1.33	2.55			2.65	1.28	1.22	4.00	5.93	
13.	"	1.22		10.42			1.13	1.07	4.22	7.10	
14.	"	1.62	3.52		3.42;	4.60	1.31	1.15	4.17	3.15	
16.	"	1.35	3.58	9.83		2.10	1.31	1.15	4.22		

The major difference between the n.m.r. spectra of the two dibenzoyl derivatives (4 and 14, Figs. 7, 8 and table 1) is the position of the quartet due to the proton at C-4, which occurs at 3.35 p.p.m. in 4 and at 3.52 p.p.m. in 14. This is consistant with an axial assignment to this proton in 4 and quasi-axial assignment in the boat form of 14 above.

Other peaks of interest in the n.m.r. spectra of 4 and 14 are the broad peaks at 4.60 p.p.m. in both isomers, not exchangeable with D_2O, which were assigned to one of the protons at C-2. Models show that the C-2 equatorial proton of 4 and the quasi-equatorial C-2 proton of 14 are close to the plane of the —N—O—CO—Ph and —N—CO—Ph groups; this may account for the remarkably low chemical shift observed.

The broad peak at 3.15 p.p.m. in the spectrum of the β-isomer, integrating to one proton, is evidently due to the proton at the C-1 bridgehead, to which nitrogen is attached. The signal for the corresponding proton of the α-isomer (Fig. 7) is part of a multiplet of three protons that also incorporates the axial C-2, and C-4 protons.

(b) The Oxime Configuration of Epoxy-oximes 8, 9, 19, and 20.

It has been shown by the de-oximation experiments

Table 2.

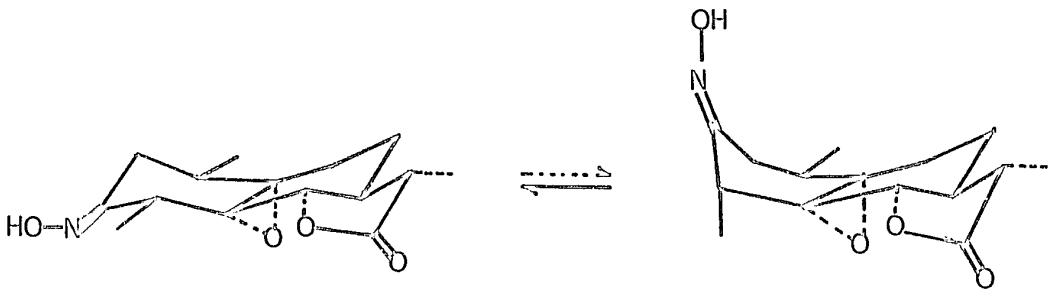
The n.m.r. spectra of compounds having a C-1 methyl group.

COMPOUND	SOLVENT	C-4 CH_3	C-4 H	OXIME H	C-2 methylene	C-1 CH_3	C-11 CH_3	C-6 H	OTHER
8.	$(CD_3)_2SO$	1.28	2.83	10.13	2.75	1.17	1.05	4.31	
9.	"	1.10	3.61	10.20	2.45	0.95	0.85	4.26	
8.	$CDCl_3$	1.35	3.01	8.75	3.01	1.23	1.09	4.18	
9.	"	1.37	3.60		2.82	1.24	1.06	4.22	
XXVIII	"	1.45	3.28		3.28	1.18	1.05	4.15	2.90
10.	"	1.12	3.25		3.25	1.12	0.99	4.50	5.40
11.	"	1.94			2.72	1.15	1.02	4.50	5.32
12.	"	2.17		10.40	3.11	1.23	1.01	4.70	5.65
19.	"	1.54	3.50	10.20	2.60	1.10	1.07	4.37	
20.	"	1.45	3.20	9.87	2.60	1.20	1.12	4.30	

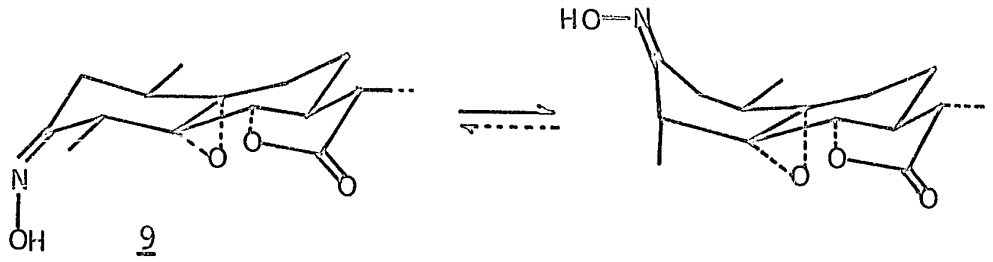
discussed earlier and by relation of all four epoxy-oximes to (-)α-desmotroposantonin (12) that the stereochemistry of the lactone ring at C-5, C-6 and C-11 is the same in both the α- and β- series of compounds. It follows therefore that the four epoxy-oximes arise by stereoisomerism at C-4 and at the oxime grouping. The formulae 8, 9, 19, and 20 are based on a study of the n.m.r. spectra described below.

The signal due to the C-4 proton in each of the epoxy-oximes gives rise to a quartet (J = 7.0 c.p.s.), as it is coupled to the protons of the C-4 methyl group. This quartet occurs at lower field (3.60 p.p.m.) in the epoxy-oxime 9 than it does in 8 (3.01 p.p.m.) from which it was derived. It is known (35) that protons having a syn- relationship with the OH group of oximes resonate at lower field than the corresponding anti- protons. The epoxy-oximes 8 and 9 accordingly have the oxime configurations as shown (chart 1). Moreover, the signal assigned to the C-2 equatorial protons which are multiplets at 3.01 p.p.m. in 8 and 2.82 p.p.m. in 9, show similar behaviour.

Both 8 and 9 can adopt two half-chair conformations, or a boat conformation in ring A, as shown below.



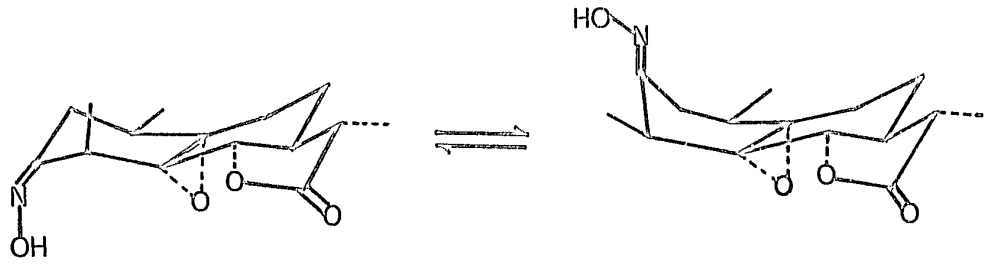
8



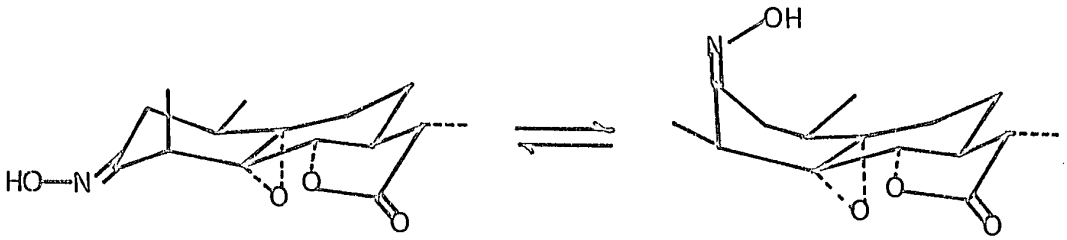
9

The chair form is likely to be favoured by 8, but due to the proximity of the oxime OH group and the C-4 methyl in the syn-oxime 9, the boat form is more likely, in which the proton and not the methyl group at C-4 is eclipsed with the oxime grouping. The sharpness and resolution of the C-4 and C-2 proton signals in 8 and 9 indicate that the conversion from one conformation to the other is slow and that the equilibrium concentration of the less stable conformer is small (34, 35).

In the same way, the epoxy-oxime 19 is assigned the syn- configuration and 20 the anti- configuration. Thus the C-4 proton is at lower field in 19 than in 20 (3.50 p.p.m. vs 3.20 p.p.m., table 2). Neither of the C-2 protons in these two isomers gives rise to well resolved peaks. The half-chair and boat forms of these two isomers are shown below:



19



20

The chair conformation is favoured in both 19 and 20 in this case; the boat form of 19 would have the C-4 methyl group eclipsed with the oxime group thus adding to the usual factors that render boat forms less stable

than chair forms. In the half-chair form of 20 the interaction between the C-2 axial hydrogen and the C-4 methyl group would not be expected to be as great as the 1:2 hydrogen non-bonding interactions typical of boat conformations. Confirmation for these observations comes from the fact that the n.m.r. peak for the C-4 methyl group is at higher field (table 2) in 19 and 20 than the same peak in 8 or 9, indicating the axial assignment as shown in 19 and 20 and the equatorial and quasi-axial assignments in 8 and 9 (36).

As the epoxy-oxime (8) is the sole product from the decomposition of the nitroso compound (7) it is evident that 7 and its precursor, hydroxylaminosantonin oxime-α (3) must be homogeneous compounds (confirming the conclusions drawn from t.l.c. studies of 3 and 7) and they both must have the anti- configuration.

In the same way, the simultaneous formation of the syn- and anti- epoxy-oximes (19) and (20) from the nitroso compound (18) confirms the fact that hydroxylaminosantonin oxime-β (13) and its nitroso derivative (18) are mixtures of syn- and anti- oximes, as concluded earlier from t.l.c. studies.

The isomerisation of 8 → 9 is remarkable, since one would have expected the anti- isomer 8 to be slightly more stable. Apparently this is not the case in this instance.

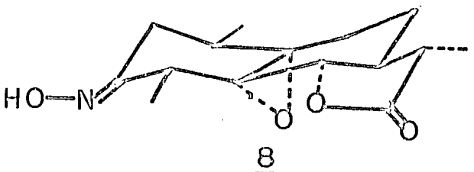
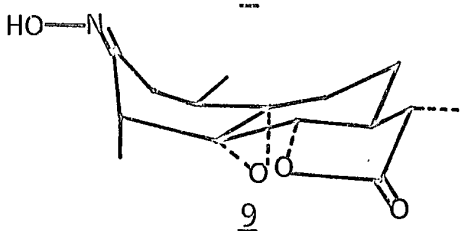
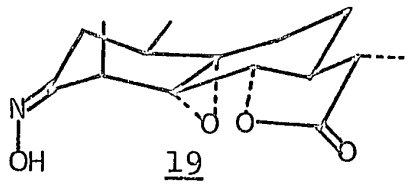
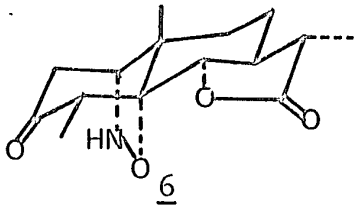
(c) The C-4 Methyl Configuration of the Epoxy-oximes 8, 9, 19, 20.

Further evidence that the C-4 methyl group is α- in the α- series and β- in the β- series came from a study of the chemical shifts of the n.m.r. peaks on going from deuterochloroform to benzene solution. It is known (37, 38) that methyl groups α-to carbonyl show either an upfield or a downfield shift on going from deuterochloroform to benzene solution, and that these shifts depend on whether the methyl group is axial or equatorial. The effect is also observed for methyl groups α- to the carbonyl of lactones (39, 40), and might be expected to hold for methyl groups α-to oxime functions.

The upfield shift of axial methyl groups is usually 0.20 - 0.40 p.p.m, and the downfield shift of equatorial methyls varies from zero to 0.30 p.p.m. The shifts are small if the methyl groups are quasi-axial or quasi-equatorial, (e.g. the C-11 methyl group of santonin (39)). The mechanism of this differential solvent shift

TABLE 3

Solvent shifts in the n.m.r. spectra of compounds 6, 8, 9, 19.

	C-4 methyl	C-1 methyl	C-11 methyl
 8	1.35	1.23	1.09
	(-0.16)	(+0.33)	(+0.21)
 9	1.37	1.24	1.06
	(-0.26)	(+0.34)	(+0.29)
 19	1.54	1.10	1.07
	(+0.37)	(+0.10)	(+0.27)
		C-10 methyl	
 6	1.33	1.24	1.06
	(+0.36)	(+0.78)	(+0.29)

is still in dispute but nevertheless the method has useful applications.

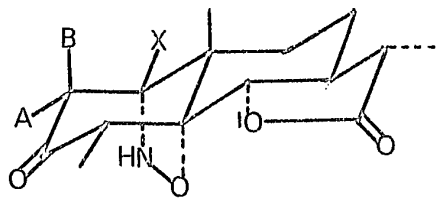
The C-4 methyl group of 8, 9, 19, and 20 is adjacent to an oxime function, but nevertheless distinct solvent shifts are observed. In table 3 the shifts on going from deuterochloroform to benzene are shown in parenthesis and are expressed as parts per million (+ or -) depending on whether the peak is shifted upfield or downfield. The results for the epoxyimino ketone (6) are also included (see also Fig. 34).

The different behaviour of the two epoxy-oximes 8 and 9 of the α- series compared to that of 19 from the β- series is dramatic, and the shifts are equal to or greater than those observed for many α-methyl ketones in the literature (37).

The epoxy-imino ketone (6) showed the greatest shift (+ 0.78 p.p.m.) for the C-10 methyl group, well removed from both the oxime and lactone carbonyl groups. The C-4 methyl showed a shift of + 0.36 p.p.m., in spite of the fact that this methyl is certainly equatorial. These facts are consistant with other observations (37)

that angular methyl groups can reduce or alter solvent shifts for equatorial methyl groups.

Other peaks of interest (Fig. 34) in the n.m.r. spectrum ($CDCl_3$) of the epoxyimino ketone (6) include one exchangeable proton as a broad peak at 5.93 p.p.m. due to the NH group, and a well resolved triplet (1 proton) at 3.30 p.p.m., (J = 3.0 c.p.s.). The latter is assigned to the bridgehead proton (X) split by the methylene protons (A, B) on C-2, the three protons forming an ABX system. The AB part is evidently centered at 2.65 p.p.m., but as the chemical shift between them is small, the expected eight lines are condensed, and also overlap with the quartet expected for the proton at C-4. Because the X proton appears as a triplet and not a quartet, $J_{(AX)}$ may

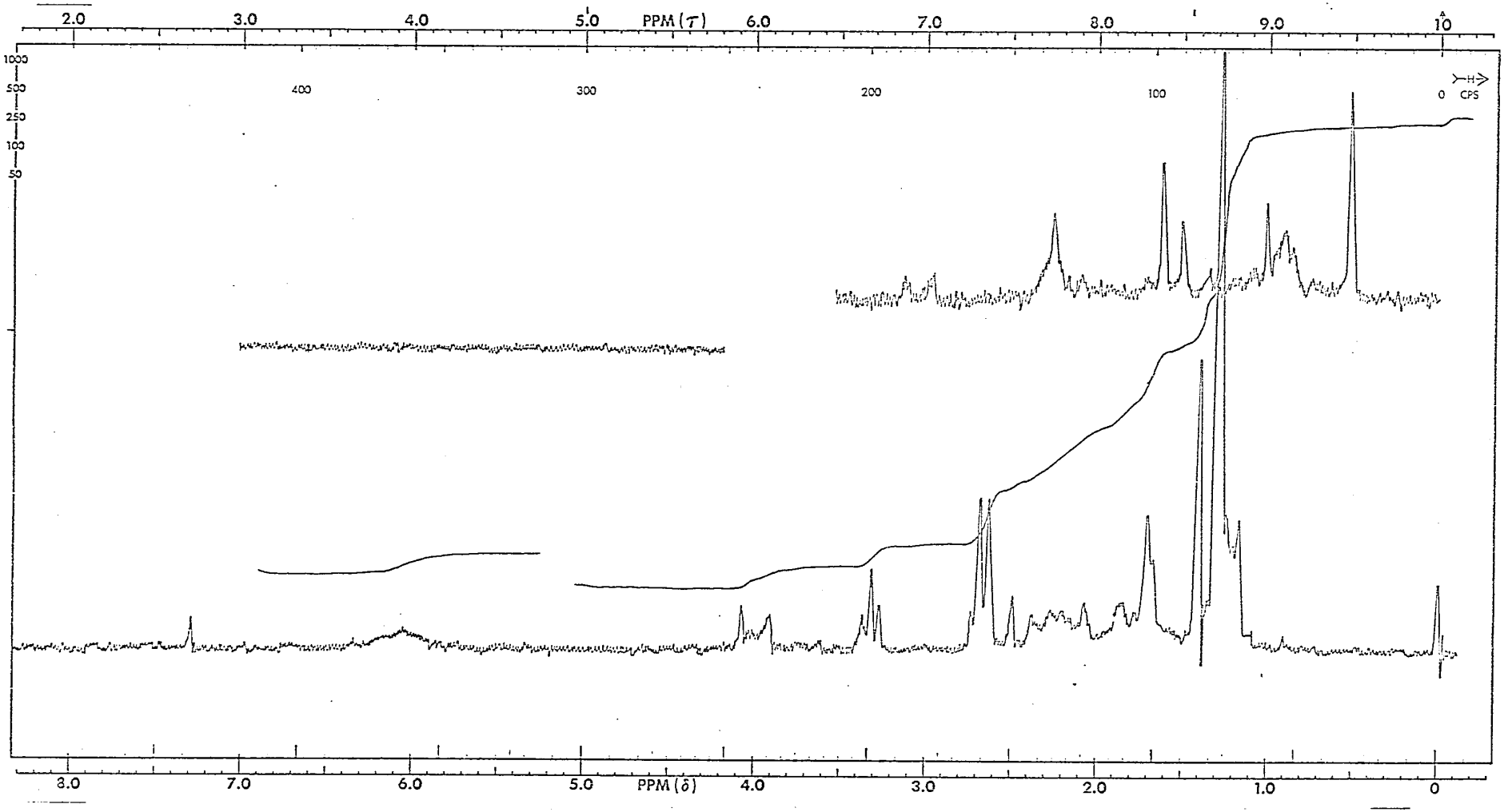


6

be equal to $J_{(BX)}$ (41, 42). It is apparent from a study of molecular models that the epoxyimino bridge must be linked to the carbon skeleton by two axial bonds, with

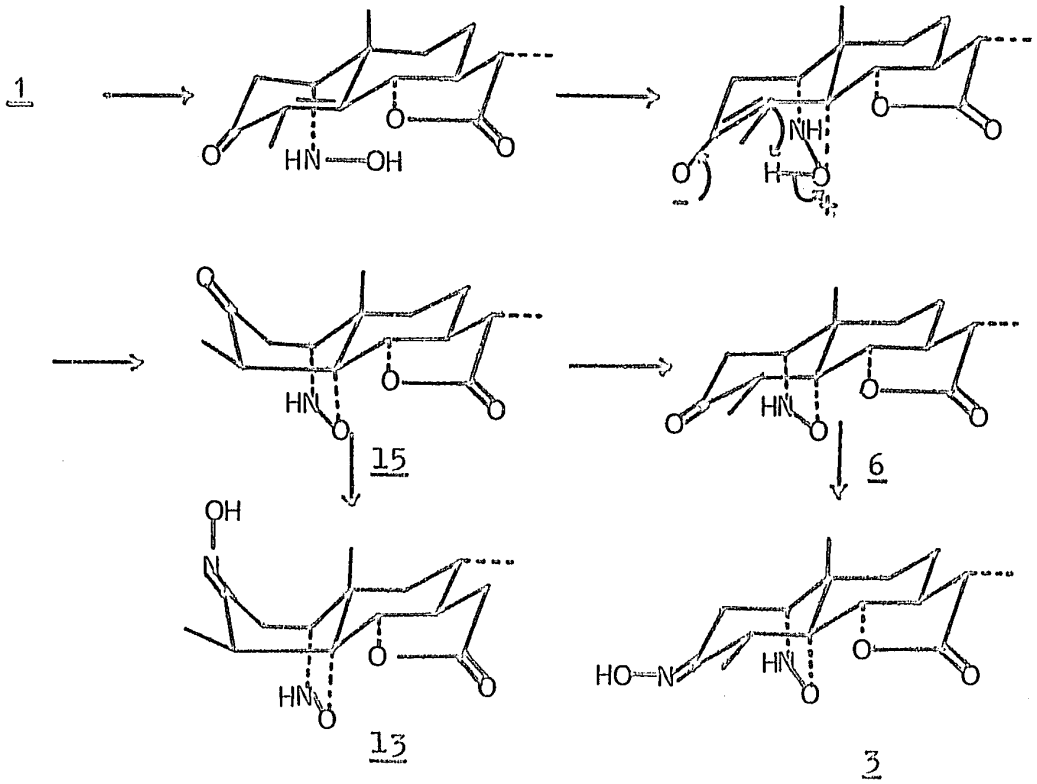
Figure 34.

The n.m.r. spectrum of 5,1-(α-epoxyimino)-4α-tetrahydrohyposantonin (6).


2.0
3.0
4.0
5.0
PPM (τ)
6.0
7.0
8.0
9.0
10
1000
500
250
100
50
400
300
200
100
0 CPS
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

respect to the cyclohexanone ring. The proton at the bridgehead must then be equatorial, and its bond axis bisects the angle between the bonds of the C-2 methylene hydrogens. The Karplus relationship (36, 43) would predict a coupling constant $J_{(AX)}$ and $J_{(BX)}$ of 3.5 cycles, in good agreement with the observed value.

The ketones 6 and 15 are probably intermediates in the reaction of santonin with hydroxylamine. When excess hydroxylamine hydrochloride is present, the hydroxylamine attacks the double bonds first to give 15, the boat form of which can be oximated to give the

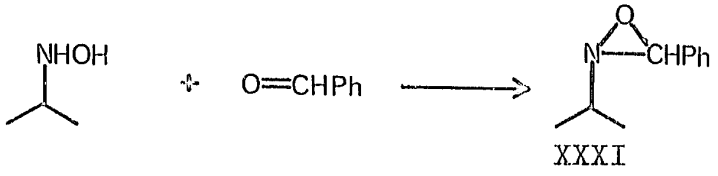


β-isomer 13. When excess sodium methoxide is present, as in the preparation of the α-isomer, the intermediate (15) is epimerised to 6, and then reacts further with hydroxylamine to give the α-isomer (3).

The high degree of stereospecificity in the addition of hydroxylamine to the double bonds at lower pH to give a β- C-4 methyl and an α- C-4 hydrogen can only be interpreted by assuming that the hydrogen comes not from the solvent but from the hydroxylamine OH group, which, as shown above, is much closer to C-4 in the proposed intermediate than any solvent protons in the solvation shell.

9. Reaction of Hydroxylaminosantonin Oximes-α and β- with benzaldehyde.

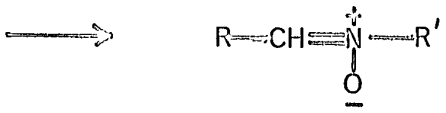
Assuming that the two isomers of their "hydroxylaminosantonin oximes" (I) contained the -NHOH group, Francesconi and Cusmano (3) reacted them with benzaldehyde in an attempt to prepare the corresponding aldonitrones at that time represented by XXXI.



XXXI

They isolated two crystalline derivatives that had the correct elemental analysis ($C_{22}H_{26}N_2O_4$). It is now known that nitrones have the structure XXXIII, the reactions

XXXII



XXXIII

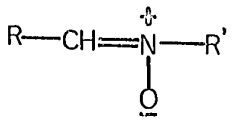
and spectra of which are described in a recent review by J. Hamer and A. Macaluso (44). The ultraviolet spectra observed for some typical nitrones are shown in table 4. The shorter wavelength band is due to transitions within the benzene ring, and the longer wavelength band to transitions involving the benzene ring and nitrone grouping in conjugation with it (45). These data preclude the oxazirane structure such as XXX for pure freshly prepared nitrones.

However, on exposure to sunlight, both the

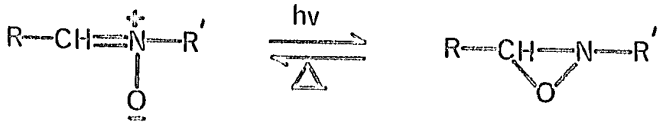
TABLE 4

The ultraviolet spectra of some aldonitrones.

R	R'	λ_{max}	ϵ_{max}	λ_{max}	ϵ_{max}
phenyl	phenyl	227	9,850	315	14,000
phenyl	methyl	221	6,932	288	16,540
phenyl	cyclohexyl	223	6,904	291	17,597



N-alkyl and N-aryl nitrones are isomerised to the oxazirane structure (XXXIV; 44-46)



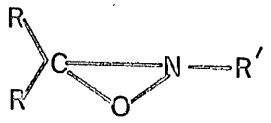
XXXIII XXXIV

This isomerisation is accompanied by the disappearance of the two original bands in the ultraviolet spectrum, and the appearance of a new band near 235 mμ. The oxazirane is itself isomerised to an amide, XXXV, by the action of heat or light (44, 45) thus accounting for the band at 235 mμ.

XXXIV XXXV

If a ketone is used instead of an aldehyde in the original condensation reaction, and the reaction mixture is irradiated, the oxazirane XXXVI can be isolated. Both types of oxazirane give not only amides on heating,

but also some of the original nitrone (44).



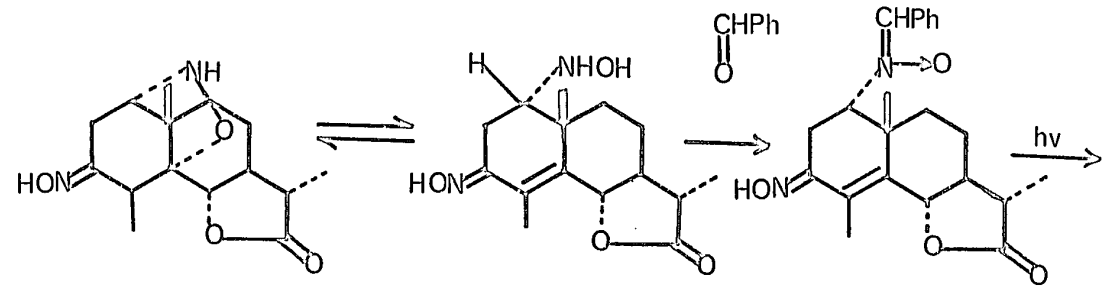
XXXVI

A literature survey did not reveal any work on the reaction of O,N-disubstituted hydroxylamines with benzaldehyde, but it might be expected not to yield a stable compound; hence, the facility with which this reaction proceeds with the hydroxylaminosantonin oximes gave rise to some doubts that they could contain an epoxy-imino grouping as shown in formula 3.

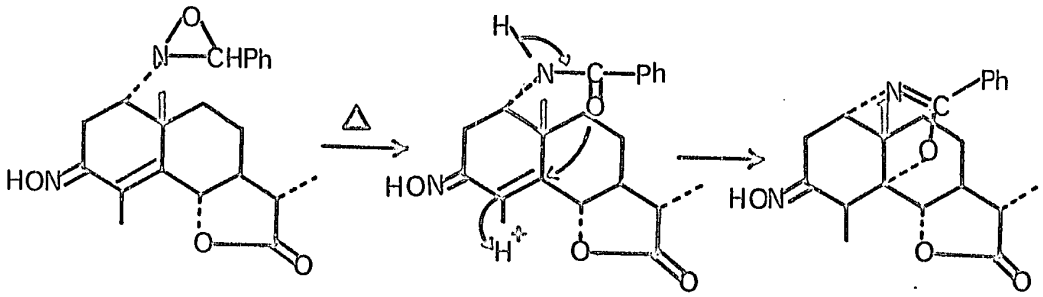
The two compounds were accordingly prepared using Francesconi's procedure (3). Hydroxylaminosantonin oxime-α was refluxed with one molar equivalent of benzaldehyde in absolute ethanol until t.l.c. analysis showed all the starting material to be consumed. After concentration at reduced pressure, the product crystallised from the reaction mixture and had the properties quoted by Francesconi and Cusmano (3) m.p. 215-217°. The compound gave a single spot on t.l.c. analysis, (R_f (b) 0.65).

The product from the reaction of benzaldehyde and

the β-isomer (13) was similarly prepared, but did not have the melting point quoted (lit. m.p. 100-140° (3)). Our compound had m.p. 219-220°, mixture melting point with the product from the α-isomer 190-200°. However, Francesconi and Cusmano stated (3) that their compound crystallised with "solvent of crystallisation" from methanol, which may have resulted in the lower melting point observed. Our material was dried at 80° under vacuum for 24 hours.



3, 13 I A



B C 5, 16

The spectral properties of these compounds immediately excluded the nitrone formula A. The intense band at 1662 cm^{-1} in the infra-red spectrum (Fig. 35) of the α-isomer, and 1665 cm^{-1} in the β-isomer (Fig. 36) lies outside the range normally quoted for nitrones (47), but could be assigned to the C=O stretching vibration of an amide (Amide I band), or to a conjugated C=N stretching vibration. The region of the spectrum above 3000 cm^{-1} showed several broad peaks due to hydrogen bonded OH stretching vibrations. It was not possible to assign any of these bands unequivocally to an NH stretching vibration.

The n.m.r. spectrum of the α-isomer (Fig. 37) showed the C-4 methyl group as a doublet (1.42 p.p.m.) and the C-6 proton resonating at the same position as in 3, indicating the absence of the double bond at C-4. Only one proton, the oxime OH, was exchangeable with D_2O. There was no absorption near 6.0 p.p.m., the region where the original benzaldehyde protons of aldonitrones normally absorb (48).

The foregoing evidence excludes structures A, B, and C for these compounds. Apparently, a cyclic structure is again involved, with a rearrangement of the epoxyimino bridge.

Figure 35.

The infra-red spectrum of 5,1-(α-epoxy-phenylmethenonitrilo)-4α-tetrahydro-santonin anti-oxime (5).

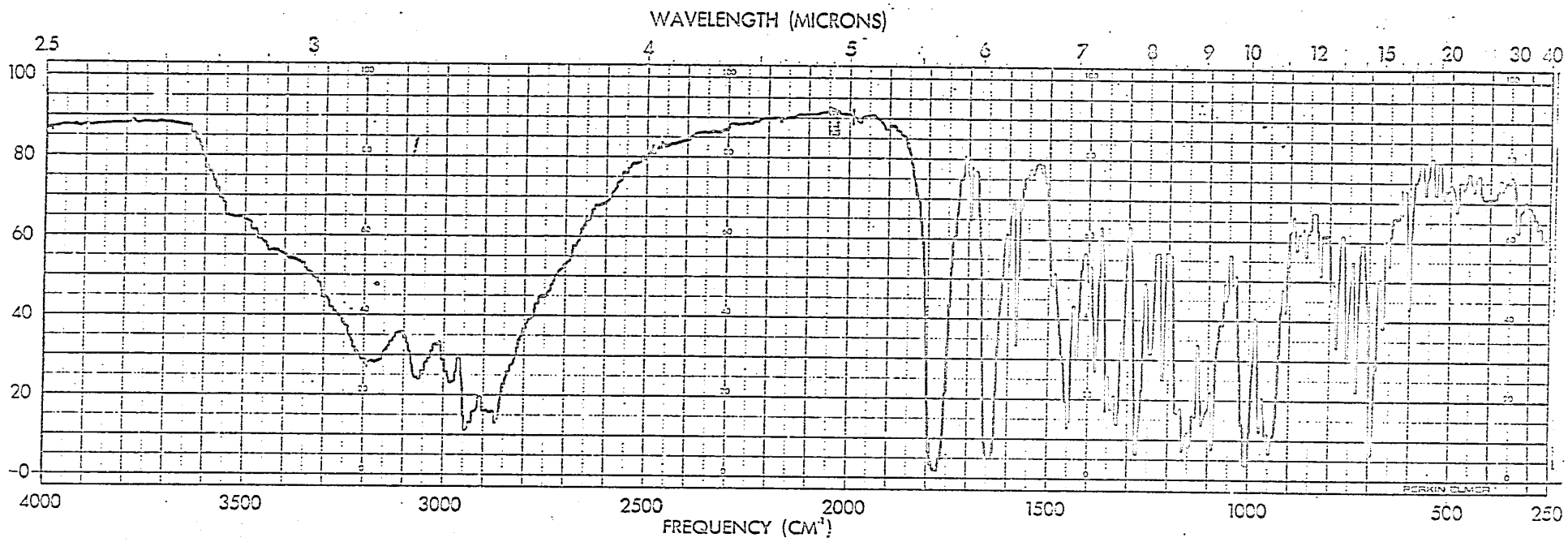

WAVELENGTH (MICRONS)
2.5
3
4
5
6
7
8
9
10
12
15
20
30
40
100
80
60
40
20
0
4000
3500
3000
2500
2000
1500
1000
500
250
FREQUENCY (CM-1)
PERKIN ELMER

Figure 36.

The infra-red spectrum of 5,1-(-epoxy-phenylmethenonitrilo)-4 -tetrahydro-santonin syn-oxime (16).

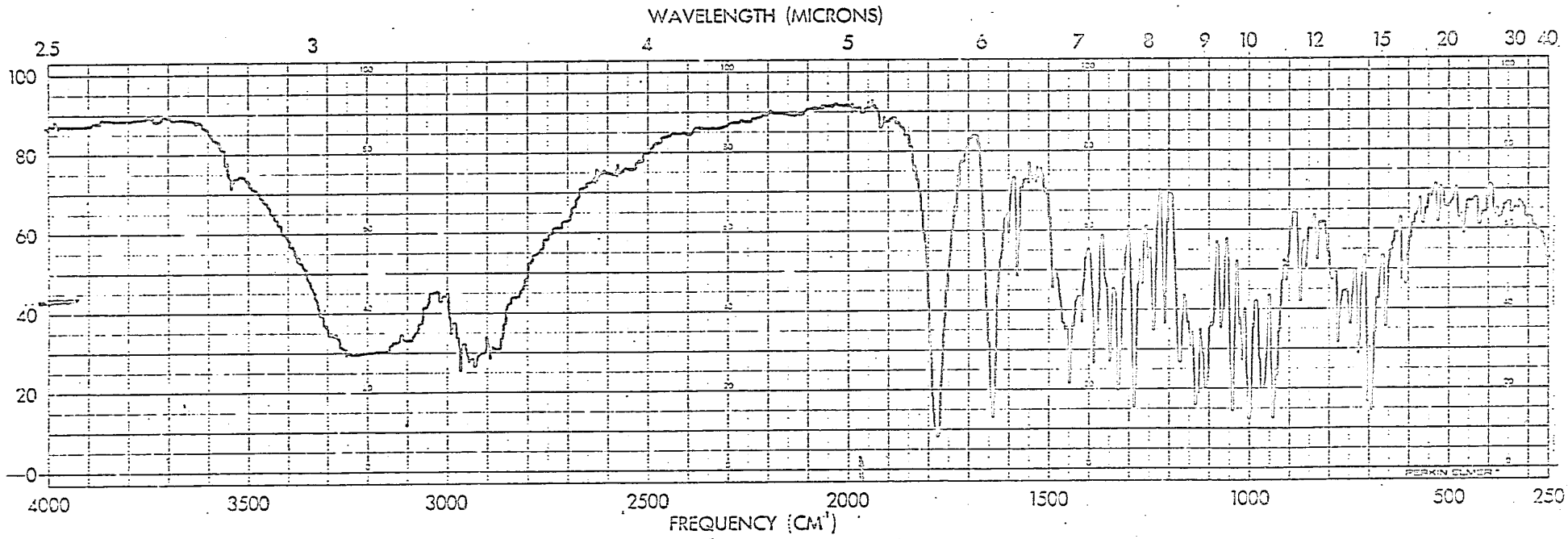
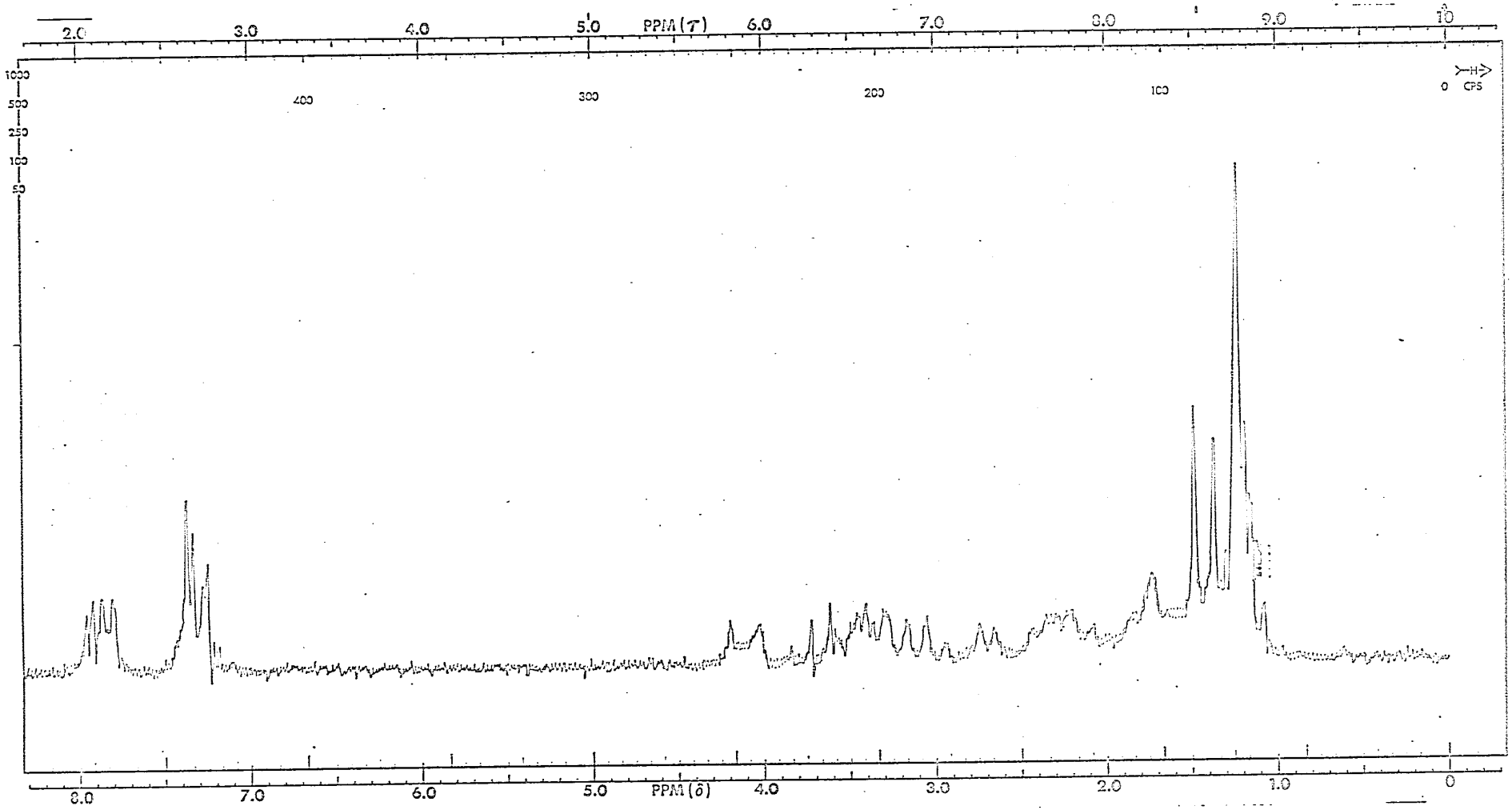

WAVELENGTH (MICRONS)
2.5
3
4
5
6
7
8
9
10
12
15
20
30
40
100
80
60
40
20
0
4000
3500
3000
2500
2000
1500
1000
500
250
FREQUENCY (CM-1)
PERKIN ELMER

Figure 37.

The n.m.r. spectrum of 5,1-(α-epoxy-phenylmethenonitrilo)-4α-tetrahydro-santonin anti-oxime (5).


2.0
3.0
4.0
5.0
PPM (τ)
6.0
7.0
8.0
9.0
10
400
300
200
100
0 CPS
1000
500
250
100
50
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

The most likely possibility is the benzimidate structure 5, and 16, possibly arising by cyclisation of the intermediate C. The presence of a benzimidate grouping was confirmed by the ultraviolet absorption of the compounds in neutral and acid solution (Figs. 38, 39), which compares well with values reported in the literature for ethyl benzimidate (49). Furthermore, the pK_{BH^+} of the two compounds (4.65 and 4.70) determined from the change in absorption with pH from Figs 38 and 39 by the usual method (50) was in good agreement with the expected values (51).

The mechanism of this remarkable reaction remains obscure. A possible mechanism might involve the formation of the free hydroxylaminosantonin oxime I from 3 or 13, followed by the sequence I⟶A⟶B⟶C⟶5,16. This mechanism can be excluded because it would require hydroxylaminosantonin oxime-α to be isomerised to the β-isomer in refluxing ethanol (via the intermediate I) under the conditions of the reaction with benzaldehyde. No such isomerisation is observed. Furthermore, the presence of the nitrone intermediate (A) could not be detected during the reaction. Thus, ultraviolet spectroscopic examination of the reaction mixture showed an absorption peak at 235 mμ, but no peak in the 250 - 350 mμ region. The same result was obtained when the reaction was conducted with complete exclusion of light.

Figure 38.

The ultraviolet absorption spectrum of 5,1-(α-epoxyphenylmethononitrilo)-4α-tetrahydroxanthonin anti-oxime (5) in buffers of various pH.

Curve.	pH.
(a)	8.9
(b)	6.6
(c)	4.5
(d)	3.7
(e)	1.0
(f)	-1.0

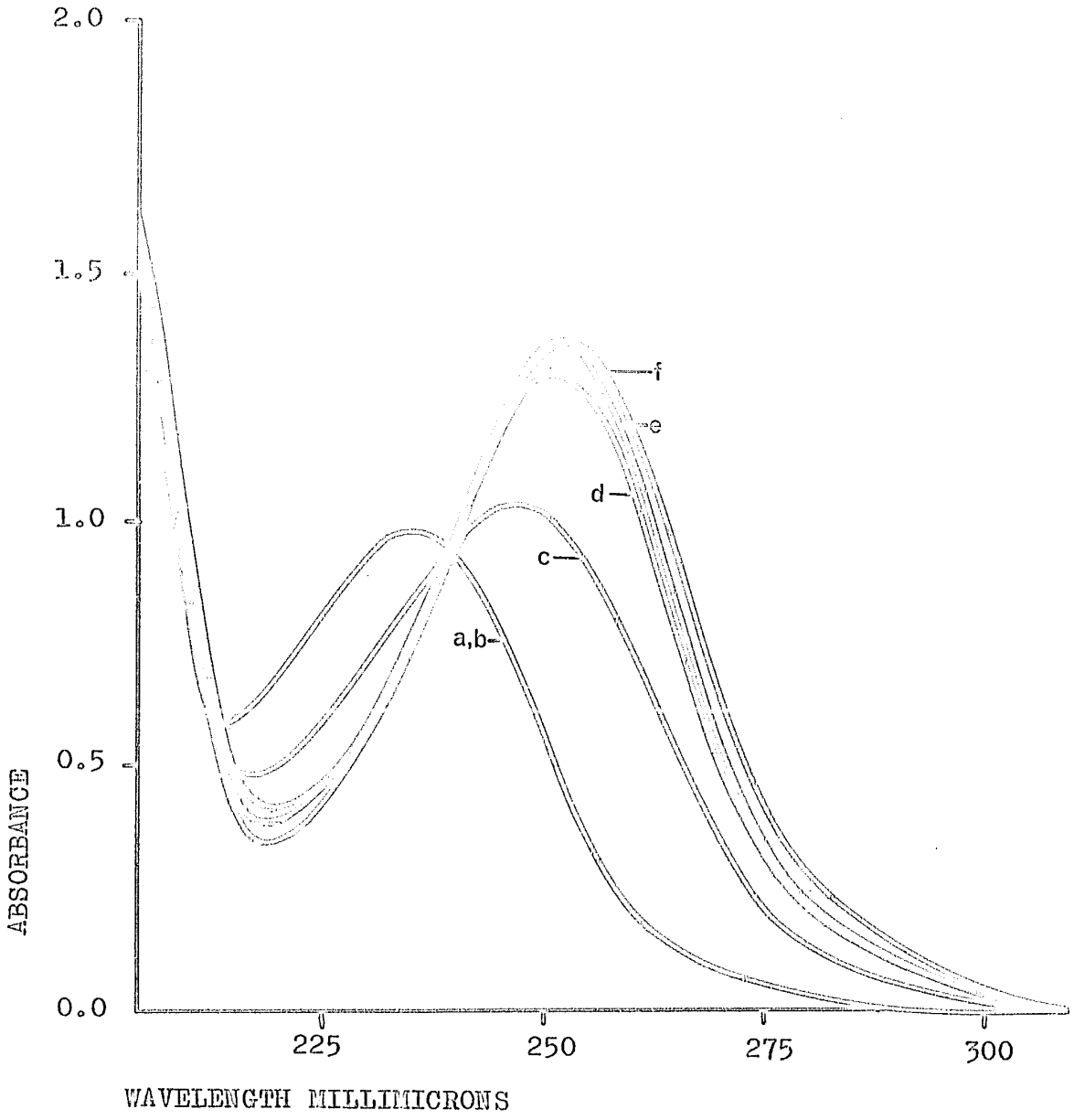
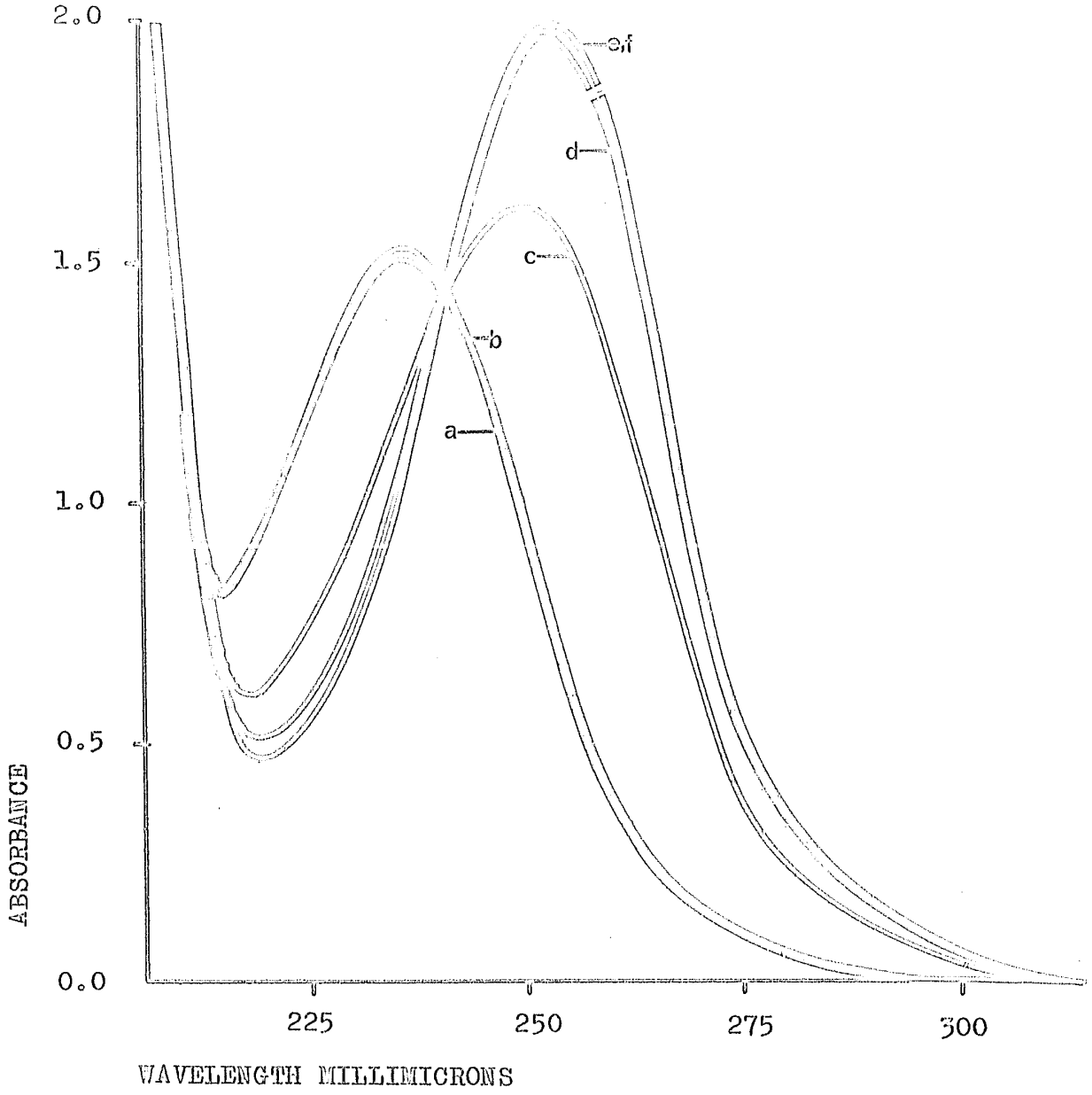

2.0
1.5
1.0
0.5
0.0
ABSORBANCE
225
250
275
300
WAVELENGTH MILLIMICRONS
f
e
d
c
a,b

Figure 39.

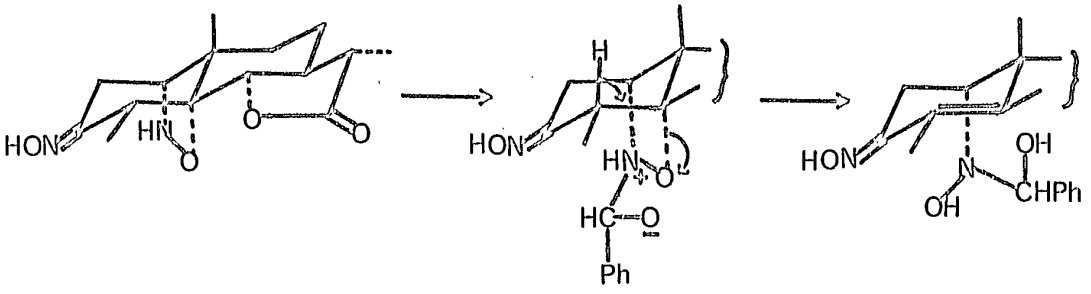
The ultraviolet absorption spectrum of 5,1-(*o*-epoxyphenylmethenonitrilo)-4*a*-tetrahydrosantonin syn-oxime (16) in buffers of various pH.

Curve.	pH.
(a)	8.9
(b)	6.6
(c)	4.5
(d)	3.7
(e)	1.0
(f)	-1.0

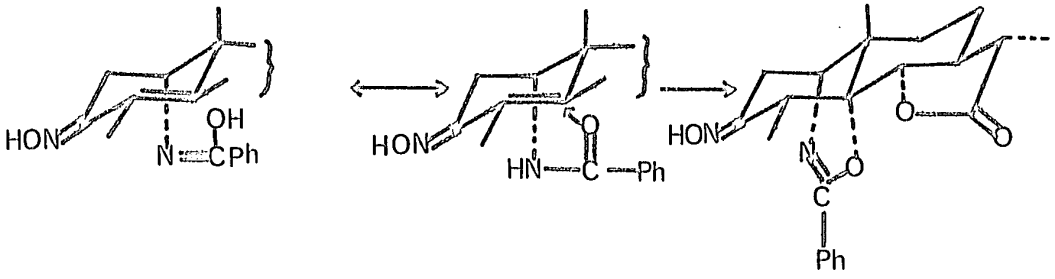

2.0
1.5
1.0
0.5
0.0
ABSORBANCE
225
250
275
300
WAVELENGTH MILLIMICRONS
e,f
d
c
b
a

If a nitrone intermediate is formed at all in these reactions, it must be formed in such small amounts as to be undetectable by ultraviolet spectroscopy, or it must be thermally decomposed before it can accumulate in solution. The latter is not very likely as many aldonitrones can readily be isolated (44-46).

A possible mechanism is the following, in which the initial condensation of benzaldehyde with the epoxy-imino groups of 3 and 13 assists the elimination of oxygen



3 D E

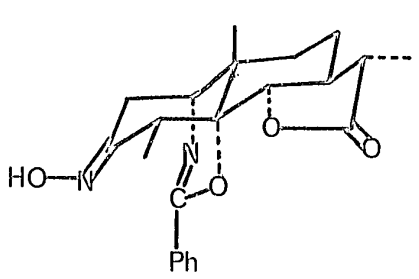


F G 5

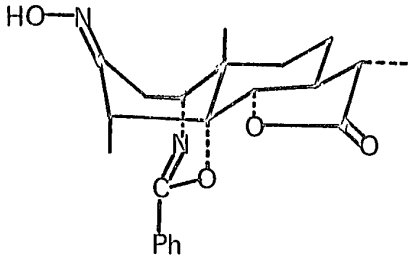
β to the oxime group to give the unsaturated species E-G, (which is required in any plausible mechanism for formation of 5 and 16).

If this mechanism is correct, then both the α- and β-isomers must proceed through the intermediates E, F, G, and must therefore have the same C-4 methyl configuration. The compounds would therefore be identical, except that the configuration of the oxime group may be different in the two isomers (5, 16).

A comparison of the n.m.r. spectra of 5 and 16 (Figs. 37 and 40, and table 1) indicate that the α-isomer 5 has the anti- oxime and the β-isomer the syn- oxime configuration.



5

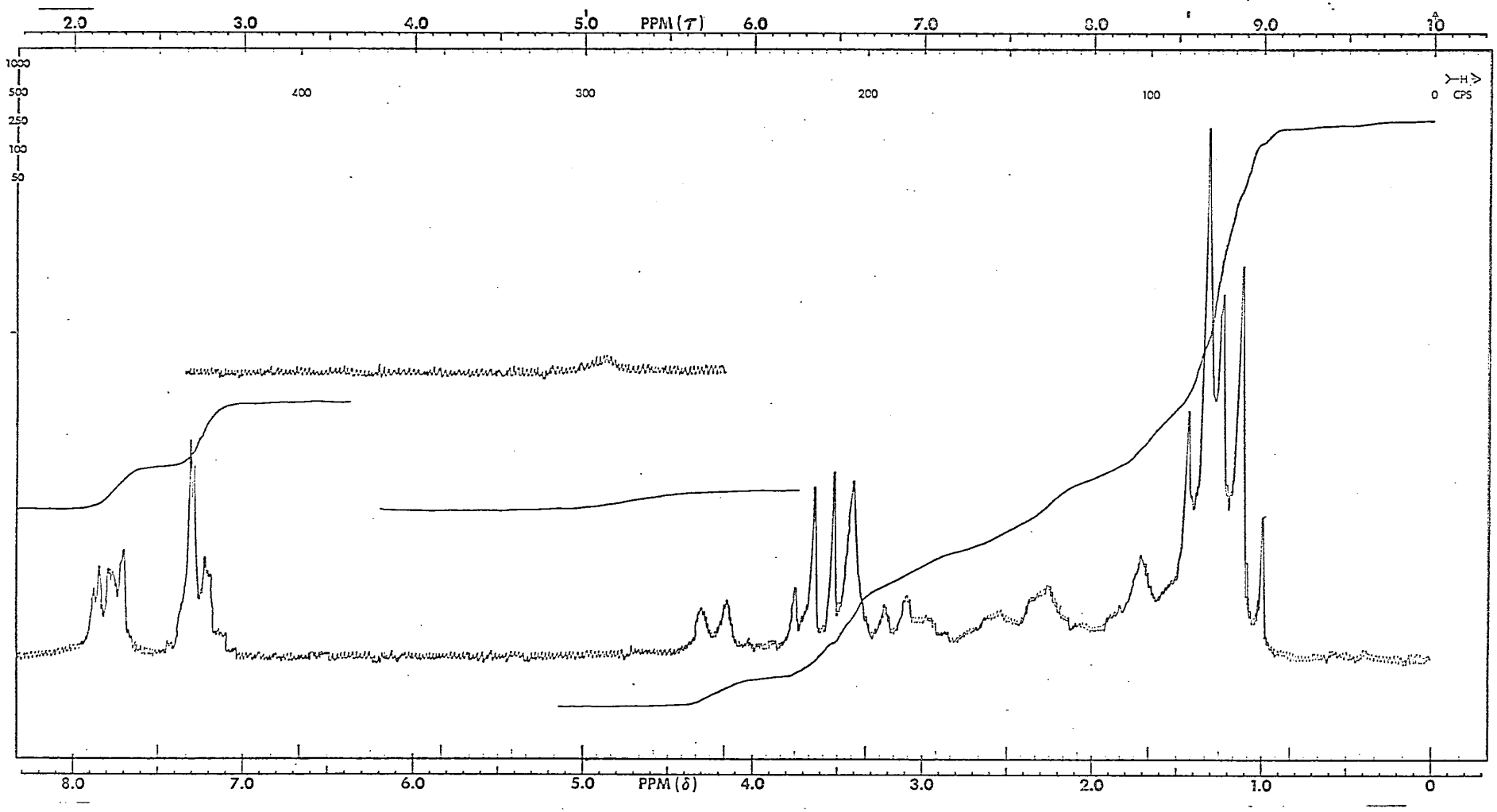


16

For the same reasons as discussed for the epoxy-oximes (p. 86) the α-isomer probably has the chair conformation and the β-isomer the boat conformation as shown above.

Figure 40.

The n.m.r. spectrum of 5,1-(α-epoxyphenyl-methenonitrilo)-4α-tetrahydrosantonin-syn-oxime (16).

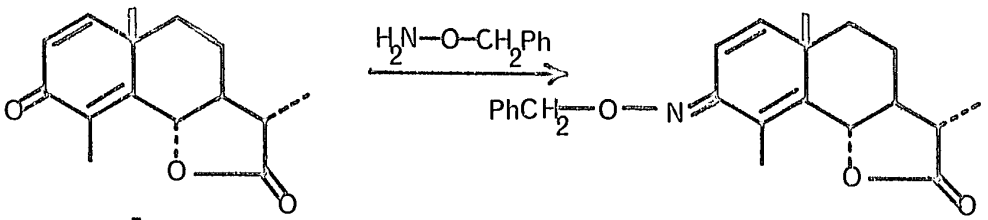

2.0
3.0
4.0
5.0
PPM (τ)
6.0
7.0
8.0
9.0
10
1000
500
250
100
50
400
300
200
100
0
CPS
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

The major difference between the two n.m.r. spectra is the position of the quartet due to the C-4 proton. It is at higher field in the spectrum of 5 (3.11 p.p.m.) than in 16 (3.58 p.p.m.).

This is consistent with the fact that the 5,1-(α-epoxyimino)-4α-tetrahydrosantonin oxime (3) was assigned the anti- configuration and the 4β-isomer was considered to be a mixture of syn- and anti- oximes, though the relative amounts were not known.

10. Reaction of Santonin with O-Benzylhydroxylamine.

The reaction of santonin with O-benzylhydroxylamine was investigated in the hope of obtaining the di-O-benzyl ether of I. The reaction gave the substituted oxime of santonin in 90% yield. The product melted at 151°,



1 XXXVII

(lit. 151° (52)), and had no OH or NH stretching bands in

the infra-red spectrum. The n.m.r. spectrum showed the presence of two olefinic protons and the C-4 methyl group as a singlet similar to the spectrum of santonin oxime (2).

O-benzylhydroxylamine apparently attacks the carbonyl faster than the double bonds, hence only the simple oxime was isolated. No compounds resulting from attack of the double bonds could be detected, since t.l.c. analysis of the reaction mixture showed the oxime (XXXVII) as the only product.

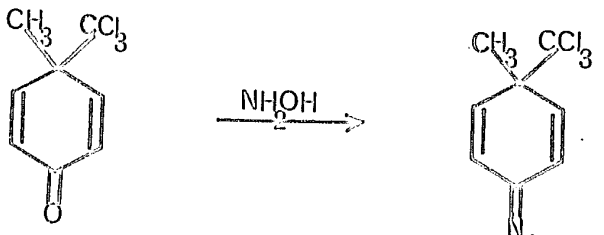
11. Reaction of Hydroxylamine with some other Cyclic Dieneones.

(a) With 4-Methyl, 4-trichloromethyl cyclohexa-2,5-dieneone (XXXVIII).

When 4-methyl, 4-trichloromethyl cyclohexa-2,5-dieneone (53) was allowed to react with excess hydroxylamine in methanol, the only product was the simple oxime (XXXIX) m.p. 134° (lit. m.p. 134° (53)), λ_{max} 252.5 mμ, ϵ_{max} 18,000. T.l.c. analysis showed no other products in the reaction, the oxime (XXXIX) being obtained in 90% yield.

The same result was obtained when 0.30 moles of

sodium methoxide was added to the reaction mixture, and

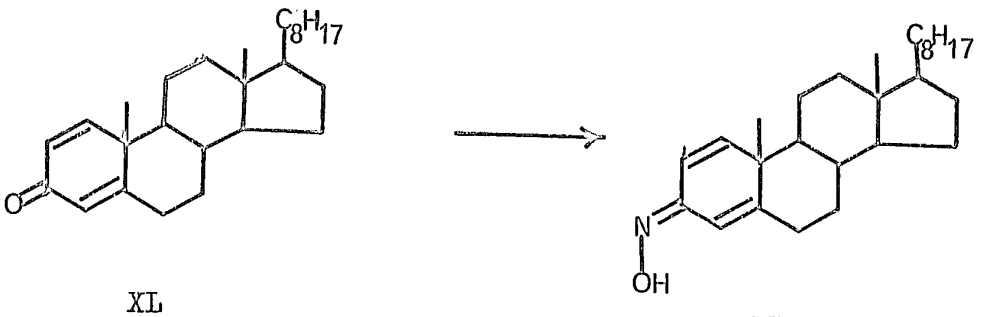


XXXVIII XXXIX

also when 0.30 moles of hydroxylamine hydrochloride was added. The reaction was complete within three hours in all cases.

(b) With Cholesta-1,4-diene-3-one (XL).

When cholesta-1,4-diene-3-one (XL; 54, 55) was



XL XLI

refluxed with a three molar excess of hydroxylamine in

methanol, the product was mainly the oxime (XLI), R_f (c) 0.50, obtained as minute crystals from aqueous methanol. The mother liquor contained the remainder of (XLI) and two other compounds, (R_f (c) 0.30 and 0.25). The latter were separated from XLI by column chromatography, but could not be crystallised. The infra-red spectrum of the two component mixture showed bands at 1730 cm^{-1} (s) evidently a saturated carbonyl absorption, and bands at 1605, 1580, 1490 (m), 1280, 1120 and 1070 (s) cm^{-1}. There was no OH or NH absorption, and the mixture was not soluble in dilute hydrochloric acid, as might be expected if the -NHOH or -NH-O- groups were present.

As the compounds were present in minor amounts ($< 10\%$) and the mixture turned brown on standing, they were not studied further. It appears from these preliminary investigations that santonin has a much greater tendency than other cyclic dieneones to add hydroxylamine and form bridged epoxyimino compounds. No plausible reason for this can be advanced at the moment.

EXPERIMENTAL

General Methods.

Melting points were determined using a Gallenkamp electrical apparatus, and are corrected. Infra-red spectra were obtained with Perkin-Elmer model 337 and Perkin-Elmer model 521 spectrophotometers. Ultraviolet spectra were obtained using a Unicam model S. P.-800 recording spectrophotometer and are for ethanol solutions unless otherwise noted. N.M.R. spectra were obtained with a Varian Associates A-60 instrument, Optical rotations were determined with a Carl Zeiss automatic polarimeter at 25^{o}, using a I.0 dm. cell, and concentrations of about 8% in ethanol. Analyses were carried out by Dr. C. Daessle, Montreal.

Mass spectra were taken by Morgan Schaffer Corp., Montreal, on a Hitachi Perkin-Elmer R.M. 960 Mass Spectrometer. Molecular weights of samples sent for mass spectral analysis were confirmed by osmometry using a Mechrolab Inc. Vapour Pressure Osmometer model 301A, with purified benzil as the calibration standard, and methanol as the solvent. Silica gel G and calcium sulphate were used for preparative thick layer chromatography and for t.l.c., and silica gel (Grace Davison Chemical, grade 923) for column chromatography. Santonin was supplied by MacFarlan, Smith, Ltd.,

Montreal. Unless otherwise noted, three solvent mixtures were used to elute t.l.c. plates and R_f values are indicated as R_f (a), R_f (b), R_f (c), where (a) refers to 50% benzene, 50% ether; (b) to 45% benzene, 45% ether, 10% ethanol and (c) to a mixture of chloroform (15 ml), ether (10 ml), methylene chloride (15 ml), methanol (2 ml).

5,1-(@-Epoxyimino)-4@-tetrahydrosantonin anti-Oxime (3).

(a) From the Reaction of Santonin with Hydroxylamine.

The general method of Francesconi and Cusmano (3) was used, with slight variations that achieved somewhat better yields. In a typical run, a solution of sodium methoxide prepared from sodium metal (46.6 g., 2 moles) and methanol (1 l) was mixed with a solution of hydroxylamine hydrochloride (140 g., 2 moles) in methanol. After removing the sodium chloride by filtration, more sodium methoxide (from sodium metal (7 g., 0.3 moles)) was added, and the solution was concentrated to 1 l. Santonin (1; 120 g.) was added, and the solution refluxed under nitrogen until all the santonin was shown by t.l.c. to be consumed, (about 24 hours). The solution was concentrated to a volume of 150 ml

under reduced pressure, and water (100 ml) was added. The clear solution at room temperature deposited fine white needles (30 g.) shown by t.l.c. to be a mixture of santonin oxime (2) and 5,1-(α-epoxyimino)-4α-tetrahydrosantonin anti- oxime (3), which gave no colour with ferric chloride solution. The solid was suspended in hot methanol (50 ml), and filtered. The residue (15 g.) was almost pure 5,1-(α-epoxyimino)-4α-tetrahydrosantonin anti- oxime (3). Evaporation of the filtrate gave only santonin oxime.

Evaporation of the mother liquor from the first crop gave a second crop of 5,1-(α-epoxyimino)-4α-tetrahydrosantonin anti- oxime (15 g., total 20%); further concentration of the filtrate gave only santonin oxime. The 5,1-(α-epoxyimino)-4α-tetrahydrosantonin anti- oxime crystallised from methanol in fine white prisms giving a single spot on t.l.c. analysis and turning brown at about 200°, melting with evolution of gas at 230°, $[\alpha]_D^{25}$ + 46.5°, (lit. m.p. 229-230°, $[\alpha]_D^{12}$ + 47.44° (3)), υ_{max} (KBr) 3550 (s), 3250 (s) 1750 (s), 1650 (w) and 1630 (w) cm^{-1}. The ultraviolet spectrum showed no absorption peak above 200 mμ.

Anal. Calcd. for $C_{15}H_{22}O_4N_2$:
C,61.20; H,7.53; N,9.52; mol. wt. 294.34.
Found: C,60.66; H,7.28; N,9.40; mol. wt. 297 ± 1% (osmometry), 294 (mass spectrum).

(b) From the Reaction of 5,1-(α-epoxyimino)-4α-tetrahydrosantonin (6) and hydroxylamine.

The ketone 6 (0.192 g.) was treated with hydroxylamine in methanol (5 ml). The reaction was complete in three hours at 100°. T.l.c. analysis showed the gradual disappearance of the ketone (R_f (a) 0.24) and the appearance of a spot having the same R_f values (R_f (a) 0.45; R_f (b) 0.50) as 5,1-(α-epoxyimino)-4α-tetrahydrosantonin anti- oxime (3). On cooling the reaction mixture, colourless prisms were obtained, identified as 3 by melting point (229-230°), mixture melting point, optical rotation ($[\alpha]_D^{25}$ + 46.5), and I.R. spectrum.

5,1-(α-Epoxyimino)-4β-tetrahydrosantonin syn- and anti- Oximes (13).

The following procedure is an improvement over that of Francesconi and Cusmano (3). Santonin, hydroxylamine hydrochloride and sodium methoxide were allowed to react under the conditions used in the preparation of the α-isomer, the mole ratio of hydroxylamine hydrochloride to sodium methoxide now being 1.15: 1.00. After 24 hours refluxing the solution was concentrated to about 200 ml; on cooling, santonin oxime (30 g.) crystallised out. On addition of water (300 ml), a further 35 grams of santonin oxime

precipitated and was removed by filtration. The filtrate gave a strong violet colour with ferric chloride. After being washed several times with chloroform to remove santonin oxime, the aqueous solution was boiled for 15 minutes. On cooling, 5,1(α-epoxyimino)-4β-tetrahydrosantonin syn- and anti- oximes (13) separated as colourless needles (25 g., 16.5%).

These were crystallised from aqueous dimethyl sulphoxide, and gave two overlapping spots (R_f (b) 0.50) on a t.l.c. plate. The compound turned brown at about 200°, and melted with evolution of gas at 232-233°; mixture melting point with the α-isomer (3), 210°; $[\alpha]_D^{25}$ 0.0° (lit. m.p. 232-233°, $[\alpha]_D^{12}$ - 3.0° (3)). The infra-red and ultra-violet spectra were similar to those of the α-isomer.

Anal. Calcd. for $C_{15}H_{22}N_2O_4$:
C,61.20; H,7.53; N,9.52.
Found: C,60.54; H,7.14; N,10.07.

Levulinic Acid Treatment of 5,1(α-epoxyimino)-4α-tetrahydrosantonin anti-oxime (3).

5,1-(α-Epoxyimino)-4α-tetrahydrosantonin anti-oxime (3; 1 g.) was heated on the steam bath with levulinic

acid reagent (15 ml) for four hours (18). Neutralisation with sodium bicarbonate and extraction with chloroform removed a white crystalline product (0.78 g.), found by mixture melting point, I.R., and n.m.r. spectra to be identical with santonin oxime (2).

The same result was obtained when 5,1-(α-epoxyimino)-4β-tetrahydrosantonin oxime (13) was refluxed with levulinic acid.

5,1-(α-Epoxyimino)-4α-tetrahydrosantonin (6).

(a) From 5,1-(α-epoxyimino)-4β-tetrahydrosantonin oximes (13).

5,1-(α-Epoxyimino)-4β-tetrahydrosantonin oximes (1.5 g.) in ethanol (20 ml) was treated with a solution of sodium bisulphite (2.8 g., 3.5 equivalents) in water (10 ml). Partial precipitation of both reagents occurred. The mixture was refluxed on the steam bath with vigorous bubbling of nitrogen to keep the solids in suspension. After half an hour all the reagents had dissolved and t.l.c. analysis showed the starting material (R_f (a) 0.35) and three other spots, the first of which was of low intensity and had the

same R_f value as santonin (0.70); the second spot, approximately 40% of the reaction mixture, had R_f (a) 0.24. The third, (R_f (a) 0.00) accounted for 50% of the reaction mixture. After four hours all the starting material was consumed, and t.l.c. analysis showed a new spot (R_f (a) 0.55). The solution was concentrated to 10 ml, transferred to a separatory funnel and acidified with cold dilute HCl (50 ml), and extracted with chloroform (2 x 50 ml). Evaporation of the solvent gave a yellow oil (0.250 g.) which crystallised on addition of ether and cooling as white platelets, m.p. 171°, identified by its I.R. and U.V. spectra as santonin.

The aqueous layer from the extraction was neutralised with solid sodium bicarbonate and extracted with chloroform (2 x 50 ml). Evaporation of the solvent gave a yellow crystalline product (0.50 g.). Two crystallisations from 96% ethanol gave colourless needles, (0.20 g., R_f (a) 0.24), m.p. 190.5°, $[\alpha]_D^{25}$ + 13.9°; λ_{max} 294 mμ, ϵ_{max} 17; υ_{max} (KBr) 3260 (s), 1775 (s), 1710 cm^{-1} (s).

Anal. Calcd. for $C_{15}H_{21}NO_4$:
C,64.49; H,7.58; N,5.01.
Found: C,64.39; H,7.55; N,5.10.

The mother liquor showed the spot (R_f (a) 0.55),

as well as santonin (R_f (a) 0.70) and 6, (R_f (a) 0.24). When the mother liquor was made alkaline with a trace of sodium methoxide, and allowed to stand at room temperature for three minutes, the spot (R_f (a) 0.55) was shown by t.l.c. analysis to have completely disappeared.

(b) From 5,1-(α-epoxyimino)-4α-tetrahydrosantonin anti- oxime (3).

5,1-(α-Epoxyimino)-4α-tetrahydrosantonin anti- oxime (0.5 g.) was allowed to react under the conditions described above for the β-isomer. Santonin (0.125 g.) was recovered by chloroform extraction of the acidified reaction mixture. After neutralisation with sodium bicarbonate, chloroform extraction gave a crystalline product (0.225 g.), m.p. 190°, identical by mixture melting point, I.R., U.V. and n.m.r. spectra with the product (6) from 5,1-(α-epoxy-imino)-4β-tetrahydrosantonin syn- and anti- oximes (13). The mother liquors from which this compound separated showed only santonin and 6 (R_f (a) 0.24), but no spot with R_f (a) 0.55.

5,1-(α-Epoxyphenylmethenonitrilo)-4α-tetrahydro-santonin anti- Oxime (5).

The method of Francesconi and Cusmano (3) was used.

5,1-(α-epoxyimino)-4α-tetrahydrosantonin anti-oxime (3; 1.0 g.) and benzaldehyde (1 ml) were refluxed in absolute ethanol (10 ml) until t.l.c. showed the reaction to be complete (36 hours). The pale red solution was concentrated and cooled. A precipitate was removed by filtration, washed with a little cold ether, and recrystallised from aqueous methanol. The needles obtained (0.75 g.) gave a single spot (R_f (b) 0.65) on a t.l.c. plate, m.p. 215-217°; λ_{max} 235 mμ, ϵ_{max} 11,230; υ_{max} (KBr) 3550 (w), 3200 (s), 3080 (s), 1790 (s), 1662 (s), 1600 (w), 1615 (w), 1510 (m) and 1490 (m) cm^{-1}.

Anal. Calcd. for $C_{22}H_{26}N_2O_4$:
C,69.08; H,6.85; N,7.33.
Found: C,69.36; H,6.89; N,7.54.

5,1-(α-Epoxyphenylmethenonitrilo)-4α-tetrahydrosantonin syn-Oxime (16).

The above procedure, applied to the β-isomer (13) gave colourless needles (0.75 g.) decomposing above 170°, m.p. 219-220°; mixture melting point with the product from the α-isomer, 190-200°; λ_{max} 235 mμ, ϵ_{max} 10,600; υ_{max} (KBr) 3450 (w), 3250 (s. broad), 1787 (s), 1655 (s), 1612 (w), 1592 (m) and 1505 (m) cm^{-1}.

Anal. Calcd. for $C_{22}H_{26}N_2O_4$:
C,69.08; H,6.85; N,7.33.
Found: C,68.80; H,7.05; N,7.12.

Determination of Basic Strength of Cyclic Imidates 5 and 16.

Standard spectrophotometric procedures were used (50). For the dilutions 1 ml of a stock solution, prepared from the imidate 5 (0.0121 g.) in methanol (25 ml), was added to a 50 ml volumetric flask and made up to 50 ml with aqueous buffer solution. The pH of the mixture was determined before the U.V. measurement was made. The pK_{BH^+}, calculated from the absorption curves at 245 and 255 mμ was 4.65 ± 0.20. The pK_{BH^+} for the imidate 16, determined in the same way, was 4.70 ± 0.20.

O,N-Dibenzoyl-5,1-(α-epoxyimino)-4α-tetrahydrosantonin anti-Oxime (4).

To 5,1-(α-epoxyimino)-4α-tetrahydrosantonin anti-oxime (3; 1 g.) in pure pyridine (0.75 ml) in a stoppered flask at room temperature was added benzoyl chloride (1 ml). The reaction mixture was poured into dilute aqueous hydrochloric acid, and the precipitate taken up in ether. The

ether solution was washed with 5% sodium bicarbonate solution, water, and dried ($MgSO_4$). An oily product was obtained, very soluble in ethanol and methanol, from which nothing could be crystallised. The product was dissolved in ether and placed in the refrigerator. After two weeks minute crystals (0.030 g.) separated, m.p. 175-178°, υ_{max} (KBr) 1785 (s), 1750 (s), 1640 (s), 1600 (m), and 1505 (w) cm^{-1}.

Anal. Calcd. for $C_{29}H_{30}N_2O_6$:
C,69.30; H,6.02; N,5.57.
Found: C,68.10; H,6.05; N,6.01.

O,N-Dibenzoyl-5,1-(α-epoxyimino)-4β-tetrahydrosantonin anti-Oxime (14).

This compound was reported previously (3); however, the procedure reported above for the 4α-isomer was considerably more convenient. The product (0.80 g.) was recrystallised from methanol as needles, giving a single spot on a t.l.c. plate (R_f (b) 0.75), m.p. 185-186°, λ_{max} 233.5, ϵ_{max} 25,000, and λ_{max} 273, ϵ_{max} 4,785,(methanol); υ_{max} (KBr) 1785 (s), 1750 (s), 1640 (s), 1615 (m), 1582 (m) and 1505 (m) cm^{-1}.

Anal. Calcd. for $C_{29}H_{30}N_2O_6$:
C,69.30; H,6.02; N,5.57.
Found: C,69.42; H,6.13; N,5.96.

5,1-(α-Epoxynitrosoimino)-4α-tetrahydrosantonin anti-Oxime (7).

The procedure of Francesconi and Cusmano (3) was followed. 5,1-(α-Epoxyimino)-4α-tetrahydrosantonin anti-oxime (3; 5.0 g.) in water (50 ml) containing HCl (0.65 g., 1 equivalent) was treated with sodium nitrite (1.15 g.) in water (5 ml). A pale yellow precipitate formed, which was digested in hot ethanol (25 ml), and then filtered off to give 5,1-(α-epoxynitrosoimino)-4α-tetrahydrosantonin anti-oxime (7). A portion was recrystallised from methanol and obtained as minute needles, very faintly yellow, giving a single spot on t.l.c. analysis. The needles turned brown at 160° and melted at 164-165° with evolution of gas, $[\alpha]_D^{25}$ - 112.9°, λ_{max} 246 mμ, ϵ_{max} 7650; υ_{max} (KBr) 3425 (s), 1775 (s), 1630 (w), 1570 (w) and 1350 (s) cm^{-1}.

Anal. Calcd. for $C_{15}H_{21}N_3O_5$:
C,55.72; H,6.55; N,13.00.
Found: C,55.89; H,6.29; N,12.86.

No n.m.r. spectrum could be obtained due to the compound's low solubility, and facile decomposition in solution.

5,1-(α-Epoxynitrosoimino)-4β-tetrahydrosantonin Oximes (18).

This compound was prepared from the β-isomer (13) as described above for the α-isomer (3), except that glacial acetic acid was used as the solvent. The product crystallised from methanol as large bright yellow crystals, gave a double spot on t.l.c. plates (R_f (b) 0.30, 0.45), turned brown at 160°, evolved gas at 168°, and melted at 172°; mixture melting point with the α-isomer 152-154°; λ_{max} 245 mμ, ϵ_{max} 7,300; υ_{max} 3425 (s), 1775 (s), 1630 (w), 1570 (w) and 1360 (m) cm^{-1}.

Anal. Calcd. for $C_{15}H_{21}N_3O_5$:
C,55.72; H,6.55; N,13.00.
Found: C,56.85; H,6.71; N,12.37.

On standing it decomposed slowly, and after a few days another less polar compound was shown by t.l.c. analysis to be formed (R_f (b) 0.70), the same R_f (b) as 19 and 20. The poor analysis was probably due to decomposition to the compounds 19 and 20; a 12% decomposition would lead to the analytical figures found.

3-anti-Oximino-5,10(α-epoxy)1β,4α-hexahydrohypo-santonin (8).

The 4α-nitroso compound 7 (1.025 g.) was suspended in 50% acetic acid (10 ml), in a round bottom flask connected via a reflux condenser to a trap cooled in liquid air. The apparatus was flushed out with nitrogen, and the flask was heated on a water bath. The solid slowly dissolved, and the gas evolved was collected in the trap, as a white solid. On warming to room temperature, the gas was allowed to fill a previously evacuated I.R. cell. The gas had υ_{max} 3840 (w), 3487 (s), 3460 (s), 3370 (w), 3340 (w), 2790 (m), 2470 (s), 2450 (m), 2210 (s), 1300 (s), 1270 (s) and 1265 (m) cm^{-1}, identical to the spectrum of N_2O in the literature (27).

The pale yellow solution from the reaction flask, on addition of water, gave a white precipitate (0.683 g.) which crystallised from aqueous methanol as beautiful prisms giving a single spot on a t.l.c. plate, (R_f (a) 0.50), m.p. 199-200°; $[\alpha]_D^{25}$ + 220° (lit. m.p. 199-200°; $[\alpha]_D^{25}$ + 219° (3)). The ultraviolet spectrum showed no absorption peak above 200 mμ; υ_{max} (KBr) 3440 (s), 1760 (s) and 1653 (w) cm^{-1}.

Anal. Calcd. for $C_{15}H_{21}NO_4$:
C,64.49; H,7.58; N,5.01.
Found: C,64.78; H,7.32; N,5.05.

3-anti-Benzoyloximino-5,10-(α-epoxy)-1β,4α-hexahydrohyposantonin XXVIII.

The benzoate (XXVIII) was prepared in the usual way from 8 (0.526 g.) in pyridine (5 ml) and benzoyl chloride (0.75 ml). The reaction was complete after 15 minutes at room temperature; the reaction mixture was poured into water (20 ml). After extraction with ether, and two crystallisations from methanol/ether, the benzoate (0.3 g.) was obtained as plates, giving a single spot on t.l.c. analysis (R_f (a) 0.75), m.p. 134-138° (decomp.); υ_{max} (KBr) 1775 (s), 1738 (s), 1620 (m), 1595 (m), 1575 (m) and 1250 (s) cm^{-1}.

Anal. Calcd. for $C_{22}H_{25}NO_5$:
C,68.91; H,6.57; N,3.65.
Found: C,68.71; H,6.10; N,3.81.

Levulinic Acid Treatment of 3-anti-Oximino-5,10-(α-epoxy)-1β,4α-hexahydrohyposantonin (8).

(a) At room temperature.

The oxime 8 (0.5 g.) was stirred for 15 hours in levulinic acid (18 ml) and 1.0N HCl (2 ml) at room temperature. T.l.c. analysis showed two spots, one the same as the

starting material (R_f (a) 0.50), and a less polar one (R_f (a) 0.60). The mixture was poured into water (50 ml), filtered to remove some resinous material (0.10 g.), and neutralised with sodium bicarbonate. A precipitate formed which was taken up in ether. The ether solution was washed with sodium bicarbonate solution, water, and evaporated to yield a white crystalline product (0.330 g.). This product was chromatographed on five silica gel plates eluted with solvent (a).

Fraction 1 (9; R_f 0.50) was recovered as a white crystalline solid (0.119 g.). Recrystallisation from aqueous methanol gave colourless prisms, m.p. 187-190°; mixture melting point with 8, 173°. The ultraviolet spectrum showed no absorption peak above 200 mμ; υ_{max} (KBr) 3450 (s), 1750 (s), and 1636 (m) cm^{-1}.

Anal. Calcd. for $C_{15}H_{21}NO_4$:
C,64.49; H,7.58; N,5.01.
Found: C,64.66; H,7.42; N,5.04.

Fraction 2 (10; R_f 0.60) was obtained as white crystals (0.084 g.) from cold ether, and gave a single spot on t.l.c. analysis, but decomposed to a brown solid at about 130° (depending on rate of heating). The compound, on sodium

fusion, gave a positive test for halogen, negative for nitrogen; υ_{max} (KBr) 3425 (s), 1763 (s), 1705 (s) and 682 (s) cm^{-1}.

Anal. Calcd. for $C_{15}H_{21}O_4Cl$:
C,59.99; H,7.03.
Found: C,59.55; H,6.83.

(b) At 100° for four hours.

The oxime 8 (1.17 g.) was heated with levulinic acid reagent (30 ml) on the steam bath for four hours. The product was worked up as above to give white crystals of 3-oxo-$\Delta^{4,9}$-1β-dihydrohyposantonin (11) which on recrystallisation from aqueous methanol had m.p. 108-109°, and gave a single spot on a t.l.c. plate, (R_f (a) 0.75); λ_{max} 288 mμ, ϵ_{max} 11,100, and λ_{max} 232.5, ϵ_{max} 3,800; υ_{max} (KBr), 1780 (s), 1660 (s) and 1620 (m) cm^{-1}.

Anal. Calcd. for $C_{15}H_{21}O_3$:
C,73.14; H,7.37.
Found: C,73.60; H,7.12.

(c) At 100° for fifteen hours.

More prolonged treatment (15 hours) of the oxime 8

(1.0 g.) with levulinic acid reagent (30 ml) at 100° followed by working up as above, gave a different white crystalline compound (0.44 g., R_f (a) 0.65), m.p. 194°. Its U.V. spectrum (λ_{max} 289 mμ, ϵ_{max} 3,800) and I.R. and n.m.r. spectra were identical with those of an authentic sample of (-)α-desmotroposantonin (12).

Acid Treatment of 5,1-(α-Epoxynitrosoimino)-4β-tetrahydrosantonin Oximes (18).

The 4β-nitroso compound 18 (0.95 g.) was treated with 50% acetic acid and worked up exactly as described above for the α-isomer 7. Evolution of N_2O gas was observed, and a crystalline product was isolated in two crops. The first crop was shown by t.l.c. analysis to consist of at least three compounds (R_f (a) 0.50; 0.58; 0.80); the second crop was almost pure (R_f (a) 0.80). This compound (R_f (a) 0.80) was readily separated from the other two in the first crop by crystallisation from methanol, in which it was much more soluble. After two crystallisations from methanol, pure white crystals of 3-anti-oximino-$\Delta^{4,9}$-1β-dihydrohyposantonin (21) were obtained, m.p. 255° (decomp.); λ_{max} 276 mμ, ϵ_{max} 24,870; υ_{max} (KBr) 3400 (s), 3035 (w), 1750 (s), 1602 (w) and 1590 (w) cm^{-1}.

Anal. Calcd. for $C_{15}H_{19}NO_3$:
C,68.94; H,7.33; N,5.36.
Found: C,69.06; H,7.59; N,5.34.

The other two compounds (R_f (a) 0.50, 0.58) were partially separated on a silica gel column, and finally purified on t.l.c. plates. One, (R_f (a) 0.50), crystallised from aqueous ethanol as fine white needles of 3-syn-oximino-5,10-(α-epoxy)-1β,4β-hexahydrohyposantonin (19), m.p. 186.5°. The U.V. showed no absorption peak above 200 mμ; υ_{max} (KBr) 3560 (s), 3200 (s. broad), 1760 (s) and 1660 (m) cm^{-1}.

Anal. Calcd. for $C_{15}H_{21}NO_4$:
C,64.49; H,7.58; N,5.01.
Found: C,64.73; H,7.65; N,5.21.

The second compound (R_f (a) 0.58) crystallised from aqueous ethanol as white platelets of 3-anti-oximino-5,10-(α-epoxy)-1β,4β-hexahydrohyposantonin (20), m.p. 196.5°. The U.V. spectrum (methanol) showed no absorption peak above 200 mμ; υ_{max} (KBr) 3500-3450 (s), 1760 (s) and 1630 (w) cm^{-1}.

Anal. Calcd. for $C_{15}H_{21}NO_4$:
C,64.49; H,7.58; N,5.01.
Found: C,64.63; H,7.83; N,4.90.

Acid Treatment of the Mixture of 3-syn- and 3-anti-Oximino-5,10-(α-epoxy)-1β,4β-hexahydrohyposantonins (19 and 20).

The mixture of 19 and 20 (0.20 g.) was refluxed with 50% acetic acid (15 ml) for one hour. After cooling, and addition of water, a precipitate was obtained (0.120 g.), that was identified as the unsaturated oxime 21, by its melting point, R_f value, and infra-red spectrum.

Levulinic Acid Treatment of 5,1-(α-Epoxynitrosoimino)-4β-tetrahydrosantonin Oximes (18).

The 5,1(α-epoxynitrosoimino)-4β-tetrahydrosantonin oximes (18; 1.0 g.) were heated to 100° with levulinic acid reagent (15 ml) for six hours. The reaction mixture turned a dark colour. After dilution and neutralisation, ether extraction gave a yellow syrup, which crystallised from ether, as colourless plates (0.350 g.), m.p. 171°. The compound, by mixture melting point, U.V. spectrum (λ_{max} 240 mμ, ϵ_{max} 13,400; λ_{max} 260 mμ, ϵ_{max} 10,650) and I.R. spectra, was shown to be santonin.

On a t.l.c. plate, the crude reaction product showed spots indicating the presence of (-)α-desmotroposantonin

(12), (R_f (a) 0.65) and the oxime 21 (R_f (a) 0.80). They were not isolated.

Santonin Oxime O-Benzyl Ether (XXXVII).

Santonin (2.5 g.) was added to a solution of O-benzylhydroxylamine in methanol, prepared from O-benzylhydroxylamine hydrochloride (4.76 g.) and sodium metal (0.85 moles/mole of hydrochloride) in methanol. These conditions thus corresponded to those for the preparation of 13 above. After 24 hours, t.l.c. analysis showed about half the reactants to be consumed. On cooling, beautiful crystals, m.p. 151° were obtained. These proved to be santonin oxime O-benzyl ether (XXXVII, lit. m.p. 151° (52)). No other products could be detected in the reaction mixture.

4-Methyl-4-trichloromethyl Cyclohexa-2,5-dieneone Oxime (XXXIX).

A solution of 4-methyl-4-trichloromethyl cyclohexa-2,5-dieneone (XXXVIII, 10 g.) was refluxed for three hours with a solution of free hydroxylamine in methanol (100 ml) prepared from hydroxylamine hydrochloride (25 g.) and sodium metal (6.15 g.). On evaporation and addition of water, a white precipitate (9.9 g.), giving a single spot (R_f (a) 0.25)

on a t.l.c. plate, was obtained. Recrystallisation from aqueous ethanol gave the di-unsaturated oxime as white needles m.p. 134° (lit. m.p. 134° (53)), λ_{max} 252.5 mμ, ϵ_{max} 18,000. When the reaction above was repeated with equimolar amounts of hydroxylamine hydrochloride and sodium methoxide, the same product (10.2 g.) was obtained.

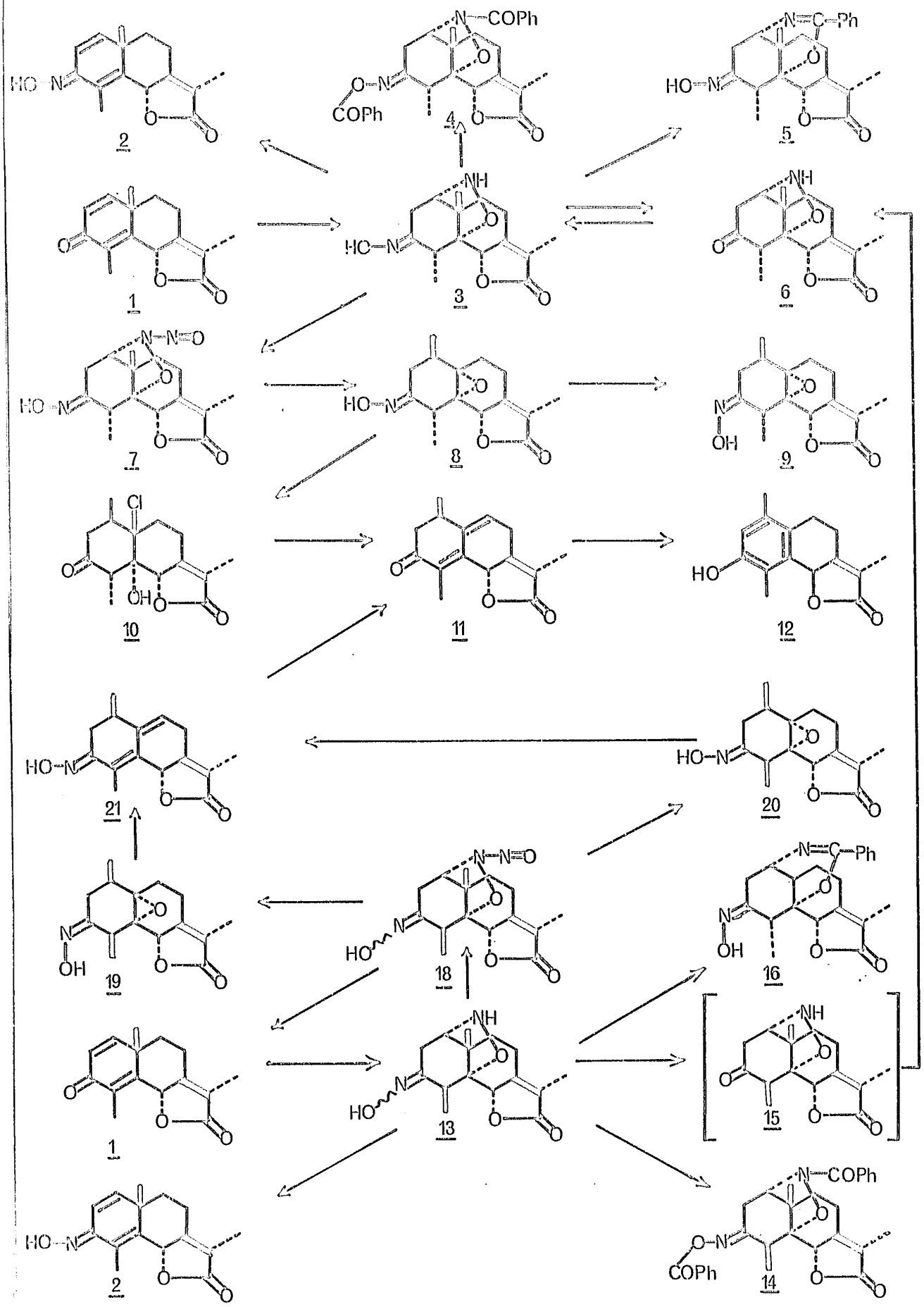
Cholesta-1,4-diene-3-one Oxime (XLI).

To a solution of cholesta-1,4-diene-3-one (XL; 0.40 g.) in methanol (10 ml) was added a solution of hydroxylamine (3 molar excess) in methanol. The reaction mixture was heated on the steam bath. After 24 hours, t.l.c. analysis showed all the ketone to be consumed. The major product had R_f (c) 0.55, the same as an authentic sample of cholesta-1,4-diene-3-one oxime. Two minor products (R_f (c) 0.30 and 0.25) were detected.

The same product ratio was observed when cholesta-1,4-diene-3-one (0.40 g.) was refluxed with hydroxylamine and a 10% excess of sodium methoxide, or with hydroxylamine and a 10% excess of hydroxylamine hydrochloride. The three reactions were combined, and concentrated to about 4 ml. Water (20 ml) was added, and the product separated as an oil. The oil was taken up in ether, the ether solution was washed

with water and dried ($MgSO_4$). On evaporation of the ether an oil was obtained (0.8 g.), very soluble in hexane, benzene, and chloroform, from which nothing could be crystallised.

The oil was dissolved in methanol and water was added. Minute crystals were obtained (0.60 g.), m.p. 142-145°, R_f (c) 0.50, identical with cholesta-1,4-diene-3-one oxime. The mother liquor on concentration gave an oil (0.150 g.), identified by t.l.c. as a mixture of the oxime above, (R_f (c) 0.50), and the two minor products (R_f (c) 0.30 and 0.25). The mixture was chromatographed on a silica gel column. The oxime was eluted with benzene 90%: ether 10%, and the two other products together, with benzene 50%: ether 50%. Evaporation of the solvent from the latter fractions gave an oil (50 mgm.), insoluble in 10% HCl, υ_{max} 1730 (s), 1605 (m), 1580 (m), 1490 (m), 1280 (s), 1120 (s) and 1070 (s) cm^{-1}, which could not be crystallised.


HO
N
O
2
N—COPh
O—N
COPh
4
N=C—Ph
HO—N
5
1
NH
HO—N
3
6
N—N=O
7
8
OH
9
Cl
OH
10
11
HO
12
21
20
OH
19
18
16
1
13
15
2
14

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SUMMARY AND CLAIMS TO ORIGINAL RESEARCH

1. The reaction of hydroxylamine with santonin has been shown to give tetracyclic compounds, hydroxylamine being added across the two double bonds of santonin to form an epoxyimino bridge.

2. The position of attachment of the epoxyimino bridge has been shown to be to the C-5 and C-1 positions of santonin, and is oriented α- to the santonin molecule.

3. New structures have been proposed for:

(a) The hydroxylaminosantonin oximes -α and -β.

(b) Their nitroso derivatives.

(c) Their dibenzoyl derivatives.

(d) The compounds formed by reaction of hydroxylaminosantonin oximes -α and -β with benzaldehyde.

4. The "hydroxysantonin oximes" have been shown to have a rearranged structure having the same carbon skeleton as hyposantonin. The presence of an epoxide ring has been demonstrated, instead of a free hydroxyl group. Four stereoisomers have been isolated and characterised.

5. Mechanisms have been proposed for the addition

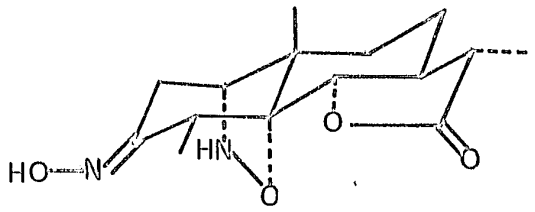
of hydroxylamine to santonin to account for the formation of two stereoisomers of hydroxylaminosantonin oxime. A mechanistic interpretation has also been given, where appropriate, for the other compounds mentioned.

6. Some other cyclic dieneones have been treated with excess hydroxylamine, but no bridged compounds were obtained.

APPENDIX

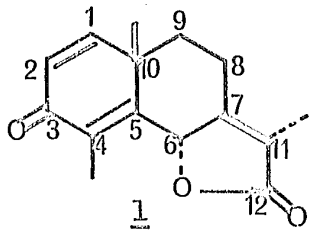
Nomenclature.

The fully systematic names for some examples of the compounds discussed and their method of derivation is described below. However, as these names were very lengthy and were not suitable for rapid reference to the compounds, a less formal but shorter series of names was devised, based on the carbon skeleton of santonin and hyposantonin. The formulae of the compounds are given first, followed by the derivation of the shorter names used in this work, and lastly the derivation of the systematic names, with the parent ring system from which they were derived (56).



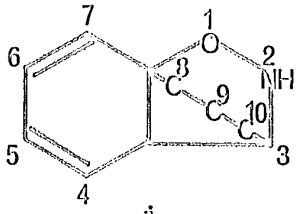
3

Short name: 5,1-(α-epoxyimino)-4α-tetrahydro-santonin anti-oxime, derived from santonin (1).



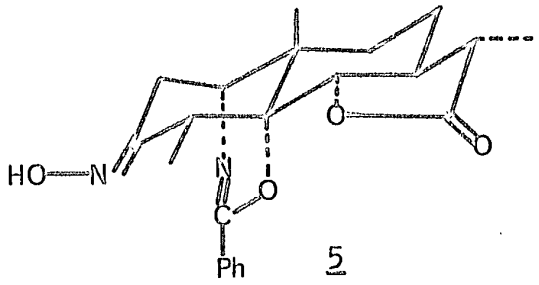
1

Systematic name: 3α,3a,4,5,6α,7-hexahydro-7α-hydroxy-α,3aβ,8-trimethyl-9-oxo-2H-3,7aβ-propano-1,2-benzisoxazole-6-acetic acid, γ-lactone oxime, derived from a 2H-3,7a-propano-1,2-benzisoxazole (i) shown below:



i

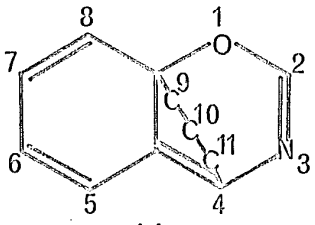
The product from the reaction of benzaldehyde and hydroxylaminosantonin oxime-α is named as follows:



5

Short name: 5,1-(α-epoxyphenylmethenonitrilo)-4α-tetrahydrosantonin anti-oxime, also derived from santonin.

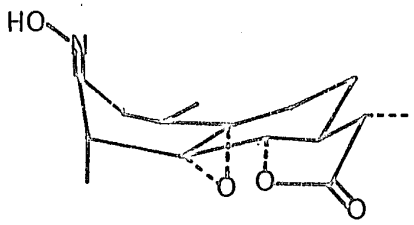
Systematic name: 4α,4a,5,6,7α,8-hexahydro-8α-hydroxy-α,4aβ,9-trimethyl-10-oxo-2-phenyl-4,8aβ-propano-8aH-1,3-benzoxazine-7-acetic acid, γ-lactone oxime, derived



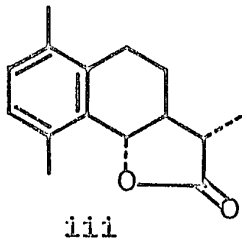
ii

from 4,8a-propano-8aH-1,3-benzoxazine (ii) above.

The epoxy-oxime 9 is named as follows:



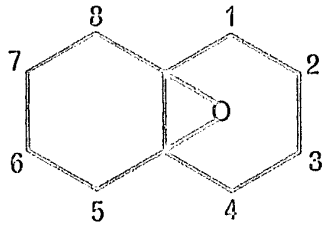
9



iii

Short name: 3-syn-oximino-5,10-(α-epoxy)-1β, 4α-hexahydrohyposantonin, derived from hyposantonin (iii; (58)).

Systematic name: 4aβ,8aβ-epoxy-1,2β,3,4,4a,5, 6,7,8,8a-decahydro-1β-hydroxy-α,5α,8α-trimethyl-7-oxo-2-naphthaleneacetic acid, γ-lactone oxime, derived from 4a, 8a epoxynaphthalene (iv).



iv

In the short names above, the name for the bridge results from combination of the appropriate prefixes, e.g. epoxy (-O-), phenylmethene (-C(Ph)=CH-) and nitrilo (-C=N-) from the literature (57).

In the indexes of Chemical Abstracts, the systematic names above would all be inverted, the underlined portion coming first. The compounds are all named as open-chain hydroxy acids, that have been closed to give lactones.

There are no rules in the systematic scheme for assigning the configuration of groups on bridges or side-chains, and as the C-4 methyl and C-11 methyl groups of santonin in the compounds above are situated on a bridge and a side-chain respectively, the systematic scheme cannot adequately describe them. For purposes of description and structure elucidation therefore, the less formal nomenclature is preferred.