# Some Studies in the Synthesis of Medium Ring Ketones

THESIS

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by

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**Summary of M.Sc. Thesis** **J.G. Hamilton, 1961**

Synthetic routes to 9 and 10 membered ring systems have beeh investigated as follows:-

Birch reduction of naphthalene yields isotetralin (1:4:5:8 tetrahydronaphthalene) which has been converted through its mono epoxide (9:10-oxido: $\Delta^{2:6}$ hexahydronaphthalene) to trans $\Delta^{2:6}$ hexahydronaphthalene-9:10-diol and this substance has been cleaved by means of lead tetraacetate to cyclodeca-3:8 dien-1:6-dione. The product has been characterised as its bis-2:4-dinotrophenylhydrazone. Attempts to introduce further unsaturation into the ring were unsuccessful.

A similar series of reactions was carried out on indane, and yielded in turn, 4:7-dihydro-8:9-oxidoindene, the corresponding diol, $\Delta^{5:6}$ hexahydroindene-8:9-diol and cyclonon-7en-1:5-dione. The structure of this end product was rigorously established by its reduction under special conditions to cyclononan-1:5-diol. This product was isolated as a mixture of stereoisomers, one of which was found to be identical with an authentic sample kindly supplied by Professor V. Prelog of Zurich. Under different conditions the reduction proceeded anomalously. In an attempt to isomerise the double bond into conjugation with one of the carbonyl functions, the ene dione was treated with ethanolic potassium acetate. The product was not the expected conjugated dione. An exhaustive investigation, employing both chemical and spectroscopic methods has shown that the potassium acetate treatment promotes a transannular aldol condensation yielding initially 4:5:6:7-tetrahydroinden-7-one which dimerises fairly rapidly. The structure of the dimer has been tentatively assigned on the basis of its proton magnetic resonance spectrum.

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# DECLARATION

I wish to state that the contents of this thesis are my own work, carried out in the University of Glasgow.

# C O N T E N T S

## SUMMARY

The diol III (Chart VI) was prepared from Naphthalene via isotetralin by the method of Huckel and Schlee[1] and its reaction with lead tetraacetate investigated. It was found to yield the ketone IV but in poor yield. Attempts to prepare the corresponding fully conjugated dione (VI) by bromination followed by dehydrobromination were not successful. The diol (IX) obtained from indane via dihydroindane by the method of Giovanni and Wegmuller[2] was treated with lead tetracetate under a variety of conditions and a diketone obtained in high yield whose structure was shown to be (X). On treatment with potassium acetate under very mild conditions X was transformed into a compound whose structure is represented by C or D.

# INTRODUCTION

A considerable number of natural products contain medium sized rings of nine or ten carbon atoms and examples of these are given in Chart I. The construction of rings of this size in good yield has always given rise to considerable difficulty and many attempts have been made to find better synthetic routes. Five of these are worth mentioning in detail and are illustrated in Chart II (Page 28).

An early method was that of Ruzicka[3] who distilled rare earth salts of dicarboxylic acids in vacuo, or alternatively passed the vapour of the acid over the oxide. The yields of the cyclic ketones in the range $C_{9-11}$ was only about 0.5%. The high dilution method of Ziegler, Eberle and Ohlinger[4-8] was an improved method of obtaining the intramolecular condensation product in good yield and involved the treatment of an α-ω dinitrile with lithium ethylanilide, so forming the monolithium salt which cyclises as shown in Chart II. In this case too, however, the yield in the ring size range $C_{9-11}$ is negligible. A further method of synthesising large membered rings is that of Hunsdiecker.[9-10] This is also a high dilution method and involves cyclisation of an ω-halogenoacylacetic ester to give a cyclic β-keto ester. The diketen method is another whereby large membered rings may be constructed. This method involves preparation of an α-ω diketen by treating an α-ω dicarboxylic acid chloride with ethereal triethylamine. This ~~rearranges and~~ is hydrolysed with alkali to give the two ketones shown in Chart II. Here again the yields in the range $C_{9-11}$ are poor. A better preparative method is that which employs the acyloin condensation.[13-14] This is carried out by heating an α-ω dicarboxylic ester in xylene solution with molten sodium under vigorous stirring. In the region where a poor yield was given by the previous methods, i.e. $C_{9-11}$ yields of around 30-40% are obtainable. The reason for the relative success of this method is probably that the two electrophilic residues of the molecule can be absorbed on the electron rich surface of the finely divided molten metal. They can then readily approach each other, this requiring less energy than ~~for~~ removal of the molecule from the metal surface. Chart III shows the approximate yields of ring compounds of various sizes obtained by the different methods.

The Demjanov and diazomethane ring expansions are also applicable in some cases to the synthesis of medium rings.

An alternative approach which has been used is the opening up of a bridge between two rings. An example of this was the original synthesis of cyclooctatetraene from ψ-Pelletierine by Willstatter[15-17] using exhaustive methylation by the Hoffmann method (see Chart IV). The synthesis of azulene by the method of Plattner and Pfau[19] involves cleavage of the double bond in $\Delta^{9:10}$ octalin with ozone. Recyclisation across the ten membered ring occurs readily as shown in Chart IV. Other methods of synthesis of medium membered rings involving removal of a bridge between two rings have been devised by Cope[20-22, 25] and co-workers (see Chart IV).

The method which we have studied involves the use of lead tetraacetate for cleaving the single bond between two fused rings in napthalene and indane derivatives. This reaction has previously been studied by Criegee[21, 22] and co-workers, who found that cis-diols of this type reacted most readily but that trans-diols would also react in some cases. Compounds which were cleaved by these workers included the diols (XIV) and (XV) (Chart IV).

Grob and Schiess[26] used the technique of carrying out the treatment of the diol (III) with lead tetraacetate in methanol in the presence of trichloroacetic acid using careful control of temperature. In this way they obtained the ketal (V) in high yield.

## DISCUSSION

In this work it was decided to investigate a possible method of synthesising some nine and ten membered ring compounds using the cleavage of trans 1:2 diols with lead tetraacetate. We had in mind a synthesis of the caryophyllene skeleton by the route outlined in Chart V.

Napthalene was reduced to isotetralin I (Chart VI) as described by Birch, Murray and Smith.[27] The melting point of the recrystallised material was found to be in agreement with that reported by Huckel and Schlee[1] but higher than that given by Birch, Murray and Smith.[27] It was also found, in agreement with Huckel and Schlee[1] that the ~~purified~~ isotetralin, once thoroughly purified and free from alkali, no longer became brown and sticky on standing in air.

The product was epoxidised by the method of Huckel and Schlee[1] using a chloroform solution of perbenzoic acid. When only one mole of perbenzoic acid at 0°C is added to a solution of one mole of isotetralin, epoxidation of the tetrasubstituted double bond occurs preferentially, leaving the disubstituted ones untouched. The product is II, as already demonstrated by Huckel and Schlee.[1]

The hydrolysis of the epoxide to the trans-diol (III) was carried out by the literature method, i.e. warming with dilute acetic acid followed by recrystallisation of the product from water. The infra-red spectrum of the product suggested that there was a trace of acetate present in the diol, because there was a weak carbonyl peak in the appropriate position (1735 cm.) This was, however, eliminated by recrystallisation from water.

In order to check the identity of the diol a portion was converted into its diacetate[1] by warming gently with excess of acetyl chloride. The ready formation of the diacetate is of considerable interest as it is unusual for tertiary hydroxyl groups to be so readily acetylated.

It was found that 1:6-diketocyclodeca-3:8-diene (IV) could be prepared in the pure state by cleavage of the diol (III) with lead tetraacetate. However the yield varied between 8% and 12%. After the preparation had been carried out by us Grob and Schiess[26] published details of a method of cleaving the diol (III) to a mixture of the dione (IV) and its tetramethylketal (V), the latter compound being obtained in good yield. The method devised by them involved adding lead tetraacetate to a solution of the diol in methanol containing trichloroacetic acid, the reaction being carried out at room temperature. This preparation was repeated by us using their method, with the object of hydrolysing the ketal to the dione (IV). Difficulty was encountered however in carrying out this hydrolysis and only poor yields of the purified dione were obtained ( 15%). Attempts were made to prepare the corresponding fully conjugated dione (VI) by addition of bromine to the ketal followed by dehydrobromination and hydrolysis of the ketal. At room temperature excess of bromine in chloroform solution gave a purple solution which on evaporation gave mainly carbon with loss of hydrogen bromide. Under the same conditions chlorine gave a glassy solid which rapidly darkened on treatment with acid or base. With the theoretical quantity of bromine in pyridine at room temperature the bromine was slowly decolourised, a yellow resin being isolated from the mixture, but attempts to obtain its 2:4-dinitrophenylhydrazone in a sharply melting state were unsuccessful. The tetramethylketal (V) was treated with iodine and silver acetate using Woodward's procedure[30]. However the ester so produced only yielded a black tar on treatment with alkali.

As an alternative approach to the synthesis of the fully conjugated dione (VI) the diol was treated with excess of bromine to give its tetrabromide (VIa), and after characterisation of this compound, attempts were made to cleave this with lead tetraacetate both in refluxing tetrahydrofuran and in anisole. In both cases it was returned unchanged.

A similar series of reactions was carried out on indane with the object of preparing the corresponding nine membered ring diketone (X). The first stage in this synthesis was the preparation of 4:7-dihydroindane (VII) by the method of Giovanni and Wegmuller[2] using the Birch reduction of indane with sodium and methanol in liquid ammonia. Spectrophotometric (ultra-violet) determinations carried out on the colourless product indicated a small residual quantity of indane, but repeated reduction reduced this to a still smaller value. The effect of adding the sodium to the liquid ammonia after the indane and methanol mixture was investigated, instead of adding the sodium before it as recommended by Giovanni and Wegmuller[2]. Little difference in the result was observed however. The colourless, twice reduced (but undistilled) product (VII) was used directly for the epoxidation.

Perphthalic acid was employed for the epoxidation using essentially the same technique as Giovanni and Wegmuller.[8] The crude epoxide (VIII) yielded by this method as a colourless liquid, was hydrolysed at 0°C with very dilute perchloric acid to give the crystalline trans diol (IX).

It was found that the trans diol (IX) could be cleaved to the dione (X) by refluxing in benzene solution with excess of lead tetraacetate. However, a much better yield was obtained by using the technique applied by Grob and Schiess to the napthalene diol (III), i.e. using a solution of the diol in methanol in the presence of trichloroacetic acid at room temperature. If purified diol was used as starting material and the reaction temperature carefully controlled a pure product could be obtained in high yield. The dione (X) was the sole product, no appreciable quantity of ketal being produced since no ether bands were detectable in the infra-red spectrum even of the crude product. This is in contrast to the preparation of the tetramethylketal (V) from the napthalene diol (III). Some experiments were carried out in order to confirm the structure of the dione (X). Firstly a hydrogenation was carried out using palladium charcoal as catalyst. Surprisingly, the indane derivative (XII) was formed directly from the reduction and was characterised by analysis of the semicarbazone. The 2:4-dinitrophenylhydrazone and oxime were also prepared. The melting points of the semicarbazone and 2:4dinitrophenylhydrazone ~~oxime~~ showed no depression, on mixing with authentic samples provided by Professor V. Prelog.[26] A further batch of the dione (X) was reduced with lithium aluminium hydride followed by hydrogenation using palladium charcoal as catalyst. The stereoisomeric diols so produced were separated by chromatography using the method of Prelog, Schenker and Küng,[28] one in the pure state and the other in the form of its p-nitrobenzoate. From a mixture of the authentic p-nitrobenzoates supplied by Prelog one of the p-nitrobenzoates was isolated in the pure state and found to be identical with the p-nitrobenzoate prepared from the dione. This latter experiment clearly establishes that the dione (X) has in fact a nine membered ring. In addition to obtaining a correct analysis for the dione (X) itself, the 2:4-dinitrophenylhydrazone was prepared and found to give appropriate analyses for carbon and hydrogen. When prepared under mild conditions, i.e. reaction with 2:4-dinitrophenylhydrazine in aqueous methanol in presence of a little sulphuric acid at 10°C, filtering off the product after one minute and purifying, it was yellow in colour, indicating that the double bond in the nine membered ring had not moved into conjugation with the carbon-nitrogen double bond. The infra-red and ultra-violet spectra of the dione also showed that the carbonyl group was not conjugated, and the ultra-violet indicating an $\beta\gamma$-unsaturated ketone.[31] (I.R. peak at 1710 $cm^{-1}$; U.V. in ethanol peaks at 201 $m\mu$., $\epsilon$ = 3,766 and 292, $\epsilon$ = 1190). If the 2:4-dinitrophenylhydrazone was allowed to stand in presence of acid it turned red with lowering of the melting point indicating conjugation of the carbonyl group. Ozonolysis and also bromination of the dione (X) was carried out but the products were not identified. Nevertheless the above experiments confirm that the dione has the formula (X).

Attempts were now made to move the double bond in X into conjugation with the carbonyl group in order to attempt a proposed synthesis of a caryophyllene derivative (see Chart V).

Dilute alkali yielded a red resin from which no definite product could be isolated. A specimen of the dione (X) in benzene solution was refluxed with one molecular proportion of ethylene glycol and a little p-toluenesulphonic acid in an attempt to block one of the carbonyl groups. Water was found to distil off with the refluxing benzene in approximately the theoretical quantity indicating formation of a ketal but the product could not be characterised. A further procedure which was tried was the treatment of the pure dione (X) in ethanol with excess of potassium acetate. An intense crimson colour developed at room temperature. After the working up of the mixture, the brown resinous product was distilled under vacuum yielding a pale yellow liquid which slowly solidified. In spite of the relative volatility of the distillate, the resin required heating to about $200^{\circ}$C in high vacuum and the product solidified only slowly even on seeding the liquid. The solid analysed as the simple aldol condensation product formed by elimination of one molecule of water from one molecule of the dione, i.e. XVI or XVII. The molecular weight obtained by the mass spectrometric method was 134. On the other hand, it seemed unlikely that such a compound would be solid and have such a high boiling point. Moreover, these structures are both equally reactive being both dienes and dienophiles, and it seemed likely that they would dimerise. Reinspection of the mass-spectrum chart revealed an extremely weak peak at 268. An ebullioscopic determination in benzene gave a value of 236 indicating that the product was indeed a dimer. It seemed likely that the product was a dimer of XVI or XVII formed by a Diels Alder condensation between two molecules. This would account for the unexpectedly high melting point (110°C) and the peculiar distillation characteristics. It must be presumed that the dimerisation was reversed in the high energy beam of the mass spectrometer, and that distillation also produced monomer which slowly redimerised. That this is so was shown by catalytic reduction of the dimer (XI) followed by a molecular weight determination by the mass spectrophotometer, on the crude product. The value was found to be 272. This shows that by removing the double bonds and so eliminating the opportunity for a reverse Diels Alder, the mass spectrum gives the true molecular weight.

Spectral studies also support the dimeric structure. Ultra-violet spectrum in ethanol: peaks at 249 mμ. $\epsilon$ = 9,120; 55,136 205 mμ. $\epsilon$ = 5,493. From consideration of Woodward's Rules neither XVI nor XVII would be expected to absorb at this wavelength. The infra red spectrum showed three well defined peaks in the carbonyl region and the effect on these of using different solvents was investigated. The positions of the peaks and their half band widths are tabulated for the three solvents, hexane, carbon tetrachloride and chloroform (see Chart VII).

The following points were noted:-

(1) As carbonyl values shift with change of solvent and as the carbon to carbon double bond values are constant,[34] it can be seen that we have two types of carbonyl.

(2) The saturated carbonyl frequency is low and the small shift (only 10 $cm^{-1}$ ) means that there is a highly substituted α-position; the 1680 $cm^{-1}$ band must be due to an unsaturated carbonyl in a six membered ring.

(3) the 1680 $cm^{-1}$ band is sharp in hexane and there is nothing at 1680 $cm^{-1}$ in chloroform or carbon tetrachloride, therefore the middle peak only indicates one carbonyl.

(4) The conjugated carbonyl peak shifts considerably, therefore it is not very hindered.

(5) The relative intesities suggest a saturated and an unsaturated carbonyl. (The middle peak corresponds to the ~~being~~ unsaturated function).

(6) The 1630 $cm^{-1}$ band is sharp and has little shift which suggests a carbon to carbon double bond.

These results fit four probable formulae for XI, namely A, B, C and D.

The condensation product (XI) was reduced with sodium borohydride, the carbonyl peak in the infra red being completely removed. After one recrystallisation from ether the reduced product did not melt sharply (m.p. 130-150°C) probably owing to its being a mixture of stereoisomers. It was verified by mixed melting point and similarity of infra red absorption spectra that a product obtained by chromic acid oxidation of this borohydride reduced product was identical with the original condensation product (XI). This reoxidation proved that no over-reduction had taken place during the borohydride treatment. (Cases are known where carbon to carbon double bonds can be reduced under these conditions.)[32, 33] Consequently, the ultra-violet absorption spectrum of the borohydride product should reveal the presence or absence of a conjugated diene system in XI. No absorption was found above 220 mμ. and this further eliminates structures XVI and XVII. A mass spectrum of the sodium borohydride reduced product gave a peak at 272 together with some dissociation peaks immediately below this, but also some peaks in the range 285-286 and 311-315, probably due to the presence of some borate esters. In order to distinguish between structures A or B and structures C or D the Nuclear Magnetic Resonance spectrum was recorded in chloroform solution. The substance showed <u>three</u> vinyl protons, two of these split by coupling ($\tau$ = 3.25; 3.55 and 4.27) This evidence eliminates A and B and is consistent with C or D, both of which have three vinyl protons, two of which are on adjacent carbon atoms. We are unable to make a choice between structures C and D.

Due to our inability to produce a nine membered ene-dione with a conjugated double bond, our original synthesis has been abandoned.

## EXPERIMENTAL

**Preparation of isotetralin**[27]:- To anhydrous liquid ammonia (250 c.c.) in a three litre flask cooled by solid carbon dioxide and ethanol was added a solution of pure napthalene (10 gm.) in "super dry" ethanol (40 c.c.) and anhydrous ether (50 c.c.) with vigorous stirring in order to produce a very fine suspension. Sodium (15 gm.) in small pieces was then added slowly and a further 150 c.c. of ammonia added. After one hour the cooling bath was removed and most of the ammonia allowed to evaporate until a white pasty mass remained (about 1½ hours). Water (200 c.c.) was added and the crude product filtered off, washed well with water and dried, and then recrystallised from methanol (m.p. 58-59°C; yield 4.7 gm. 46%).

**Oxido - $\Delta^{26}$ - Hexahydronapthalene (II)**[1] Perbenzoic acid (550 c.c.) containing 4 mgm. of active oxygen per c.c. in chloroform solution was added in 50 c.c. portions to a solution of isotetralin (20 gm.) in chloroform (50 c.c.) at 0°C and stirred for ten minutes. The solution was then washed with normal sodium hydroxide solution to remove benzoic acid, and then washed and dried ($Na_2SO_4$.) The solid product obtained on evaporation of the chloroform was recrystallised from petrol (b.p. 60-80°C) to give needles of m.p. 58-60°C. (Yield 14 gm. 64%).

### $\Delta^{2:6}$ Hexahydronaphthalene - 9:10-diol (III)[1]

9:10 oxido-$\Delta^{2:6}$ hexahydronaphthalene (II) (10 gm.) and 15% aqueous acetic acid (70 gm.) were warmed together for four hours. The solution was then cooled to 0°C and the crystals filtered off. The product was recrystallised from hot water and dried over silica gel in vacuo, the white needles crumbling to a white powder with loss of water (m.p. 76-78°C); yield 5.5 gm. (50%). A portion was warmed with normal potassium hydroxide, the product being filtered off after cooling and recrystallised from hot water as before, the melting point and infra-red spectrum after drying being unchanged.

### Diacetate of trans $\Delta^{2:6}$ Hexahydronaphthalene-9:10 diol

The diol (III); (1 gm.) was stirred with acetyl chloride (10 gm.) at 30°C until it went into solution (about 30 minutes) hydrogen chloride being evolved. The solution was then poured into water and the solid obtained filtered and washed. The crude diacetate was twice recrystallised from methanol (m.p. 168-170°C.)

### 1:6-Diketocyclodeca-3:8 diene (IV)

The trans diol (III); (5 gm.) and lead tetraacetate (20 gm.) in benzene (100 c.c.) were refluxed for 30 minutes and then cooled. Enough ethylene glycol was then added dropwise to give a colourless solution and a negative starch-iodide test. The benzene solution was then washed with a little water, dried ($Na_2SO_4$) and evaporated to dryness. A white solid remained (0.42 gm; 8%) which after recrystallisation twice from benzene/petrol had m.p. 178-180°C.

| | | |
|---|---|---|
| | found | % C = 73.05 % H = 7.11 |
| $C_{10}H_{12}O_2$ | requires | % C = 73.14 % H = 7.37 |

## Bis 2:4-Dinitrophenylhydrazone

This was prepared by treating a solution of the diketone in aqueous methanol with excess of Brady's reagent (a solution of 2:4-dinitrophenylhydrazine in aqueous methanol containing a little sulphuric acid). The precipitate was filtered and dried ~~and~~ recrystallised twice from nitrobenzene and washed ~~washing~~ well with alcohol and ether (m.p. 205°C).

found %C = 50.46 %H = 3.82 %N = 21.27

$C_{22}H_{20}O_8N_8$ requires %C = 50.38 %H = 3.84 %N = 21.37

## 1.1.6.6 - Tetramethoxycyclodeca - 3:8 diene V[36]

To a solution of the diol (III) (25 gm; 0.3 mol) and trichloroacetic acid (74 gm; 0.9 mol) in anhydrous methanol (4000 c.c.) was added with stirring finely powdered lead tetraacetate (100 gm; 0.45 mol) slowly and with vigorous stirring during 15 minutes, the temperature being maintained below 30°C.

The stirring of the yellow reaction mixture was continued for four hours at room temperature, and after cooling to 0°C the solid was filtered off and wqshed with methanol. The filtrate was then evaporated to a third of its bulk and the solid which separated again filtered. To free them from lead salts the combined crops of crystals were suspended in water (250 c.c.) and after stirring filtered off and thoroughly washed and dried. The product was then recrystallised from chloroform/methanol to give white plates of m.p. 199-200°C (Yield 22 gm; 54%).

The free ketone could only be obtained in poor yield by warming this tetramethylketal on the steam bath for 30 minutes with 10% aqueous acetic acid and recrystallising the dark product from benzene/petrol.

The bis 2:4-dinitrophenylhydrazone of the dione (IV) was readily obtained by treating the tetramethylketal in alcoholic solution with Brady's reagent. No depression of the melting point was obtained on mixing with an authentic sample prepared directly from the dione.

### $\Delta^{2:6}$ Hexahydronaphthalene 9:10-diol tetrabromide

To the diol III (10 gm.) dissolved in chloroform at 40°C excess of bromine in chloroform was added until the colour persisted for ten minutes. The solution was now cooled and the crystals filtered off and washed with a little chloroform. The solid was then twice recrystallised from tetrahydrofuran (m.p. 203°C).

found %C = 25.00 %H = 2.96 %Br = 65.72

$C_{10}H_{14}O_2Br_4$ requires %C = 24.72 %H = 2.905 %Br = 65.82

This compound was returned unchanged on refluxing with excess of lead tetraacetate both in tetrahydrofuran and in anisole.

### 4:7-Dihydroindane (VII)*

Indane (redistilled; 30 gm.) in methanol (25 gm; dried by treatment with magnesium and iodine) was added to a solution of sodium (15 gm.) in anhydrous liquid ammonia (500 c.c.) in a three litre flask which was cooled by solid carbon dioxide and methanol. The solution was stirred vigorously throughout the addition. After two hours stirring most (but not all) of the ammonia was distilled off by placing the flask in warm water, and water (250 c.c.) added slowly. The solution was then extracted with ether (700 c.c.), washed with a little normal hydrochloric acid, and then with water and dried ($Na_2SO_4$). On removing the ether under vacuum a colourless liquid remained. Spectrophotometric determinations indicated a residual indane content of 4-8%. A repeated reduction (this time adding the sodium after the indane/methanol mixture) gave a residual indane content of 1.3% in the colourless liquid product (yield 25 gm; 82%)

### 4:7-Dihydro - 8:9-oxidoindane (VIII)[2]

To 4:7-dihydroindane (VII) (21.5 gm.) in anhydrous ether (200 c.c.) at - 3°C was added dropwise with vigorous stirring ethereal perphthalic acid (640 c.c. of a solution containing 4.42 mg./c.c. of active oxygen) the temperature being maintained below 0°C. After one hour the temperature was raised to 20°C and maintained at this value for 24 hours. A further 500 c.c. of ether was then added and the solution decanted from the precipitated phthalic acid and washed with dilute sodium carbonate solution to remove acid followed by a little ferrous sulphate and then water, and dried ($Na_2SO_4$). Evaporation of the ether yielded crude 4:7 Dihydro - 8:9 oxidoindane (VIII) as a colourless liquid (yield 18 gm; 85%).

### Trans $\Delta^{5:6}$ Hexahydroindene - 8:9-diol (IX)[2]

4:7 Dihydro -8:9- oxidoindane (VIII) (10 gm.) in 0.4N perchloric acid (100 c.c.) at 0°C was stirred for two hours, the temperature being maintained close to 0°C. The white needles of the diol were filtered off (in a few cases it was found necessary to scratch the flask in order to induce crystallisation) and washed thoroughly with ice water and dried. It was recrystallised from petroleum ether (b.p. 80-100°C) (yield 6gm, m.p. 85-86°C).

Owing to the relatively small solubility gradient with temperature of the diol in petrol it was necessary to evaporate the saturated solution to a third of its original volume in order to secure adequate recovery.

### 1:5-Diketocyclonon-7-ene (XI) Method 1

The Diol IX (5 gm; pure) and lead tetraacetate (40 gm) in anhydrous benzene (300 c.c.) was heated under reflux on a steam bath for 30 minutes. Ethylene glycol was then added dropwise to the hot solution until it became colourless and no colouration was given with starch-iodide paper. The benzene layer was then washed with water and dried ($Na_2SO_4$). ~~On removing~~ after removal of the solvent a pale yellow oil remained which after two recrystallisations from ether(cooling both the solution and the funnel in an ether/solid carbon dioxide mixture) had m.p. 23-25°C (yield 0.6gm; 14%).

### 1:5-Diketocyclonon-7-ene (XI) Method 2

To the trans diol IX (10gm; pure) and dried crystals of trichloroacetic acid (30 gm) in anhydrous methanol (220cc; dried with magnesium and iodine) at -10°C was added with vigorous stirring finely powered lead tetraacetate (50gm) in small portions. After one hour the cooling bath was removed and replaced by one at 15°C, the stirring being continued for a further two hours. Most of the methanol was now removed under vacuum without applying any heat, and water (700cc.) added. The mixture was transferred to a five litre beaker and chloroform (2 litres) added. Sodium carbonate solution was now added in small portions with stirring until the mixture was faintly alkaline to litmus, the lead salts being thereby precipitated as lead carbonate and dioxide. The chloroform layer was now separated using a five litre separating funnel, stirring periodically in order to ensure separation of the chloroform layer and the aqueous layer containing the lead salts. In order to ensure complete extraction the aqueous layer was shaken with a further 400cc. of chloroform and the lead salts filtered off, the second chloroform layer then being separated. Both chloroform layers were then combined, washed with dilute sodium bicarbonate, then with water and finally dried ($Na_2SO_4$). after removal of ~~On removing~~ the chloroform under vacuum a pale yellow liquid remained which solidified slowly on standing (Yield 8.7gm; 91%) m.p. 13-20°C. After two recrystallisations from ether (carried out as described above) the melting point was 25°C (yield 4.2gm; 45%). For analysis it was distilled under high vacuum.

found %C = 70.81 %H = 8.20

$C_9H_{12}O_2$ requires %C = 71.02 %H = 7.95

The bis 2:4-dinitrophenylhydrazone was prepared by adding a solution of the ketone in methanol to Brady's reagent, the temperature being kept below 10°C and the precipitate filtered off after one minute. After washing well with methanol it was recrystallised twice from ethyl acetate (m.p. 201°C).

found %C = 49.04 %H = 4.28 %N = 21.93

$C_{21}H_{20}N_8O_8$ requires %C = 49.21 %H = 3.93 %N = 21.88

### Internal Aldol Condensation of the dione (X) with Potassium Acetate.

The dione (X) (5gm) and anhydrous potassium acetate (10gm) in ethanol (100cc) was stirred at 30°C for two hours and the ethanol then distilled off in vacuo, the temperature being maintained below 30°C. Water (100cc) and Chloroform (100cc) were now added and the mixture made slightly acid with dilute hydrochloric acid. The chloroform was separated, washed with a little water and dried ($Na_2SO_4$). After removal of the chloroform a viscous resin remained which on distillation under high vacuum yielded a pale amber liquid (b.p. 100°C under 0.1mm) which solidified on prolonged standing to give a white solid. This was twice recrystallised from methanol (m.p. 110°C, yield 0.6gm).

found %C = 80.35 %H = 7.23

$C_9H_{10}O$ requires %C = 80.56 %H = 7.51

The infra red spectrum, even after repeated recrystallisation from methanol showed three peaks in the carbonyl region (Chart VII). The most intense of the three peaks was the middle one, while the lowest one was relatively weak, the highest one being of intermediate intensity.

The molecular weight (ebullioscopic) in benzene was 236. The value obtained by the mass spectrometric method was 134 with a weak peak at 268.

Ultra violet spectrum in ethanol:

peaks at 249 m.μ $\epsilon$ = 9,400 ; 205 m.μ $\epsilon$ = 5,493

<u>Hydrogenation of 1:5-Diketocyclonon-7-ene (X)</u>

1:5-Diketocyclonon-7-ene (3gm.) in ethanol (100cc) was treated with hydrogen in the presence of palladium charcoal (1.5gm; 10%) with continual shaking, 1.25 moles of hydrogen being absorbed in five minutes. The catalyst was filtered off and after removal of the ethanol a pale yellow liquid was obtained which was distilled under vacuum. It readily yielded a semicarbazone, a 2:4-dinitrophenylhydrazone and an oxime whose melting points corresponded to those of the corresponding derivatives of the ketone (XII).

For analysis the semicarbazone was recrystallised from methanol (m.p. 253-254°C).

found %C = 62.05 %H = 7.62 %N = 21.81

$C_{10}H_{15}N_3O$ requires %C = 62.15 %H = 7.82 %N = 21.75

An authentic sample supplied by Prelog(m.p. 254-255°C) gave no depression on mixing with the sample obtained as described above.

The 2:4-dinitrophenylhydrazone was prepared and recrystallised from chloroform/methanol m.p. 247-249°C. The authentic sample supplied by Prelog melted at 248-249°C and gave no depression on mixing with the derivative of the sample obtained as described above.

The oxime was prepared by adding an alcoholic solution of the ketone to an aqueous/alcoholic solution of hydroxylamine hydrochloride and sodium acetate. The product was obtained as white needles on recrystallisation from petrol (b.p. 60-80°C) m.p. 134-136°C.

<u>Reduction of 1:5-diketocyclonon-7-ene followed by hydrogenation</u>.

To 1:5-diketocyclononene-7 (3gm) in anhydrous ether was added lithium aluminium hydride (2gm) with vigorous stirring and the mixture refluxed for four hours, followed by stirring overnight. A saturated solution of sodium sulphate was now added and the mixture shaken for thirty minutes. The solid was now filtered off and washed with ether. The ether extracts were now combined and after removal of the solvent a colourless oil remained. This was then dissolved in ethanol (100cc) and palladium charcoal (10%; 0.5gm) added and the oil hydrogenated at

room temperature and atmospheric pressure, 0.8 moles being absorbed in five hours. After filtering off the catalyst and evaporation of the alcohol a viscous oil with a camphoraceous odour remained, which was chromatographed over basic alumina of activity III. From the benzene/ether fraction a crystalline material was obtained which after three recrystallisations from petrol had m.p. 60-64°C. From the ether eluate after treatment with p-nitrobenzoyl chloride in pyridine was obtained a p-nitrobenzoate which after recrystallisation from chloroform/methanol melted at 178-180°C.

An authentic sample of the mixed p-nitrobenzoates supplied by Prelog was chromatographed over neutral Woelm alumina (Grade IV). From the benzene ether eluate was obtained a solid which after repeated recrystallisation from chloroform/methanol had m.p. 179-181°C. No depression of melting point was observed on mixing this compound with the specimen prepared by reduction of the diketone (X).

## Reduction of the Aldol Condensation product with sodium borcehydride.

The aldol condensation product (XI ; 0.5gm) in ether (100cc) was shaken with a saturated aqueous solution of sodium borohydride (15cc) for two hours and the mixture allowed to stand overnight. The ether layer was washed with water and dried ($Na_2SO_4$) and the aqueous layer extracted with chloroform (20cc), the chloroform extracted being washed and dried ($Na_2SO_4$). The combined ether and chloroform extracts were evaporated to dryness and the solid so obtained recrystallised from chloroform/methanol. The melting point was diffuse (120-135°C). The infra-red spectrum showed the absence of a carbonyl peak and there were no significant peaks in the ultra-violet (only one at 219 m.$\mu$ ).

<u>Reoxidation of the borohydride reduced product back to the Aldol condensation Product (XI)</u>

The recrystallised borohydride reduction product (0.1gm) was dissolved in ether (200cc) and 100cc of normal sulphuric acid added followed by a slight excess of sodium dichromate solution and the mixture placed in a water bath at 30°C with occasional shaking for six hours. The ether layer was separated and the aqueous layer extracted with a further 500cc of ether in two portions. The combined ether extracts were then washed with water dried ($Na_2SO_4$) and the ether removed. The white solid which remained was recrystallised twice from methanol (m.p. 108-110°C). The melting point was not depressed on mixing with a purified sample of the original aldol condensation product.

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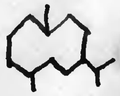
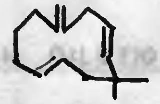
# CHART I

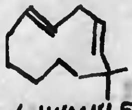
## EXAMPLES OF NATURALLY OCCURRING RING STRUCTURES.

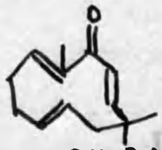

GERMACRANE


HUMULANE

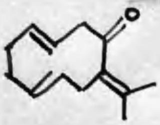
α-BETULENOL


β-HUMULENE

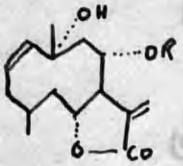

α-HUMULENE



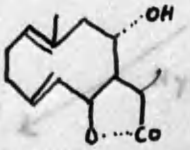
ZERUMBONE



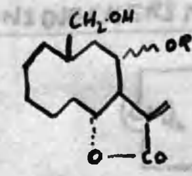
GERMACRONE



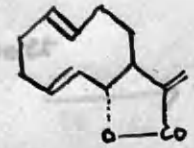
ARCTIOLIDE



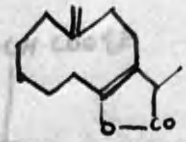
BALCHANOLIDE



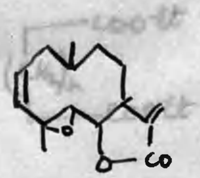
CNICIN



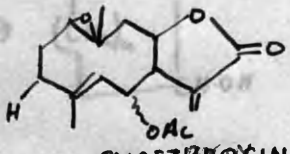
COSTUNOLIDE



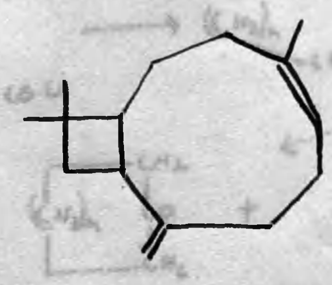
ARISTOLACTONE

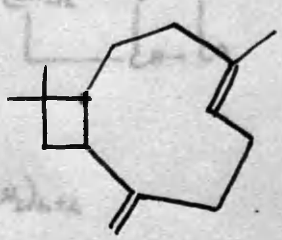


PARTHENOLIDE



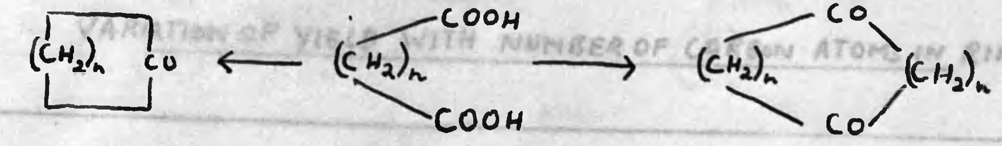
PYRETHROSIN


ISO - CARYOPHYLLENE.

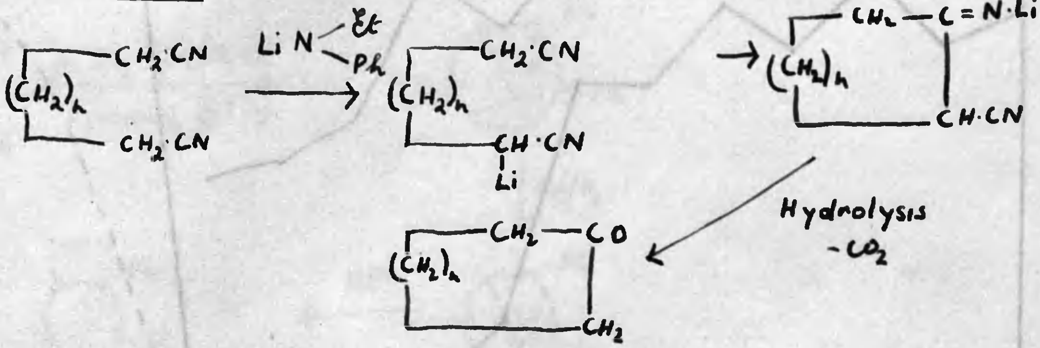

CARYOPHYLLENE

# CHART II

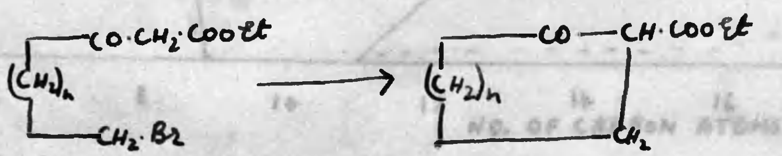
## RUZICKA'S METHOD



## HIGH DILUTION METHOD

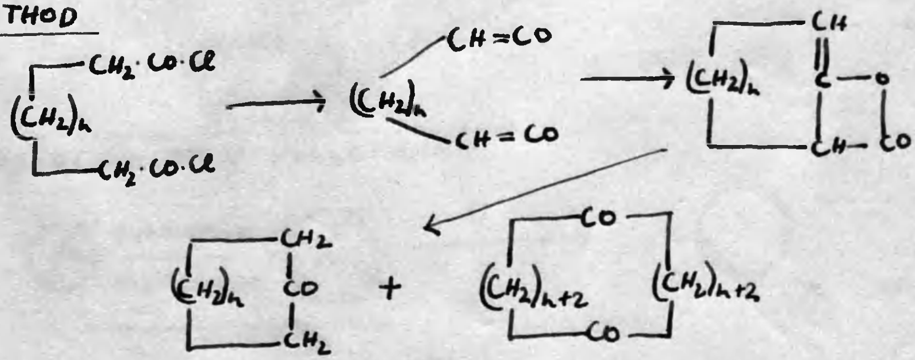


## HUNSDIECKER'S METHOD



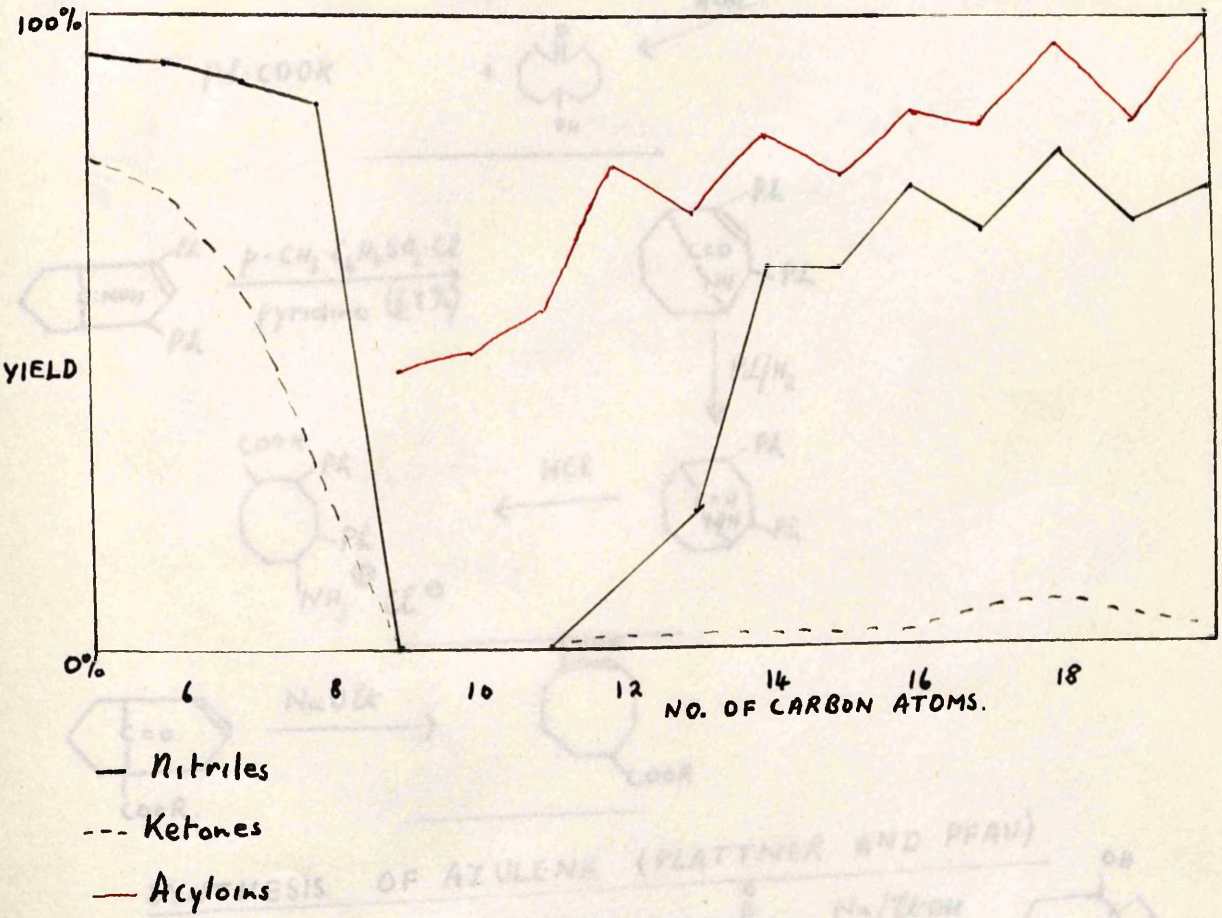
## ACYLOIN CONDENSATION

## DIKETEN METHOD



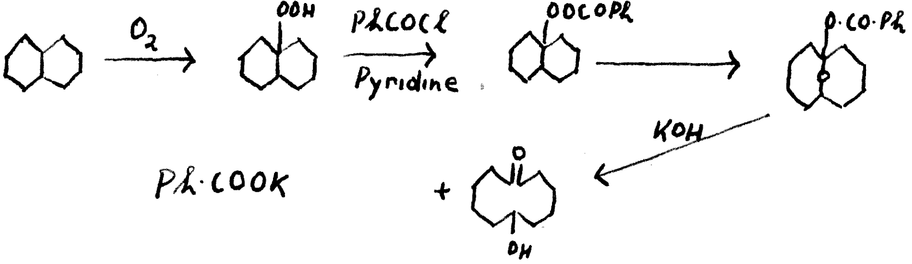
## CHART III

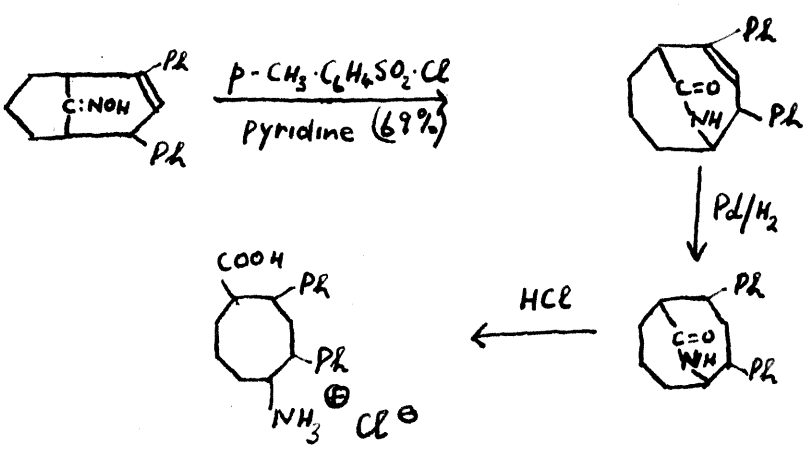
### VARIATION OF YIELD WITH NUMBER OF CARBON ATOMS IN RING

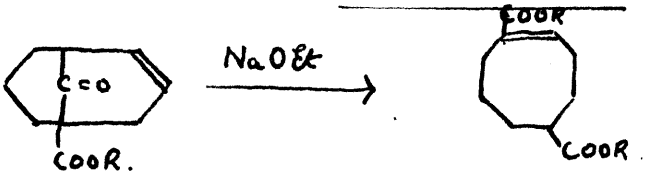


# CHART IV

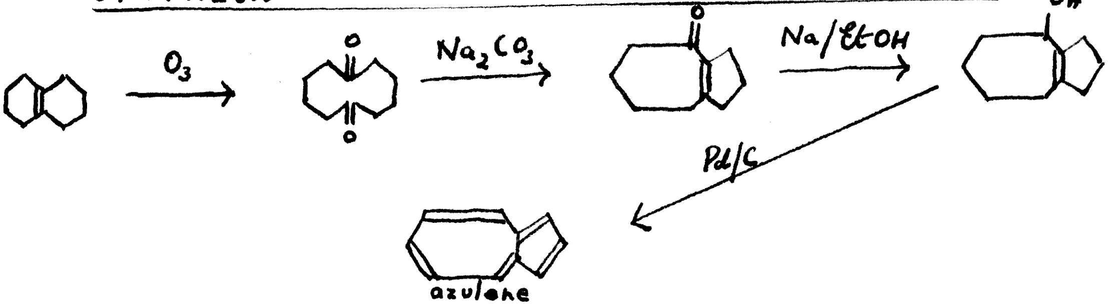
## SYNTHETIC REACTIONS INVESTIGATED BY COPE (et al.) INVOLVING CLEAVAGE OF THE BRIDGE BETWEEN TWO RINGS.



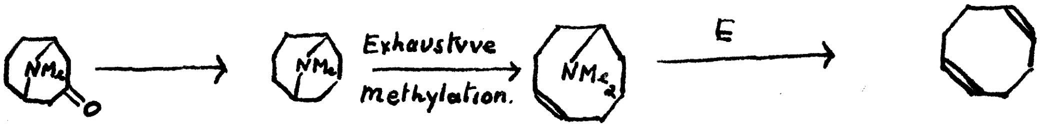


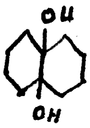


## SYNTHESIS OF AZULENE (PLATTNER AND PFAU)

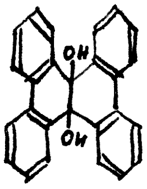


## DEGRADATION OF ψ-PELLETIERINE.





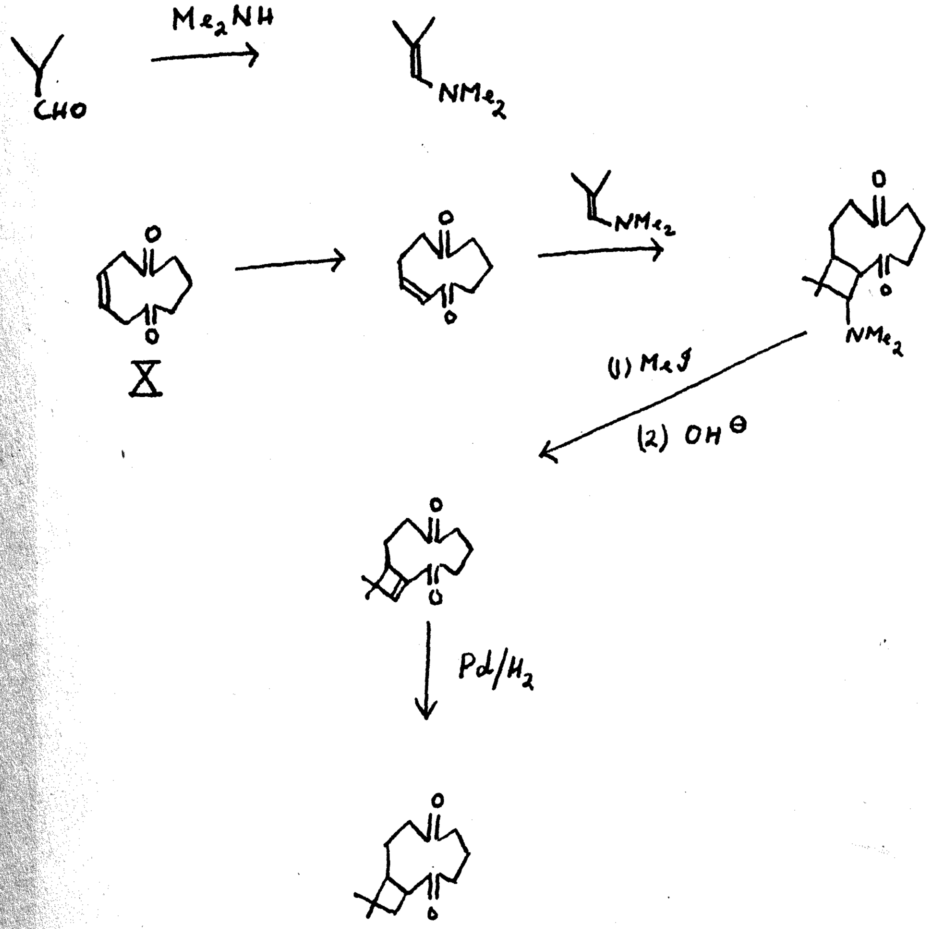
XIV



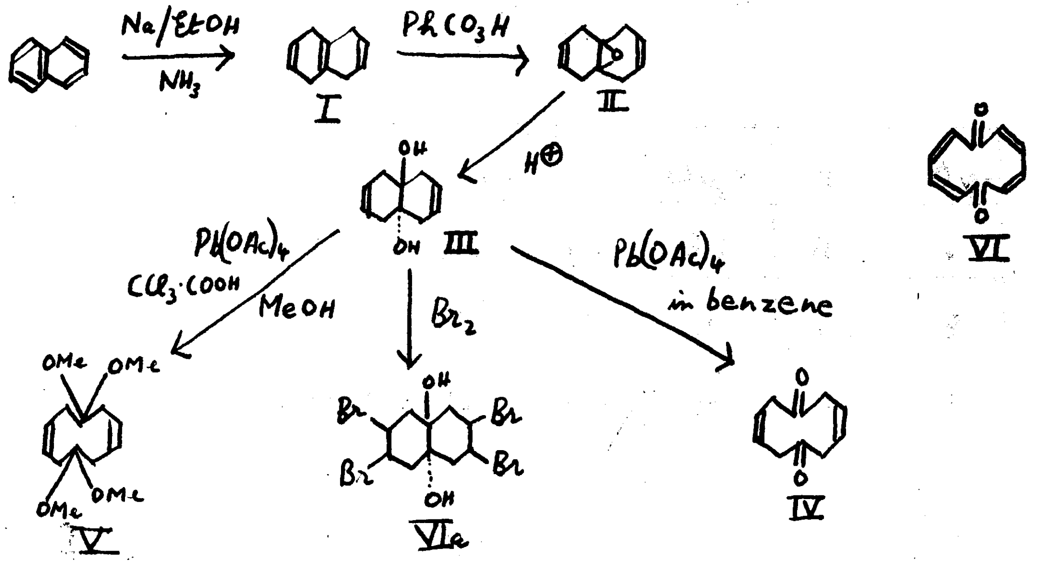
XV

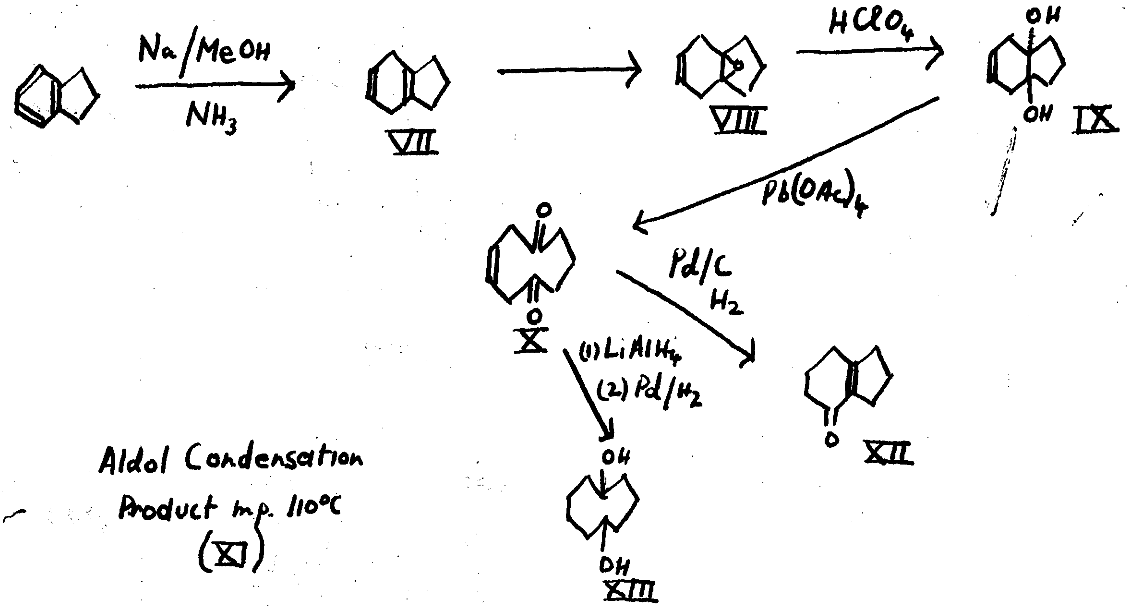
# CHART V

## PROPOSED SYNTHESIS OF A CARYOPHYLLENE DERIVATIVE FROM X



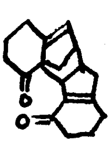
# CHART VI



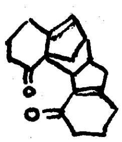


## POSSIBLE STRUCTURAL FORMULAE FOR XI

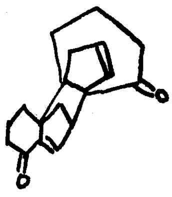
A



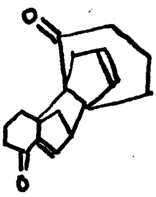
B

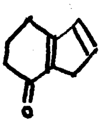


C

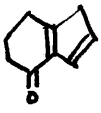


D





XVI



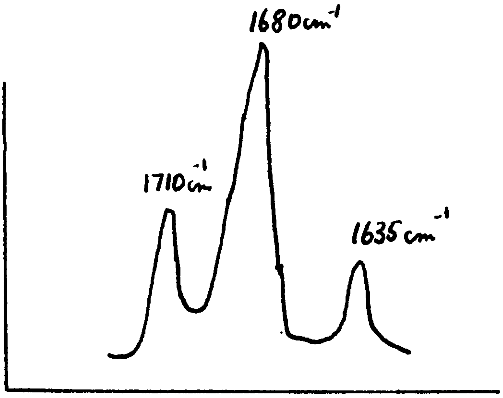
XVII

# CHART VII

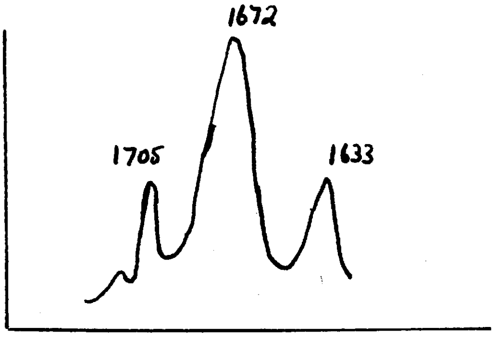
## INFRA RED SOLUTION SPECTRA OF XI (CARBONYL REGION).

| Solvent | $\nu(cm^{-1})$ | $\Delta\nu_{\frac{1}{2}}a$ | $\nu\ cm^{-1}$ | $\Delta\nu_{\frac{1}{2}}a$ | $\nu(cm^{-1})$ | $\Delta\nu_{\frac{1}{2}}a$ |
|---|---|---|---|---|---|---|
| Hexane | 1710 | 4·3 | 1680 | 3·5 | 1635 | 6 |
| $CCl_4$ | 1705 | 8 | 1672 | 11 | 1633 | 8 |
| $CHCl_3$ | 1700 | 12 | 1658 | 10 | 1631 | 9 |

Hexane



$CCl_4$



$CHCl_3$