CHAPTER II

A SYNTHESIS OF CARISSONE
An efficient five-step synthesis of (+)-carissone (I) starting from (-)-α-santonin (XI) is reported. The conjugated keto acid (XV) obtained from (XI) by a slightly modified procedure, on decarboxylation with lead tetraacetate, furnishes the keto acetate (XXVI) which is saponified with alcoholic potassium hydroxide and subsequently oxidised with chromic acid to the diketone (XII). Reaction of (XII) with methylmagnesium iodide furnishes (+)-carissone, the C-11 carbonyl group of the diketone (XII) being selectively attacked. It is worthy to note that the conjugated carbonyl group of santonin and other intermediates is not protected in this synthesis.

Methylmagnesium iodide reacts similarly selectively with the C-20 carbonyl group of progesterone.
Carissone (I), $C_{16}H_{24}O_2$, m.p. 78-79° was first isolated by Reichstein\(^1\) from the roots of the Australian Shrub Carissa Laceolata (R. Brown) and was later found in the oil of Eucalyptus macarthurii\(^2\). One of the oxygen atoms of carissone was shown to be present in the form of an $\alpha$, $\beta$-unsaturated ketone $\lambda_{\text{max}} 250 \text{ m} \mu \lambda 15000$. IR bands of 1638 cm\(^{-1}\) (C = O of conjugated ketone), 1595 cm\(^{-1}\) (C = C of conjugated ketone)\(^7\). The IR spectrum also showed the other oxygen atom to be present in the form of a hydroxyl group (band at 3570 cm\(^{-1}\)). But since carissone was recovered unchanged after oxidation with chromic acid and also could not be acetylated with acetic anhydride and pyridine, it was concluded that the hydroxyl group must be tertiary.

Barton\(^3\) showed that the dehydration of 2,4-DNP of carissone under controlled conditions furnished 2,4-DNP of $\alpha$-cyperone. Since the structure of $\alpha$-cyperone had already been established\(^4\) as (II) by degradative and synthetic methods, the above correlation was useful in arriving at the gross structure of carissone. A partial synthesis of (+) carissone was carried out by Ayer and Taylor\(^5\) who showed that $\alpha$-eudesmol (III) on treatment with nitrosyl chloride furnished the oxime (IV) of carissone. Since the absolute configuration\(^6\) of $\alpha$-eudesmol has been established through correlation with steroids and also the C-7 side-chain of $\alpha$-eudesmol has been shown to be cis to the C-10 angular methyl group, the stereochemical structure of carissone is represented by (I).
(I)  

(II)  

(III)  

(IV)  

(V)  

(VI)  

(VII)  

(VIII)  

(N(C₂H₅)₂ • CH₃I)

H₂C—C=CH₂ + O=C—CH₂—CH₃  →  (I)
The structure and absolute configuration of (+)-carissone was confirmed by a synthesis reported by Pinder. Reaction of α-cyperone (II) with perbenzoic acid furnished the monoepoxide (V) which on reduction with LAH furnished the diol (VI). On oxidation with manganese dioxide in chloroform, the diol yielded (+) carissone (I). Another synthesis of (+)-carissone by Robinson-Mannich condensation of 1-diethylaminopentan-3-one methiodide (VII) with the keto-alcohol (VIII) has been reported by Mukherjee et al. in a preliminary communication, but the details of this work have not been published and further more the synthesis is not stereospecific.

**PRESENT WORK**

(+)-Carissone has proved useful in the preparation of a number of eudesmanic compounds such as β-cyperone, α-eudesmol and γ-eudesmol and appears to be a potential intermediate for the synthesis of a number of related eudesmanic compounds. Hence it was considered of interest to explore routes for the synthesis of such an important compound from some suitable and easily accessible material.

α-Cyperone (II) was initially chosen as the starting material. Pinder has already brought about the transformation of α-cyperone to (+) carissone but he has used the epoxidation
method as explained earlier. A more convenient approach appeared to us to be the addition of acetic acid\(^{32}\) (in presence of phosphoric acid), or trifluoroacetic acid to the isopropenyl group of \(\alpha\)-cyperone to furnish the derivatives (IX) and (X) respectively. Saponification of these derivatives would give carissone. The addition of acetic acid or trifluoroacetic acid to olefines proceeds under relatively mild conditions (room temp.) It was anticipated that though there are two double bonds in \(\alpha\)-cyperone, the \(C_4 - C_5\) ethylenic linkage would be unreactive as the availability of electrons for the protonation step is reduced due to the presence of a conjugated carbonyl group at C-3. The attack was therefore expected to proceed only at the non-conjugated ethylenic linkage. In order to verify this point, the addition reactions were first studied with the readily available carvone which was chosen as a model compound since it has the same structural features as \(\alpha\)-cyperone- a cyclic double bond in conjugation with the carbonyl function and another double bond in the isopropenyl side-chain. However since the results of experiments with the model compound were not encouraging and as also the \(\alpha\)-cyperone content in the cyperus rotundus oil* handled by us was very low, it became necessary to explore some other new route.

*The oil was purchased from S.H. Kelkar and Co., Bombay. We could not procure sufficient quantity of the oil since its extraction was discontinued by S.H. Kelkar and Co.
Our attention was then focussed on (-) α-santonin (XI) as the starting material since it has proved very useful in this laboratory and elsewhere for the synthesis of a number of eudesmanic and related compounds. The feasibility of using santonin as the starting material for the synthesis of carissone was considered on the following grounds.

1) Carissone (I) and santonin (XI) have a close structural resemblance. Both have
   (a) eudesmanic skeleton
   (b) same absolute configuration at C₇ and C - 10
   (c) oxygen function at C₃
   and (d) ethylenic linkage at C₄ - C₅

2) Stereochemistry of santonin has been rigorously established both by chemical and X-ray analysis methods.

3) Santonin is readily available.

4) It is a highly crystalline compound and its purity can be easily checked.

As a first step in the synthesis of carissone, it was considered necessary to transform santonin into the diketone (XII) which appeared to us to be a potentially important intermediate. The carbonyl group at C₃ of the diketone is in conjugation with the ethylenic linkage and hence it is expected to be less vulnerable to the attack of a nucleophilic reagent than the non-conjugated carbonyl group at C₁₁.
A reagent like methyl magnesium iodide would react somewhat selectively with the non-conjugated carbonyl group of the diketone and furnish carissone. It was thought desirable to verify this point by studying the reaction of methyl magnesium iodide with the readily available model compound, progesterone (XIII) since it has two types of carbonyl groups in environments comparable to those of the diketone (XII). In accordance with our expectation methyl magnesium iodide attacked selectively the C₂₀ carbonyl group of progesterone and furnished the keto-alcohol (XIV). This keto-alcohol was separated from the rest of the reaction products by chromatography over alumina and identified by comparing its properties with those of the authentic sample reported in literature. The product gave IR bands at 3500 (−OH), 1660 (conjugate C=O) and 1600 cm⁻¹ (conjugate C=C), but no band around 1710 cm⁻¹ corresponding to the non-conjugated carbonyl of the starting material. NMR spectrum (NMR-1) showed signals at 7 9.12 (CH₃ on C₁₃), 8.80 (−C − C −OH) and 8.68 (CH₃ on C₁₀). This spectral data was consistent with the structure (XIV).

Encouraged by these results, we were quite hopeful that the diketone (XII) would follow a similar course of reaction as progesterone and hence we concentrated our attention to find out some method by which santonin could be converted into the diketone (XII). A close study of the
structures of santonin and the diketone revealed that the transformation would require

1) reduction of the less substituted C₁ - C₂ double bond without affecting the more substituted C₄ - C₅ double bond of santonin.

ii) cleavage of the C₆ - O linkage allylic to the C₄ - C₅ double bond.

iii) modification of the C-7 side-chain of the acid (XV) which would be obtained by effecting the changes (1) and (ii) above.

With these factors in view we were in search of some method that would transform santonin first into the keto-acid (XV) so that the conversion of the latter into the diketone (XII) could be explored later on.

As regards the changes (1) and (ii), Bruderer and co-workers¹⁷ have reported that by metalamine reduction, both these changes could be accomplished in a single operation and santonin could be converted into the keto-acid (XV) in 90% yield. When we tried this reaction, we found that though the reaction product was obtained in good yield, it was of a gummy nature and the keto-acid could not be crystallised out from the gummy material. The reaction was repeated several times, but every time the same difficulty was encountered. At this stage we came across a publication by Piers and Cheng¹⁸ who tried to prepare pure methyl ester (XVI) of the acid by
reducing santonin according to the procedure of Bruderer and co-workers and subsequently treating the crude product with diazomethane. However, they got a mixture of compounds which proved difficult to separate into individual components. The metal-amine reduction method thus appeared to be disappointing for our work and we were required to search for some other method for effecting the transformation of santonin into the keto-acid. Various hydrogenation results with different catalysts and under different experimental conditions have been reported. In most of these cases either di- or tetrahydro products were obtained but in almost every case the C6 - O linkage remained practically unaffected. The difficulty encountered in cleaving the lactone ring between C6 and O is partly attributed to the equatorial to orientation of the C6 - O linkage. If this is the case, then it was thought that changing the orientation of the linkage from equatorial to axial might make it susceptible to attack during hydrogenolysis.

Nakazaki and Naemura brought about this change in orientation by epimerising (-)-α-santonin (XI) at C-6 by the action of hydrogen chloride in dimethyl formamide in accordance with the procedure developed by Ishikawa. They treated the 6-epi compound (XVII) thus obtained, with zinc dust and a limited quantity of acetic acid and refluxed the mixture only for 3 minutes since they wanted to hydrogenolysis.
\[(XV) \; R = H\]
\[(XVI) \; R = \text{CH}_3\]

\[(XI)\]
\[(XVII)\]

\[(XVIII)\]
\[(XIX)\]

\[(XX)\]
the compound and retain intact both the double bonds at $C_1 - C_2$ and $C_4 - C_5$. By following this method, they obtained the expected product (XVIII). Piers and Cheng, for the same purpose refluxed a similar mixture for 15 minutes and they also got the same expected product (XVIII). In the case of 6-epi-β-santonin (XIX), Cocker wanted to hydrogenolyse the compound and also reduce the double bond at $C_1 - C_2$. He therefore used in the reducing mixture a large excess of acetic acid and refluxed the mixture for a very long period (30 hours). He claims to have obtained the expected acid (XX) but he has not given the yield. We converted $\alpha$-santonin (XI) into (-) 6-epi-$\alpha$-santonin (XVII) by the procedure developed by Ishikawa. Since we were interested in the hydrogenolysis of the 6-epi compound as well as the reduction of the $C_1 - C_2$ double bond, we adopted the same experimental conditions as were used by Cocker. However the reaction product appeared to be a bit complex and its NMR showed that even the $C_4 - C_5$ double bond was reduced since there was no signal for a 'methyl on a double bond' near about 8.2 - 8.57. The product also recorded a low m.p. 90° and since the reaction product was not the expected keto-acid (XV) this method had also to be abandoned.

Having no other practical method available for preparing the keto-acid (XV) in good yields, we again
reverted to the metal-amine reduction method mentioned above and carefully examined the reduction of santonin. The NMR spectrum of the product showed that there was no signal near about 8.27, thus indicating that in this case also the C₄ - C₅ double bond was reduced. This was probably due to the prolonged reducing action of the metal-amine complex in whose contact the compound was left overnight. After conducting a series of experiments, we were able to modify the method followed by Bruderer and co-workers and avoid further reduction. This modification consists in allowing santonin to react with the lithium-ammonia complex only for 20 minutes and then decomposing the complex by adding just sufficient quantity of solid ammonium chloride. As a result of this modification we obtained the desired keto-acid (XV) in a satisfactory yield (80%) from which the pure acid was obtained by crystallisation. NMR spectrum (NMR-2) of the purified sample gave signals at J, 8.78 (angular methyl at C-10), 8.77 (d, J = 7 cps, CH₃ on C₁₁), 8.25 (CH₃ on a double bond) and -1.03 (-COOH). These results were quite consistent with the structure (XV).

Having obtained the keto-acid (XV) in hand, we proceeded to investigate the possibility of its conversion into the diketone (XII). Bacha and Kochi²⁴ have reported that the oxidative decarboxylation of acids with lead tetraacetate in presence of cupric acetate furnishes alkenes in high yields.
NMR-2. 3-OXO-11β(H)-EUDESM-4-EN-13-OIC ACID (XV) (IN CHCl$_3$)
The oxidative decarboxylation of cholic acid (XXI) to \( \Delta^{22}\)-norcholesterol (XXII)\(^{23}\) may be cited as a typical example. We thought of using this method in the case of the keto-acid (XV) expected to obtain a mixture of the keto-dienes (XXIII) and (XXIIIa). Our plan was to separate out (XXIII) by some suitable method and subject it to the action of perbenzoic acid. The isolated double bond in the side-chain of (XXIII) would undergo preferential epoxidation and furnish the oxide (XXIV) which on LAH reduction would give the diol (XXV). These reactions were anticipated on sound theoretical considerations and were analogous to the method used by Pinder\(^6\) in the conversion of \( \alpha\)-cyperone (II) to the diol (VI). We further proposed to oxidize the diol (XXV) with Jones' reagent to furnish the diketone (XII).

In a preliminary experiment of the keto-acid (XV) with lead tetraacetate under the conditions used by Bacha and Kochi\(^{22}\), the product formed showed that in addition to the expected keto-diene(s), it also contained a small amount of a keto-acetate as was indicated by the IR spectrum (IR bands at 1730 and 1240 cm\(^{-1}\)). The keto-acetate was assigned a tentative structure (XXVI). On saponification of the mixture, the above acetate bands in the IR spectrum disappeared and a new band appeared at 3610 cm\(^{-1}\) (-OH). The saponified mixture was chromatographed over alumina. The less polar and major component was the keto-diene (XXIII) giving IR bands at 1660 (conjugated C=O), 1610 (C=C of conjugated ketone),
910 cm\(^{-1}\) (\(-\text{CH}=\text{CH}_2\)). The more polar and minor component appeared to be a keto-alcohol which gave IR bands at (IR-3) 1660 (conjugated C=O), 1610 (conjugated C=C) and 3610 cm\(^{-1}\) (-OH). Following the tentative structure of the keto-acetate, the keto-alcohol was also assigned a tentative structure (XXVII). NMR spectrum (NMR-2) of the keto-alcohol gave signals at J:

- 8.23 (3H, \(\text{S}_1\) \(\text{CH}_3\) on double bond at C\(_4\))
- 8.73 (3H, \(\text{S}_1\) \(\text{CH}_3\) on C\(_{10}\))
- 8.77 (3H, doublet due to \(\text{CH}_3\) on C\(_{11}\))

These results were quite consistent with the structure (XXVII). Oxidation of the keto-alcohol with Jones' reagent furnished a diketonic compound which could be represented by (XII). This diketonic compound gave IR bands at (IR-4) 1712 (saturated ketone C=O), 1667 (conjugated ketone C=O), and 1613 cm\(^{-1}\) (conjugate C=C). It also gave NMR signal (NMR-3) at J, 8.75 (angular methyl at C-10), 8.27 (\(\text{CH}_3\) on C\(_4\)), and 7.93 (\(\text{CH}_3\) -C- ). This spectral data fully supported the structure \(\text{O}^0\) (XII) assigned to the diketonic compound.

Hortmann et al\(^{24}\) following a different route have prepared a diketone to which they have assigned the structure (XII). The properties of this diketone are found to be in close agreement with those of the diketonic compound that we have prepared above. This therefore confirms the structure (XII) for the diketonic compound prepared by us and
it also confirms the structures (XXVI) and (XXVII) for the keto-acetate and keto-alcohol respectively.

When we found that this method of preparing the diketone (XII) via the keto-acetate was much simpler than the one we had planned via the keto-diene, we changed our original programme and decided to prepare the diketone via the keto-acetate. We tried to look for such experimental conditions that would minimise the formation of the keto-diene(s) and enhance the proportion of the keto-acetate. Corey and Cassanova\(^{25}\) have reported that the oxidative decarboxylation of acids with lead tetraacetate in benzene in presence of pyridine alone gives the acetates in high yields. The reaction proceeds almost exclusively along a single path and replaces the carboxylic group of acid by an acetoxy group. Thus from exo- and endo-norbornane carboxylic acids they obtained exo-norbornyl acetate in yields upto 69%. When we employed this reaction in the case of the keto-acid (XV), we obtained good yields of the keto-acetate (XXVI). The product gave IR bands at 1730, 1240 (-O-CO-CH\(_3\)), 1660 (conjugated C=O) and 1610 cm\(^{-1}\) (conjugated C=C). The product also gave NMR signals at \(\delta\) 8.78

\(^{25}\)Recently Ourisson\(^{26}\) has reported a similar but an interesting reaction of the keto-acid (XV) with lead tetra-acetate in benzene but in place of pyridine he has used lithium chloride as was used by Kochi\(^{27}\). The carboxyl group was not replaced by an acetoxy group but by chlorine and a chloro compound (XXVIII) was formed.
(angular methyl at $C_{10}$), 3.73 (d, $CH_3$ on $C_{11}$), 3.23 ($CH_3$ on $C_4$), 7.95 ($CH_3 - C -$).

On saponification with 1% ethanolic alkali under nitrogen atmosphere, the above keto-acetate gave an impure keto alcohol which was purified by chromatography over alumina. The IR spectrum of the purified sample was identical with that of the keto-alcohol (XXVII) that we had obtained previously. Oxidation of this keto-alcohol with Jones' reagent furnished the diketone (XII) which was purified by chromatography and crystallisation from pet.ether-benzene mixture. This diketone was also found to be identical with the diketone we had obtained earlier.

Having obtained the diketone (XII), our only aim was to convert it into carissone by the action of methyl magnesium iodide as explained earlier. Although the non-conjugated carbonyl group of the diketone is expected to be more susceptible to the attack of nucleophilic reagents, the conjugated carbonyl is not absolutely unreactive. It was therefore necessary to find such suitable conditions that only the non-conjugated carbonyl would be attacked. Various experiments were conducted using different conditions and different relative proportions of the Grignard and the diketone and in each case IR spectrum was taken. By comparing the relative intensities of the hydroxyl, conjugated and non-conjugated carbonyl bands in the IR spectrum, the extent to
which the reaction had proceeded could be assessed. After conducting several such experiments, it was found that the reaction using 2.5 moles of methyl magnesium iodide for every mole of the diketone and using the reaction period of 4 hours at room temp., gave moderately satisfactory yields of carissone (I). Unreacted starting material and other impurities were removed from the product by chromatography over alumina. The fraction enriched in carissone gave in the NMR spectrum, signals at $\delta$: 8.77 (C-10 angular methyl), 8.72 (C-7 hydroxy isopropyl); 8.22 (C-4 methyl on a double bond). However, a comparison of the IR spectrum of the product with that of the authentic sample of carissone showed that it still contained some impurities which could not be removed easily and this prevented the crystallisation of the product. 2,4-DNP derivative of the product was therefore prepared but this also showed a depressed melting point (158°C). Thin layer chromatography of the DNP derivative gave a major spot having the R$_f$ value the same as that of the DNP derivative prepared from an authentic* sample of carissone and a minor spot having a high R$_f$ value. The DNP derivative was chromatographed over silica-gel and crystallised from chloroform-methanol mixture to give the pure DNP derivative having m.p. and mixed m.p. 172-73°C. The NMR spectrum (NMR-4) of the purified DNP gave signals at $\delta$: 3.87 (C-10 angular methyl); 8.73 (hydroxy

*The authentic sample of carissone was supplied by Drs. Nityanand and M.M. Dhar.
NMR-4
2,4-DINITROPHENYL HYDRAZONE OF CARISSONE
(IN CHC\(_3\))
isopropyl); 8.02 (C-4 methyl on a double bond). The above NMR spectrum and also the IR spectrum (IR-5) of the DNP were found to be identical with the NMR and IR spectra of the authentic DNP derivative of carissone.

The identity of the synthetically prepared carissone was thus established through its DNP derivative. In the synthesis of carissone described above, it is of interest to note that the C-3 carbonyl group has remained intact in all the intermediates isolated. Other synthetic studies reported in literature reported in literature showed that the C-3 carbonyl group either required protection which was later on removed or it got reduced to an allylic alcohol which was later oxidised. But this involved more number of steps, which is not the case in the synthesis described above.

Although the above synthesis of carissone makes use of methyl magnesium iodide, an alternative approach involving the use of dimethyloxosulphonium methyldide was considered as possible. This new method was expected to proceed more selectively and produce better results. Experimental results actually showed that it did proceed in accordance with our expectation. But since this new approach forms a part of the next Chapter, it is described in full therein.
Dehydration of Tauremisin (Vulgarin)

Tauremisin occurring in *Artemisia Taurica* and Vulgarin occurring in *Artemisia Vulgaris L.* are one and the same eudesmanic lactone represented by the structure (XXIX). It has been synthesised in this laboratory by Honwad and Rao\(^1\), starting from α-santonin.

We procured a sample of the naturally occurring tauremisin from Professor Rybalko and studied its dehydration with a view to obtain the compound (XXX) which is potential intermediate in the synthesis of the naturally occurring desoxy-γ-santonin (XXXII).

Dehydration of tauremisin has been reported in literature. From the structure of the compound, it appeared that only two conjugated dienones (XXX) and (XXXI) are possible as dehydration products. Rybalko\(^2\) reported that in acidic medium, tauremisin readily underwent dehydration to give the exomethylene conjugated dienone (XXXI) having m.p. 138-39°. Geissman\(^3\) has reported that the treatment of Vulgarin (tauremisin) with glacial acetic acid containing a trace of con. sulphuric acid yielded a mixture of crystalline anhydrovulgarins. From the infrared, ultra-violet and NMR spectra, he concluded that the dehydration product was a mixture of two anhydrovulgarins (XXX) and (XXXI). From his experimental work it appears that these anhydro compounds could not be separated from one another and the product gave a melting range 115-25°.
The tertiary hydroxy group of tauremisin is equatorial and hence the dehydration by $E_2$-mechanism is expected to yield the conjugated dienone (XXXI) with exocyclic double bond and not the conjugated dienone (XXX). However, from the dehydration studies of $\beta$-amyrin, lupanol and other hydroxy compounds, Belton and co-workers showed that the use of thionyl chloride in benzene favoured the removal of a water molecule by cis-elimination process. In the case of tauremisin, the hydroxy group at C-4 is equatorial and $\alpha$-oriented and the hydrogen atom at C-5 is cis to this hydroxy group. Following the observations of Belton and co-workers, we thought that the use of thionyl chloride in benzene in the case of tauremisin would remove C-4 hydroxy group and the C-5 hydrogen atom in the form of a water molecule and create an ethylenic linkage at C$_2$-C$_5$, thus giving us the required compound (XXX).

However when we conducted the dehydration of tauremisin with thionyl chloride in benzene under the conditions given by Belton and co-workers, the dehydration product was found to be a mixture of the two conjugated dienones (XXX) and (XXXI). On crystallisation from carbon tetrachloride, the axomethylenic compound separated out in a pure form. The NMR spectrum (NMR 5) of this pure product gave signals at 3.06 (1H, m, C-2 olefinic proton), 4.83 (3H, m, C$_2$ and C$_{14}$ olefinic protons), 5.95 (1H, m, C$_8$ proton), 3.81 (3H, doublet ($J = 7$ cps), C$_{11}$ methyl),
8.88 (3H, C\textsubscript{10} methyl).

These spectral results were quite consistent with the structure (XXXI) and the compound gave a sharp m.p. 142°C and it appeared to be purer than the dehydration product obtained by Rybalko. But we were interested in the other conjugated dienone (XXX) which might be present in the mother liquor.

The residue from the mother liquor was recrystallised. It showed a m.p. 127°C and its NMR spectrum gave a signal at 7, 7.83, indicating the presence of a methyl on a double bond. Thus it contained the conjugated dienone (XXX) as expected but the NMR spectrum further showed it to be contaminated with the dienone (XXXI). For the complete removal of the latter and getting (XXX) in a pure form, several crystallisations were necessary. From this preliminary experiment, it became clear that a large quantity of tauremisin should be handled for dehydration experiment so that a reasonably good amount of (XXX) could be finally obtained in a pure form for further work. We had no spare tauremisin in hand but while the above work was in progress, a group of workers* in this laboratory was examining the terpenic constituents of A-Vulgaris collected from Darjeeling. It was hoped that this examination would

*The examination of the constituents of A-Vulgaris was conducted by Kundu and Rao in this laboratory.
lead to the isolation of tauremisin which would become available for our work. However the examination showed that there was no tauremisin in the material studied and because of the paucity of the starting material, further work could not be carried out.
**EXPERIMENTAL**

(-)-6-epi-α-Santonin (XVII)

(-)-α-Santonin (18 g) was dissolved in anhydrous dimethyl formamide (200 ml) containing anhydrous hydrogen chloride gas (10 g). The resulting mixture was heated to 85-90° for 3-1/2 hrs. and then allowed to stand at room temperature overnight. Most of the solvent was then distilled under reduced pressure (40 mm) and the residual concentrate was diluted with water (200 ml) and then thoroughly extracted with chloroform (3 x 200 ml). The combined extracts were washed thoroughly with saturated brine, bi-carbonate solution and then with water and after drying over anhydrous sodium sulphate, chloroform was removed under reduced pressure. The residue was a red viscous oil which was purified by chromatography over neutral alumina (Gr. II, 180 g). Elution with 500 ml benzene gave a pale yellow solid which was recrystallised from ethyl acetate to give the -6-epi-compound (10.55 g) m.p. 102-103° (literature^19 m.p. 102-105°).

**Reduction of (-)-6-epi-α-santonin (XVII)**

The above (-)-6-epi compound (9 g) was dissolved in a mixture of ethanol (360 ml), acetic acid (240 ml), and water (120 ml). Zinc dust (21 g) was gradually added to the above solution and the mixture was refluxed for 30 hours. The mixture was filtered and the filtrate distilled under reduced pressure (70-80 mm). The undistilled portion was
taken up in ether (400 ml) and washed with water (4 x 100 ml). The ether solution was treated with sodium carbonate till there was no effervescence. The aqueous portion was separated out and the organic acid regenerated from the aqueous portion by acid treatment. The acidified mixture was extracted with ether (3 x 150 ml), washed with water, dried over anhydrous sodium sulphate and ether removed by distillation. The residue was a slightly gummy mass which was recrystallised from pet.ether-benzene to give a product (6 g) with m.p. 90°. The NMR spectrum of this product gave no signal near about 8.2 - 8.5J (methyl on a double bond) and thus the product was not the expected acid (XV).

Birch reduction of santonin (XI)

Santonin (20 g) was dissolved in dry tetrahydrofuran (225 ml) and the solution was added to liquid ammonia (2.5 litres). To this mixture was added with stirring, lithium (6 g) in small pieces over a period of 10 minutes. After the addition of lithium was over, the stirring was continued for 15-20 minutes and thereafter solid ammonium chloride (55 g) was added in portions over a period of 10 minutes, resulting in the discharge of the blue colour of the reaction mixture. Ammonia was allowed to evaporate off overnight at room temp. and the residue diluted with water (500 ml) and acidified with dil. sulphuric acid till the
solution was acidic to Congo red. The acidified mixture was extracted with ether (3 x 300 ml), washed with water and the ether extract treated with saturated sodium carbonate solution till there was no effervescence. From the carbonate extract, the organic acid was regenerated by acid treatment. The acidified mixture was extracted with ether (3 x 250 ml), the ether extract washed with water and dried over sodium sulphate. After removal of ether by distillation, the residue was obtained as the crude acid (18 g) which on crystallisation from hexane-acetone furnished the pure acid XIV (16 g), m.p. 123-24° (lit. m.p. 17, 21 125-26°).

**IR bands (IR No.2):** 2941, 1718, 1675, 1618, 1597, 1449, 1420, 1401, 1370, 1326, 1311, 1289, 1233, 1220, 1190, 1176, 1139, 1121, 1087, 1064, 1046, 1022, 1007, 968, 940, 925, 915, 892, 885, 869, 850, 833, 804, 763, 722, 696, 690 cm⁻¹.

**Action of lead tetraacetate on the acid XIV in presence of pyridine and cupric acetate**

A mixture of the acid XIV (2.51 g, 10 m.moles), cupric acetate monohydrate (447 mg, 2.23 m.moles), pyridine (290 mg, 3.66 m.moles), and dry benzene (50 ml) was stirred over a magnetic molar for 40 minutes. Lead tetraacetate (8.13 g, 18.3 m.moles) and additional quantity of dry benzene (50 ml) were added to the above solution. The mixture was stirred in dark and under N₂ atmosphere for 1 hour, and then refluxed under the same conditions over water-bath for 1 hour. Excess
of lead tetraacetate was decomposed by addition of ethylene glycol (3 ml). The mixture was filtered and the filtrate was treated with sodium carbonate solution to remove the unreacted acid. The benzene layer was separated out, washed with water several times, treated with HCl to remove last traces of pyridine and then again washed with water. After drying over calcium chloride, benzene was removed by distillation and the residue was totally distilled under high vacuum (0.2 mm), to give the reaction product (1.5 g) IR spectrum of the distillate gave bands at 2959, 1730, 1660, 1610, 1445, 1412, 1366, 1342, 1323, 1314, 1287, 1240, 1199, 1180, 1145, 1079, 1015, 1005, 995, 940, 917, 875, 845, 795, 755, 699, 575 cm\(^{-1}\).

Keto-alcohol (XXVII) by saponification

The distillate (1.4 g) from the above lead tetraacetate reaction product was taken up in ethanol (40 ml) in which KOH (0.4 g) was dissolved. The mixture was refluxed under N\(_2\) atmosphere for 3 hours. On dilution with water (100 ml), it was extracted with ether (3 x 50 ml), the ether extract washed with water and dried over sodium sulphate. Ether was removed by distillation, leaving behind the crude residue (1.28 g).

The IR spectrum of the crude residue gave bands at 3546, 2945, 1667, 1608, 1447, 1427, 1372, 1348, 1316, 1287, 1202, 1181, 1170, 1122, 1095, 1081, 1044, 1016, 990, 961,
The above crude residue (1.25 g) was chromatographed over neutral alumina (Gr.II, 35 g). The fractions eluted with pet.ether, and pet.ether-benzene (70:30) gave the keto-diene XXIII (0.95 g) giving IR bands at 2985, 1667, 1608, 1447, 1427, 1372, 1348, 1316, 1287, 1202, 1181, 1170, 1122, 1095, 1081, 1044, 1016, 990, 961, 940, 912, 885, 877, 825, 813, 793, 752, 735, 698 cm⁻¹.

The fraction eluted with pet.ether-benzene (30:70) appeared to be the pure keto-alcohol XXVII (0.25 g) which gave IR bands at (IR-3): 3610, 2950, 1660, 1610, 1443, 1420, 1366, 1346, 1325, 1290, 1269, 1198, 1179, 1147, 1130, 1078, 1058, 1015, 1005, 990, 970, 943, 909, 890, 869, 840, 798, 788, 755, 699 cm⁻¹.

Diketone (XII) from the keto-alcohol (XXVII)

The keto-alcohol XXVII (0.22 g) was dissolved in pure acetone (5 ml) and the solution cooled to 0-5°. Jones' reagent was added dropwise to the cooled solution till the brown colour persisted for 15-20 minutes after the addition was over. Methanol was added in small quantity to consume the excess of the reagent and the solution turned green. The mixture was diluted with water (10 ml) and extracted with ether (3 x 25 ml). The ether extract was washed with water, dried over sodium sulphate and ether removed by distillation to give a thick crude residue which solidified on keeping at 0° for 48 hours.
It was crystallised from pet.ether to give a pale yellow crystalline product (0.16 g) with m.p. 72-74°.

**Analysis**

Calculated for $C_{14}H_{20}O_{2}$: 76.32; H, 9.15%.

IR bands (IR Spectrum 4): 2941, 1712, 1667, 1440, 1439, 1427, 1364, 1342, 1321, 1282, 1239, 1176, 1161, 1143, 1076, 1026, 1012, 960, 930, 905, 865, 830, 785, 750, 695 cm$^{-1}$.

**Action of lead tetraacetate on the acid XV in presence of pyridine**

To a solution of the acid XV (4 g, 16 m.moles) in dry benzene (150 ml) and dry pyridine (1.9 g, 24 m.moles), lead tetraacetate (15 g, 33.8 m.moles) was added and the mixture was refluxed under $N_2$ in dark for 5 hours. The reaction product was worked out in the same way as described earlier and it gave strong bands for acetate in the IR spectrum. The yield was (3.75 g).

The above reaction product (3.7 g) was saponified by refluxing with KOH (1.25 g) in ethanol (125 ml) under $N_2$ atmosphere for 3 hrs. and after working out the product as described previously it was chromatographed over neutral alumina (Gr. II, 90 g). The fractions eluted with pet.ether (40 mg), 70:30 pet.ether-benzene mixture (350 mg), 30:70 pet.ether-benzene mixture (1.4 g), benzene (0.4 g) and alcohol (0.48 g) were investigated. The fraction eluted with
30:70 pet.ether-benzene mixture (1.4 g) was the pure and proper keto-alcohol (XXVII) as indicated by the IR and NMR spectra. Oxidation of this keto-alcohol (1.4 g) by Jones reagent as described earlier gave the diketone XII (1.3 g) which gave the same IR and NMR spectra and m.p. as was given by the diketone obtained previously.

**Action of methyl magnesium iodide on the diketone (XII)**

The diketone (600 mg) dissolved in dry ether (15 ml) was added to a solution of CH3MgI (prepared from 165 mg magnesium) in dry ether (30 ml) at 0°C. The mixture was then kept at room temp. for 4 hours and poured on a saturated solution of ammonium chloride at 0°C. The ether layer was separated, washed with water, dried over sodium sulphate and ether removed by distillation, leaving behind a residue which was chromatographed over alumina (Gr.III, 18 g). The fraction eluted with pet.ether gave the unreacted starting material XII (264 mg) identified on the basis of its m.p. and IR spectrum. The benzene fraction (180 mg) was chiefly composed of carissone as revealed by the IR and NMR spectral evidence. Further purification of carissone by chromatography and crystallisation proved difficult.

**2,4-Dinitrophenylhydrazone of carissone**

From the above impure fraction of carissone, a portion (150 mg) was dissolved in ethanol (1.5 ml) and added to a hot solution of 2,4-dinitrophenyl hydrazine (300 mg) in ethanol
(12 ml) containing conc. HCl (1 ml). The deep red derivative separated out almost instantaneously and the reaction mixture was cooled quickly to room temp. and left overnight. The material was filtered, washed with cold ethanol and dried to furnish a red solid (210 mg) having m.p. 155°. TLC of this solid on silica gel (solvent system, benzene-ethyl acetate 70:30) gave a spot having Rf value identical with that of an authentic sample of 2,4-DNP derivative of carissone, and a second minor spot was also obtained having a much higher Rf value. The red solid (200 mg) m.p. 155° was chromatographed over silica gel (10 g). The fraction eluted with benzene was the less polar impurity. The benzene-ethyl acetate (80:20) fraction (150 mg) furnished pure DNP derivative having m.p. and mixed m.p. 172-73°. The IR, NMR spectra and TLC behaviour of this DNP derivatives were identical with those of the DNP derivative of authentic carissone.

Analysis

Found: N, 13.1%
Calculated for C_{21}H_{28}N_{4}O_{5}: N, 13.45%.

IR bands (IR-5): 3425, 2941, 2874, 1623, 1587, 1811, 1497, 1456, 1412, 1372, 1333, 1302, 1252, 1214, 1172, 1127, 1104, 1065, 1052, 1015, 956, 928, 917, 843, 833, 816, 769, 743, 724, 694 cm\(^{-1}\).
Action of CH₃MgI on progesterone (XIII)

Progesterone (10.4 g) dissolved in dry benzene (100 ml) was added to an ethereal solution (50 ml) of methyl magnesium iodide prepared from 1.2 g of magnesium. The mixture was stirred at room temp. for one hour and at 45-50° for 2 hr. It was then poured over saturated ammonium chloride solution at 0°. The organic layer was separated out, washed with water, dried and solvent evaporated to furnish a residue (10.8 g) which was chromatographed over alumina (Gr. III, 220 g). The fraction (4.1 g) eluted with pet.ether-benzene (50:50) was not investigated since from the NMR spectrum it appeared to be a keto-olefin probably formed by the dehydration of the keto-alcohol (XIV) and we were not interested in it. The fraction (3 g) eluted with benzene was the unreacted starting material as shown by the IR and NMR spectra. The ether-eluted fraction (3.1 g) was identified as the expected keto-alcohol (XIV); m.p. 216-18°; (α)D⁺ 80° (lit. value16, m.p. 220-22°, (α)D⁺ 83°).

Analysis

Found: C, 79.32; H, 10.21
Calculated for C₃₂H₃₆O₃: C, 79.95; H, 10.37%.

IR bands (IR No. cm⁻¹): 3500, 2900, 1660, 1600, 1450, 1405, 1365, 1340, 1320, 1265, 1227, 1188, 1155, 1115, 1100, 1063, 1035, 1020, 1005, 965, 945, 930, 915, 900, 868, 860, 844, 827, 810, 793, 777, 743, 725 cm⁻¹.
Dehydration of Vulgarin (XXIX)

A solution of vulgarin (200 mg) in dry benzene (20 ml) and freshly distilled thionyl chloride (1 ml) was refluxed on a water-bath for 4.1/2 hours. On cooling to room temp., the benzene solution was washed with water and potassium bicarbonate solution to make it free from acid. It was dried over CaCl₂ and benzene removed by distillation and the residue was crystallised from carbon tetrachloride to give a white crystalline compound (22 mg), m.p. 142°C. IR. spectrum showed absence of hydroxy group.

**Analysis**

Found: C, 72.95; H, 7.56  
Calculated for C₁₅H₁₆O₃:  C, 73.14; H, 7.37%.

The mother liquor from the above was concentrated and a second crop of crystals was obtained. This was recrystallised from CCl₄ to give a white crystalline product (115 mg), m.p. 127°C.

This product also showed absence of hydroxy function in the IR spectrum.

**Analysis**

Found: C, 73.13; H, 7.51.  
Calculated for C₁₆H₁₈O₃:  C, 73.14; H, 7.37%.
IR-1.  20-METHYL-PREGN-4-EN-20-OL-3-ONE (XIV)

(IN NUJOL)

TRANSMITTANCE (%)
IR-5. 2,4-DINITROPHENYL HYDRAZONE OF CARISSONE
(IN Nujol)
REFERENCES