STUDIES RELATED TO THE VERATRUM ALKALOIDS.

THE TOTAL SYNTHESIS OF C-NOR-D-HOMO STEROID ANALOGUES

by

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ABSTRACT

The total synthesis of trans-syn-cis-C-nor-2-methoxy-8, 11-dihydroxy-10a-methyl-4b,5,6,6a,7,8,9,10,10a,10b,11-undecahydro chrysene (87) is described. This compound has been synthesized from the C-nor-D-homo hydroxy aldehyde (67) via the olefin (71) by oxidative hydroboration. This sequence has the advantage of giving a much higher overall yield of (87). The conversion of the said compound (87), to the α-methyl ketone (74), a relay compound which has been used to synthesize verarine (76) is now nearing completion.

Contrary to previous speculations, pyrolidene enamine methylation of model compounds (77,78) did not prove as fruitful as methylation of trapped enolates (figure 13).
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INTRODUCTION

Recently, greater attention has been devoted to the study of steroids with unnatural stereochemistry as well as those with expanded or contracted ring systems. The ring expanded steroids are referred to by the prefix "homo" while those with ring contraction are denoted by "nor". The impetus for such interest was given by recent reports which show that such unnatural steroid molecules can have biological properties markedly different from the common steroids. For example, a large number of papers report alterations in biological activity for compounds which have C-18 or C-19 methyl groups removed from the steroid molecule. Another excellent example is given by the work of W.S. Johnson and his collaborators, who have synthesized several D-homo steroids. The (+)-D-homo-18-norandrostane-3,17-dione, compound (8), has been found to be as androgenically active as (+) androstane-3,17-dione. The synthesis of B-nor steroids, though more demanding synthetically, has also been reported. Finally, it is interesting to note that 9α, 10β progesterone is approximately five times as active as a progestational agent.

In the majority of the above cases, naturally occurring steroids have been used as starting materials. Although these were the logical starting materials, they offered certain limitations in synthesizing the steroid analogues of interest in our studies. These studies were concerned with chemical structure and biological activity. For this reason we initiated investigations toward the total synthesis of steroid analogues. The sequence chosen to realize the said analogues, was one in which the introduction of substituents was readily achieved. By virtue of this ready substitution, convenient alteration of the steroid skeleton could be achieved in the analogues. These alterations would not be easily
possible if natural steroids were used as starting materials. Essentially, we were interested in developing a total synthesis of the modified C-nor, D-homo type steroid skeleton. This steroid skeleton is known to be present in the naturally occurring Veratrum alkaloids. Jervine (1) and cevadine (2) are examples of the two major families of the Veratrum group.

It was felt that, by construction of appropriate C-nor, D-homo steroid intermediates, subsequent extension to the Veratrum series would be possible.

The Veratrum Alkaloids are a group of steroid alkaloids which occur in the plants of the tribe Veratreae. This tribe is part of the subfamily Melanthioideae of the family Lileaceae. Sometimes the subfamily is treated as a separate family the Melanthioideae or the Colchicaceae. The genera which have been investigated are the following: Veratrum (false hellebore), Zygadenus (death camus), Schoenocaulon (Sabadilla), Stenanthium, Amianthum (crow poison), Melanthium (bunch flowers), and Fritillaria. The species of the first three genera have received the most attention. Kupchan, Zimmerman and Alfonso have recently reviewed the occurrence and structure of alkaloids isolated from Veratreae, the classical botanical taxonomy of the Veratreae, and the implications of alkaloid occurrence and structure to the taxonomy of Veratreae. This review does not cover the work done on the Fritillaria genus.
Veratrum and related plants have been used medicinally for hundreds of years. Galenical preparations were used in the middle ages for purposes of sorcery and mystical rites. Subsequently the crude extracts have been used in the treatment of fevers, as local counter-irritants, as cardiac toxics, and as insecticides\textsuperscript{16,17}. The use of Veratrum to control hypertension, at least in the United States, dates from the report of Baker in 1859\textsuperscript{18}. During the late thirties, purified alkaloid preparations responsible for hypotensive activity of Veratrum were made available\textsuperscript{19,20}. The group of alkaloids responsible for hypotensive activity are the esters of the ceveratrum series. Cevadine (2) is an example of this family of compounds. These compounds have a heptacyclic skeleton and are highly oxygenated, usually containing up to 9 oxygen atoms. These compounds have never been found as glycosides but exist as benzoic, acetic, and other short chain aliphatic acid esters. Imperialine (3)\textsuperscript{21-25} and Verticine ("peimine") (4)\textsuperscript{26,27} are closely related to these compounds, but in contrast occur naturally as $\beta$-D-glucosides, edpetiline (5)\textsuperscript{23-25} and peiminoside (6)\textsuperscript{26}. Kupchan published a review\textsuperscript{28} on the hypotensive Veratrum ester alkaloids. More recently, a series of papers\textsuperscript{29-33} on the structure activity relationships in a series of protovertine (7) esters have appeared. The

\begin{align*}
\text{R}=\text{H}, & \quad 2 \\
\text{R}=\text{H}, & \quad 4
\end{align*}
most recent review on Veratrum Alkaloids by Kupchan and By is now in publication.

Jervine may be cited as an example of the other family of Veratrum alkaloids. This family is referred to as the Jervaratrum series. Only 2 to 3 oxygen atoms are generally present in this family's molecules. These compounds which occur as free amines or esters show very little hypotensive effect.\(^34\)

One of the most recent reviews of Veratrum alkaloid chemistry is by Narayanan.\(^35\) Since then several new alkaloids have been isolated and characterized. Yunsov and Muriddinov\(^21,22\) showed that raddeanine (3) from *Fritillaria eduardi* was identical with sipeimine and imperialine. These authors\(^22\) also report five new alkaloids, isolated from *Fritillaria sewerzoni*: korseverine (C\(_{27}H_{37}O_{3}N\)), alginidine (C\(_{27}H_{45}O_{4}N\)), korseverinine (C\(_{27}H_{43}ON\)), korseveridue (C\(_{27}H_{43}O_{2}N\)), and korseveramine (C\(_{27}H_{47}O_{3}N\)). The structure of a new alkaloid ester (8) was proposed by Yagi and Kawasaki\(^36\) but no formal name was given.
This compound (8) possessed the molecular formula \( C_{31}H_{45}O_{8}N \) and was isolated from *V. grandiflorum* (Maxim.) Loesener fil. Kupchan and co-workers determined the structure of sabadine (9) ("neosabadine", \( C_{27}H_{45}O_{7}N \)), and its 3-acetate (10) ("sabatine", \( C_{29}H_{47}O_{8}N \)). Tomko and Bendik postulated the structure of the jerveratrum alkaloid, verakamine, (11) (\( C_{27}H_{45}O_{2}N \)).

Ho and collaborators obtained evidence permitting assignment of structure (4) for verticine (\( C_{27}H_{45}O_{3}N \)), the major alkaloid of *Fritillaria verticillata* var Thumbergu Baker. Verticine was also shown to be identical with peimine. Since Fukuda, who named the pure alkaloid verticine, was the first to suggest a name, the authors chose the former name over the
latter. In 1963, Yunusov\textsuperscript{23} isolated from Petilium eduardi the following alkaloids: peimisine edpetitidine (C\textsubscript{27}H\textsubscript{41}NO\textsubscript{3}), edpetiline, and three unnamed compounds (mp 247-51°, 269-71°, and 228-31°). Acid hydrolysis of edpetiline produced D-glucose and imperialine. Recently Yunusov and collaborators\textsuperscript{24} synthesized edpetiline from imperialine and tetra-O-acetyl-α-D-glucopyranosyl bromide. In 1964, Masamune and co-workers\textsuperscript{40} isolated a new alkaloid, 11-de-oxojervine, (12) (C\textsubscript{27}H\textsubscript{41}O\textsubscript{2}N), from the roots of V. album L. var. glandiflorum Maxim. It was found to be identical with one of the Wolff-Kishner reduction products of jervine. Tomko\textsuperscript{41} has isolated a number of alkaloids from Veratrum album subsp. Lobelium (BERNH.) Suessenguth including: veralinine (C\textsubscript{27}H\textsubscript{43}ON), veraminine, verorine (C\textsubscript{27}H\textsubscript{59}ON), and veralkamine (C\textsubscript{27}H\textsubscript{43}O\textsubscript{2}N). The structure (13) was proposed for verarine. Also in 1964, the isolation of a new ester alkaloid G was reported by A.G. Smith\textsuperscript{43}, from the plant Amianthium muscaetoxicum Gray.

Communications by Wintersteiner\textsuperscript{44} and Masamune\textsuperscript{45} in 1962 presented the elucidation of isojervine (14) an isomer of jervine formed in high yield when jervine was treated with hydrochloric acid-methanol solution.
Figure 1
The final "detailed" papers on the structure of isojervine have been published by three groups; Dauben, Wintersteiner and Masamune and their respective collaborators. All three groups reached the same conclusion. Isojervine derivatives have also been studied by Wintersteiner and Moore.

The stereochemistry of these compounds has been studied by various groups. Mitsuhashi and Shinusu synthesized the C-nor-D-homo derivative (16) from hecogenin (15) (figure 1) and obtained evidence for the 9α configuration of jervine (1) and veratramine (18) (Figure 1). Similarly jervine and veratramine have been converted to a common intermediate (17) or the acetate (19) proving that they have some structural aspects in common.

Nuclear magnetic resonance and chemical evidence from Johnson's laboratory has substantiated the forementioned proposals. He also accepts Mitsuhashi's evidence for the existence of the B/C trans ring fusion. On the other hand, the configuration of C-9 was in doubt since the biogenesis of veratramine could involve a 11-keto veratramine intermediate which would render the C-9 position epimerizable. Nuclear magnetic
figure 2
resonance spectroscopy (nmr) showed that the C-19 methyl protons of the
derivative (20) (figure 1) of 11-keto veratramine and of the diketone (21)
(figure 1) resonate at exactly the same position (τ8.18). Further evidence
for the 9α configuration was provided by Mitsuhashi$^{54}$ and Masamune$^{55}$.
Mitsuhashi synthesized the C-nor-D-homo compound (22) (figure 2) from
hecogenin (15), while Masamune synthesized (22) (figure 2) from veratramine
(18). These endeavors had now established the C-9 configuration beyond
doubt. In the case of jervine (1) Masamune$^{55}$ transformed both jervine and
veratramine into compound (22) (figure 2). Jervine and veratramine have
also been converted to a common intermediate with an aromatic "D" ring
(23). It is now known that 11-deoxy-jervine (12) has the 9α configuration
since it was transformed into compound (24) (figure 2) which is a degrada-
tion product of veratramine.

W.S. Johnson and co-workers$^{56,57}$ were the first to report on the
degradation of veratramine to compound (22) which was an intermediate in
the degradation to compound (25, figure 2). The reactions leading to
(22) were also tried on compounds with a 5,6-double bond but the yields
were somewhat lower. Compound (25) could have been used to determine the
stereochemistry of some of our C-nor-D-homo compounds.

Recently published reports by Johns$^{58,59}$ and Mitsuhashi$^{60,61}$ indicate
the synthesis of etiojervane derivatives from hecogenin, a readily
available sapogenin. "Etiojervane" is a name which is applied to the
system, 17α-methyl-C-nor-D-homo-18-nor-5α,13α-androstane (26). Johns'
sequence is illustrated in figures 3 and 4. The work of Johns is pertinent
to our synthesis, since our initial goal is to synthesize compound (33; figure 4).
figure 3
(figure 5). The availability of this compound from hecogenin will thus allow us to confirm the stereochemistry of our totally synthetic C-nor-D-homo molecules. Mitsuhashi's work is very similar to that of John's. The exception is that in the Japanese paper, compound (28) instead of (27) (figure 3) was used to synthesize the C-nor-D-homo compound (32) (figure 4). This conversion was studied extensively and (29) was found to be one of the intermediates. Mitsuhashi's more recent researches described the synthesis of (33) via compound (34) (figure 4).

In the above papers there is an error which has been corrected by Coxon in some recent work. Coxon gives physical as well as chemical evidence to indicate that the double bond was at the 13,17a position not at the 17,17a position as previously stated. He also gave proof that the configuration of the C-13 position in (30) (figure 3) is α. Etiojervine derivatives have been synthesized from jervine by Kupchan and his collaborators. Some of these compounds are useful as relay substances in a subsequent synthesis of jervine since they possess an oxygen function at C-11 obtained by degradation of naturally occurring steroids to etiojervane derivatives. I would now like to turn to the total synthesis of these compounds. The only published attempts at
figure 4
figure 5
figure 6
the total synthesis of these compounds up to 1966 have been by R.A.
Barnes\textsuperscript{65,66,67} and W.S. Johnson\textsuperscript{52,53} (figure 6). Barnes attempted the
total synthesis of etiojervane derivatives by several sequences none of
which has yet been successful. The more successful hydrochrysene approach
is already known from the previous elegant total syntheses of various
steroids\textsuperscript{68-73}. More recently this elegant and powerful sequence has
been directed at the total synthesis of veratramine (figure 6). Very
recently Masamune\textsuperscript{100} and Johnson\textsuperscript{101} have published a total synthesis of
veratramine.

It is quite questionable whether Masamune's sequence constitutes
an acceptable total synthesis since the last two reactions in his sequence
proceed with yields of 2\% and 1\% respectively. Concurrently Johnson\textsuperscript{157}
has published a total synthesis of Jervine via the hydrochrysene approach.
This sequence does not lend itself to convergence as well as the sequence
developed in our laboratories.

Several years ago investigations in this laboratory\textsuperscript{76-79} and independ-
dently by Nagata and collaborators\textsuperscript{74,75} provided a synthetic sequence to
the tetracyclic ketone (36) (figure 7). The ketol (35) is a versatile
derivative since it not only provides entry into the cis-syn-cis series,
but also has enabled Roller\textsuperscript{80} and Inaba\textsuperscript{81} to successfully convert it into
\(\text{B-nor-D-homo steroids derivatives (figures 8,9,10).}\)

This thesis presents work directed toward the total synthesis of
\(\text{C-nor-D-homo-intermediates which are useful intermediate compounds for the total synthesis of Veratrum alkaloids. The Ketone (36) is utilized as the starting material. Initially the "hydrochrysene method" is}\)
figure 8
Figure 9
Figure 10
utilized to obtain the necessary hydrochrysene derivatives. Modifications of conditions and experimental technique given by Johnson were found to be essential due to differences in chemical reactivity between his compounds and ours. These differences in chemical reactivity were dictated largely by the difference in position of the methoxy group on the aromatic ring.
DISCUSSION

The differences in the two series of Veratrum alkaloids, represented by jervine and veratramine are of particular interest. The major feature of the jervine series is that these derivatives possess a ketonic function in the C-ring whereas none occurs in the veratramine compounds. An attractive possibility exists for developing a synthetic sequence leading to the two series of C-nor-D-homo derivatives. In the case of the jervine family, the carbonyl group would be retained while for the synthesis of veratramine it would be easily removed during the Birch reduction of the D-ring. With this goal in mind, the synthesis of the C-nor-D-homo compound (40) was developed. The compounds and reactions they undergo are outlined in figures 11, 12 and 13. The tetracyclic ketone (36) will be considered as the starting material for this synthetic sequence. This compound was prepared from γ-naphthol in large quantities by a well known series of reactions (figure 14). Although these reactions were repeated many times they will not be discussed here since no modifications nor new techniques were introduced.

A. THE BIRCH REDUCTION

As mentioned before, the stereochemistry of jervine containing the
figure 11
Figure 12
Figure 13
Figure 14
modified steroid "backbone" (1), has been shown to be trans-anti-trans. For this reason Birch reduction was chosen over the other available methods since the application of this reaction to hydrochrysene analogues, has been studied in considerable detail by Johnson. This reaction has the distinct advantage of producing compounds which are in general thermodynamically most stable. These considerations were discussed as well as studied extensively by Johnson and co-workers. The resulting molecules in both hydrochrysene series would be expected to have the required trans-anti-trans stereochemistry after Birch reduction. Four new asymmetric centres would be formed as a result of this reaction. The subjection of the tetracyclic ketone (36) to the reaction conditions perfected by Johnson for the hydrochrysene series containing effectively a m-methostyrene system, gave the desired reduction product in very poor yield. In order to avoid the formation of the side products resulting from a reduction of the aromatic ring, many modifications of the Johnson conditions were tried with little success. Finally a substantial improvement of yield was obtained when the reduction was carried out in an amine solvent (see below).

1. **Trans-anti-trans Isomer**

When a solution of the ketone (36) in tetrahydrofuran was treated with sodium in liquid ammonia in the presence of aniline, a good yield of the desired reduction product was obtained. Usually in this reaction the product consisted of a mixture of alcohol and carbonyl compounds but the latter could be easily reduced to the required alcohol with sodium borohydride. The ultraviolet spectra of the trans-anti-trans ketone (41) and alcohol (42) were identical with the spectrum of 1,2,3,4-tetrahydro-6-methoxy naphthalene (43), (figure 11). The ketone absorption was also detected by infra-red spectroscopy and its conversion from the
ketone with a saturated carbonyl peak at 1700 cm\(^{-1}\) to the alcohol with a hydroxyl absorption at 3450 cm\(^{-1}\) was easily observed. The nmr spectra of these reduction products were quite typical. In considering the alcohol (42a) it was noted that the hydroxyl group absorbed at \(\tau 7.63\) and disappeared on equilibration with \(\text{D}_2\text{O}\). The axial proton geminal to the hydroxyl group was observed as a broad multiplet centered at \(\tau 6.37\). This observed broadness confirms the expectation that the proton in question is indeed axial. The methyl group absorbed at \(\tau 9.17\). In the aromatic region, the C-1 proton was seen as a doublet at \(\tau 3.45\) with the usual meta coupling constant \(J_{1,3} = 3\) cps. The quartet for the C-3 proton appeared at \(\tau 3.35\) with coupling constant \(J_{3,4} = 8\) cps. The doublet for the C-4 proton was observed at \(\tau 2.84\). No evidence of para coupling was observed in any of the compounds prepared, however for compounds with C-12 keto groups, the C-1 proton was observed at lower field than the C-3 and C-4 protons.

2. Trans-anti-cis Isomer

Several of the side products were isolated from the acetate mother liquors and shown to be stereoisomers of the above compound (42b). One of these (44b), mp. 135 - 138°C analyzed for C\(_{22}\)H\(_{30}\)O\(_3\), had a twin maximum in the ultraviolet (\(\lambda_{\text{max}}\) 280, 287 \(\mu\)) which is typical for the anisole chromophore. The infrared spectrum showed an acetate carbonyl at 1720 cm\(^{-1}\). The nmr spectrum was very interesting and showed an angular methyl group at
a very high field (τ9.65). This could be considered as evidence that a cis B/C ring fusion existed in this molecule (see later). The C-8 proton appeared as a broad multiplet at τ5.5 indicating that this proton which is geminal to the acetate was in the axial orientation. From the above evidence this compound was established as trans-anti-cis-2-methoxy-8β-acetoxy-10a-methyl-4b,5,6,6a,7,8,9,10,10a,10b,11,12, dodecahydrochrysene (44b).

3. **Trans-Anti-Trans Isomer with Axial Acetate**

Another compound (45b) (mp 154-156°C) which could be completely characterized contained an axial hydroxyl group. Its ultraviolet spectrum ($\lambda_{max}$ 278, 286 μm) was superimposable on the authentic trans-anti-trans alcohol (42a). From high resolution mass spectrometry the molecular formula of the acetate derivative (45b) was determined to be $C_{22}H_{30}O_3$. This result established beyond doubt that this compound is indeed isomeric with the trans-anti-trans acetate (42b). The nmr spectrum showed an angular methyl group resonating at τ9.19, a normal region for the B/C trans ring fusion. This conclusion was warranted by a previous detailed study in this laboratory83,87 where it had been shown that cis fusion, particularly in the B/C ring, shifts the C-10a methyl group to a much higher field due to its shielding by the aromatic ring of this molecule. Further, inspection of the low field region yields some interesting information. In the spectrum of this stereoisomer, the proton geminal to the hydroxyl appears as a relatively narrow multiplet compared to the same
proton in the trans-anti-trans alcohol (42a). This multiplet is centred at \( \tau 6.3' \). The width at half height for the former is 8 cps while for the latter (47a) it is 24 cps. The first conclusion which can be drawn is that the stereochemistry at C-8 of the compound in question is different from that of the major product (42a). The broad multiplet observed for the latter compound (42a) is typical of an axial proton since it is able to couple with two other axial protons at C-7 and C-9. The coupling constant, \( J_{a,a'} \), is well established as being in the order of 8-10 cps thus giving rise to the observed broad splitting pattern. The coupling constants, \( J_{a,e} \) and \( J_{e,e'} \), are both small (3-5 cps), and it is easily deduced that as in the case under discussion, the C-8 equatorial proton would be observed as a narrow multiplet. On this basis, structure 45a is assigned to this compound. Confirmation of the assignment is obtained from nmr data on the acetate derivative of this compound.

The acetate, mp 138-139.5°C, was obtained in the usual manner. This compound had the characteristic anisole ultraviolet spectrum (\( \lambda_{\text{max}} 278, 286 \) nm) while the infrared, as expected, showed a strong carbonyl absorption at 1710 cm\(^{-1}\) due to the acetate absorption. The nmr spectrum indicated a new low field signal (\( \tau 4.98 \) for the proton geminal to the acetate function. This shift (from \( \tau 6.37 \) to \( \tau 4.98 \)) is normally observed upon acetylation of secondary alcohol groups. In addition, this downfield shift correlates very well with the shift observed upon acetylation of the trans-anti-trans
alcohol (42a). Finally, as is indicated by the spectrum, the geminal proton is once more a narrow multiplet (7 cps at half height), whereas in the trans-anti-trans acetate, the low field multiplet remains broad (24 cps at half width). From the above evidence the assignment of stereochemistry to the structure of this Birch reduction by-product may be conclusively established as trans-anti-trans-2-methoxy-8α-hydroxy-10α-methyl-4b,5,6,6α,7,8,9,10,10α,10β,11,12,-dodecahydrochrysene.

4. Anomalous Isomer Mixture

The next compound isolated from the reduction was acetylated to give a crystalline solid, mp 134.5-136°C, with molecular formula \( \text{C}_{22}^\text{H}_{30}^\text{O}_3 \) established by elemental analysis as well as high resolution mass spectrometry. This compound is therefore another stereoisomer of the trans-anti-trans acetate (42b). Thin layer chromatography on this substance showed only one spot when eluted with 10% ethyl acetate in chloroform \( (R_f 0.52) \). Ultraviolet spectroscopy produced the expected anisole spectrum \( (\lambda_{\text{max}} 278, 286 \mu \text{m}) \). While in the infrared region, the major bands were noted at 1717 cm\(^{-1}\) and 1245 cm\(^{-1}\). The nmr data consisted of the following signals: \( \tau 9.03 \) and \( \tau 8.86 \) (singlets, total area = 3H), \( \tau 6.22 \) (singlet, 3H), \( \tau 5.2 \) (1H, multiplet of 32 cps in width) a multiplet centred at \( \tau 3.15 \) for the aromatic protons. Form the above nmr data it was concluded for several reasons, that this material was a mixture of two compounds. Firstly, the two methyl singlets had unequal integral values. Secondly, the proton multiplet \( (\tau 5.2) \) geminal to the acetate group was much broader (32 cps) than that of the trans-anti-trans compounds (24 cps). Finally, this multiplet possessed more splitting than was allowable for the existing number of coupling protons (at least nine signals were counted versus five in the
trans-anti-trans case). No further effort was made to separate these stereoisomers.

5. Trans-anti-trans Olefin Mixture

A mixture of olefinic compounds (46a,b) was isolated and partially characterized. Again the ultraviolet spectrum was typical of this series ($\lambda_{\text{max}}$ 278, 286 μμ) and was superimposable on an authentic spectrum of trans-anti-trans alcohol (42a). This result indicated the presence of an unconjugated anisole system, proving that in this molecule, as well as in the other by-products studied, the double bond in C-ring had been reduced. Great difficulty was encountered in crystallizing this substance. An nmr spectrum of the solid showed the following resonances: a single methyl group at τ8.84, a methoxyl singlet at τ6.15, olefinic multiplets centered at τ4.5 and τ4.0 which integrated for two protons and the normal aromatic multiplet centered at τ3.15. From the above data the following conclusions were made: first, that the substance was a mixture; secondly, that the backbone of this mixture of compounds was most likely trans-anti-trans; finally, that the mixture resulted from the elimination of a hydroxyl group in the A ring. However, no further characterization of this compound was made at this time.
B. THE t-BUTYL CHROMATE REACTION

In order to obtain access to the C-nor-D-homo steroid skeleton, the trans-anti-trans acetate (42b) must be converted to a seco or ring-opened compound (47). For this reason, activation at the C-11 or C-12 carbon was essential. After a survey of the available methods, it was decided that the C-12 carbon was most susceptible. Wintersteiner had prepared 6-ketoestradiol diacetate (48) by direct oxidation of the benzylic position. Two related factors complicated the situation. First, in the hydrochrysene molecule (42b) there are two benzylic carbons. Second, the methoxyl group of the anisole system exists meta to the required C-12 site of activation but para-relative to the nonrequired benzylic carbon, C-4b. It was shown that attack of various reagents occurred preferentially at the C-4b carbon, even though it was tertiary rather than at the secondary and less hindered benzylic carbon. This was another deviation from the findings of Johnson and his collaborators in their studies of the hydrochrysene homologues.

In order to overcome aromatization of the C-ring by attack at the tertiary C-4b position, consideration of sterically hindered oxidizing agents was undertaken. t-Butyl chromate was found to give a substantial improvement in the yield of 12-keto-acetate (49) over the chromium trioxide method of Wintersteiner. The infrared spectrum of the desired hydrochrysene...
analogue showed bands at 1730 cm\(^{-1}\) and 1670 cm\(^{-1}\). The ultraviolet spectrum had the following maxima: 222, 254, and 322 μ. The effect of the C-12 ketone (48) on the nmr spectrum of the aromatic protons as compared to that of the parent compound was to deshield the C-1 proton so that the doublet now appeared at lowest field. This was characteristic of all C-12 keto compounds. On the average, this compound was obtained in yields of 15% with a 40% recovery of starting material. In the large number of cases this reaction was repeated, the yield of this 12-keto-acetate (49) varied from 12% to 18% while the recovery of starting material varied inversely from 50% to 32%. Separation of the desired material from the by-products of the oxidation reaction proved difficult. Careful column chromatography, combined with cross crystallization, proved to be successful in separating the desired 12-keto-acetate (49) from the mixture of products. These by-products (37, 38, and 39, figure 10), were previously isolated and characterized by T. Inaba\(^{81}\) in this laboratory. Dr. W.A.F. Gladstone of this laboratory\(^{86}\) prepared and characterized the following derivatives of these compounds (51, 52, 53).
Gladstone also isolated a small amount of a novel peroxide (54) from this reaction mixture.

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C6H5

OCH3
54
```

This compound proved to be surprisingly stable. The peroxide illustrates a possible mechanism for aromatization of the C-ring during the oxidation reaction.

When the t-Butyl chromate oxidation reaction was carried out on impure trans-anti-trans acetate, in several cases, an additional compound, mp 162-165°C, was isolated. This compound had been previously characterized and was shown to be an isomer of the 12-keto-acetate (49).

C. SODIUM BOROHYDRIDE REDUCTION

1. Normal Reduction

The trans-anti-trans keto acetate (49) was reduced with sodium borohydride to give a colourless oil in very high yield (55). Infrared spectroscopy showed, as expected, a strong hydroxyl absorption (3503 cm\(^{-1}\)) and no carbonyl band. This finding was confirmed by ultraviolet spectroscopy. In the latter case the anisole spectrum was obtained, indicating that the previously conjugated carbonyl function had been reduced. The major product of this reaction was crystallized to give a pure sample, mp 147.5-149°C. The ultraviolet spectrum had maxima at 226, 281, and 288 mμ and minima at 247 and 286 mμ. The nmr spectrum showed in addition
to the methyl group at $\tau 9.15$, and an acetoxy group at $\tau 8.03$ (each integrating for 3 protons), a multiplet centred at $\tau 5.3$ which integrated for 2 protons. This absorption was due to the proton geminal to the C-12 hydroxyl superimposed upon that of the C-8 acetoxy geminal proton. The diacetate (56), mp. 175°C, was readily prepared and as expected, its ultraviolet spectrum was virtually superimposable with that of the starting material. The infrared showed evidence for two acetoxy groups (1730, 1720 cm$^{-1}$) and no hydroxyl absorption was observed. The nmr spectrum, in addition to the usual singlet absorptions of methyl acetate and methoxyl protons, indicated two separate one-proton multiplets at $\tau 4.09$ and $\tau 5.35$. Since both of the multiplets were broad, the geminal protons were assigned axial configurations. Hence, both hydroxyl groups of the major product of the sodium borohydride reaction are equatorial. The considerations which were used to draw this conclusion were discussed extensively in the assignments of configuration to the products of the Birch reduction reaction.

2. Sodium Borohydride Reduction with Hydrolysis

If the sodium borohydride reaction mixture is refluxed, not only is the 12-ketone reduced, but the borohydride is sufficiently basic to hydrolyze the C-8-acetoxy group to give a diol (57) with the characteristic anisole ultraviolet spectrum. The major product, mp. 190°C, was sparingly soluble in all solvents except pyridine. The nmr spectrum indicated the
the methyl absorption at τ9.22 and the methoxyl absorption at τ6.38 both integrating for the usual three protons. In addition, a broad septet was observed at τ6.24, and a broad quartet at τ5.00 both integrating for one proton. The former was assigned the C-8β configuration and the latter the C-12β configuration for reasons discussed above.

3. Lead Tetra-acetate Oxidation of the Diol

When the diol (57) was subjected to lead tetraacetate oxidation in dry pyridine overnight at room temperature the major product was the 8β-hydroxy-12-ketone (50), mp 177°C. The ultraviolet spectrum was superimposable with that of the 8β-acetoxy-12-ketone (49) (λ_max 222, 253, 322, λ_min 238, 279 μm). The infrared spectrum of this compound showed a hydroxyl absorption as well as a carbonyl absorption. The minor product of this reaction was the diketone (58), mp 170-172°C. The ultraviolet spectrum (λ_max 224, 253, 320, λ_min 233, 279 μm) was virtually superimposable with that of the monoketo compound. The infrared spectrum indicated two keto groups (1708, 1672 cm⁻¹). The nmr spectrum indicated the usual singlets for C-methyl and methoxyl groups (τ8.90 and τ6.24) while a quartet due to the C-11 hydrogen was observed at τ7.21, while that of the C-11 hydrogen was partially obscured by other resonances. The coupling constant between the C-11 geminal hydrogens was found to be 16 cps.
D. PHOSPHORUS PENTOXIDE DEHYDRATION REACTION

The action of phosphorus pentoxide in refluxing benzene on the oil produced by sodium borohydride reduction at room temperature gave the desired styrene compound (59). The expected product had an ultraviolet spectrum which was characteristic of the m-methoxystyrene chromophore ($\lambda_{\text{max}}$ 221, 262.5, 270, 302, 312; $\lambda_{\text{min}}$ 247, 284 μm). The infrared spectrum showed only one saturated carbonyl attributed to the acetoxy group (1720 cm$^{-1}$), while the C-11, C-12 double bond absorbed at 1625 cm$^{-1}$. The nmr spectrum in addition to the usual C-methyl, acetate, and methoxyl singlets showed a multiplet at $\tau$8.15 which was assigned to the C-10b hydrogen atom. The usual broad septet for the C-8 hydrogen absorption was present at $\tau$5.33. In addition to the usual aromatic absorptions, two downfield one-proton quartets had appeared at $\tau$4.11 and $\tau$3.67. These latter signals were assigned to the C-12 and C-11 protons respectively.

E. OSMIUM TETROXIDE HYDROXYLATION

1. Oxidation

To pursue the original intention of entry into the C-nor-D-homo series, it was first necessary to find an efficient sequence to the "key"
compound (60) in this conversion. To synthesize the essential "C-seco" or ring-opened compound, ozonization was abandoned in favour of the much higher yielding combination of osmium tetroxide hydroxylation followed by periodate cleavage. These reactions allow the interconversion of the olefinic compound to the desired seco dialdehyde (60).

The hydroxylation reaction was carried out in ether solution at room temperature whereupon a mixture of diols was obtained in good yield. The best yields of diol were obtained when a minimum amount of ether and a minimum amount of time for work-up was employed. The diol eliminated easily in presence of moisture, giving a pair of red spots on TLC in the same ratio as the diol isomers.

Although there are two isomers of the diol (61), one is predominant. This latter compound was isolated and crystallized, mp 225-226°C. The features of its infrared spectrum included a broad absorption of the hydroxyl groups (3950 cm\(^{-1}\)) as well as the strong acetyl absorption in the carbonyl region (1704 cm\(^{-1}\)). The ultraviolet absorption was typically that of an anisole chromophore (\(\lambda_{\text{max}}\) 276, 282 \(\mu\)m; \(\lambda_{\text{min}}\) 244.5, 280 \(\mu\)m). The nmr spectrum, in addition to the usual singlets at \(\tau\)9.05, \(\tau\)8.02, and \(\tau\)6.24 due to C-methyl, acetyl and methoxy protons respectively, showed a pair of doublets at \(\tau\)8.24 and \(\tau\)7.22 which disappeared on addition of D\(_2\)O.
On this basis these latter signals were assigned to the hydroxylic protons. A multiplet, integrating for one proton, appeared at $\tau5.94$ while a quartet at $\tau5.60$ was also evident. Both of these absorptions simplified upon addition of $D_2O$, the former collapsing to a triplet while the latter was now seen as a doublet. From deshielding considerations as well as a comparison of the degree of splitting it was decided unequivocally that the absorption at $\tau5.60$ was due to the C-12 proton which was geminal to the hydroxyl while the multiplet at higher field was due to the analogous C-11 proton. The multiplet for the proton geminal to the acetate group was observed at $\tau5.3$. The coupling constant $J_{10e,11}$ was equal to $J_{11,12}$, both being 4.5 cps. Assuming that the C-10b proton is axial, this axial-equatorial interaction requires the C-11 proton to be $\alpha$, hence a $\beta$-configuration for the C-11 hydroxyl. Since an attack by osmium tetroxide on a double bond is known to produce a cis vicinal diol, the C-12 hydroxyl must also be $\beta$ oriented. This is confirmed from the result that the coupling constant $J_{11,12}$ is 4.5 cps. The best data for the stereochemistry of the diol was obtained from the diol itself. In an analogous hydrochrysene series, Johnson demonstrated that the compound (63, figure 5) gave the diol acetate (64, figure 5). The chemical proof of $\beta$-cis stereochemistry of the hydroxyl groups was established by first producing the 38, 118-diol (65, figure 5). This compound was converted to 38, 118-dihydroxy-androstane-17-one (66, figure 5), a known natural product and this evidence provided unequivocal proof for its structure and configuration.\textsuperscript{72}
2. **Acetylation**

The above compound was acetylated to give a very stable triacetate (62) mp 194.1-195.5°C. The ultraviolet spectrum was similar to that of the anisole series described above. The nmr spectrum indicated that the usual singlets of the C-methyl, C-8 acetoxyl and methoxyl protons with respect to the trans-anti-trans acetate (42b) were shifted slightly downfield and resonated at τ8.95, τ8.00, and τ6.22 respectively. Two new acetoxyl methyl resonances appeared, one at τ8.11, the other at τ7.87. By studying the deshielding effects deduced from the structural model, it was a simple matter to assign these signals to the C-11 and C-12 positions respectively. The proton geminal to the C-8 acetate group was shifted slightly upfield to τ5.33 in this compound while a multiplet at τ4.33 which integrated for two protons could be assigned to the protons geminal to the C-11 and C-12 acetate groups.

It was hoped that this compound would provide a further opportunity to study the stereochemistry of the oxygen functions but due to the overlap of protons, this hope was not realized.

F. **CLEAVAGE OF THE DIOL**

The diol mixture obtained above was reacted with periodic acid in methanol to yield a single product, mp 135-137°C which on the basis of the following data was shown to be the desired dialdehyde acetate (60). The ultraviolet spectrum with maxima at 225, 255.5 and 321 μ, and minima at 242.5 and 281 μ supported the presence of the aromatic aldehyde. The infrared spectrum, besides indicating the saturated carbonyl of the C-8 acetate (1713 cm⁻¹), showed two new carbonyl absorptions due to the
presence of the aldehyde groups (1633 cm\(^{-1}\)). The nmr spectrum indicated the usual singlets due to C-10a methyl, C-8 acetate and C-2 methoxyl protons at \(\tau 8.87, \tau 8.01,\) and \(\tau 6.23\) respectively. The C-10b proton showed up as a quartet at \(\tau 7.63\), while the benzylic C-4b proton multiplet appeared at \(\tau 5.5\). The C-8 proton geminal to the acetate appeared as the usual multiplet at \(\tau 5.3\) while the aromatic protons absorbed in their normal region. Most importantly two aldehydic protons which appeared as a doublet at \(\tau 0.50\) and a singlet at \(\tau -0.27\) could be assigned to the aliphatic and aromatic aldehyde functions. Irradiation of the \(\tau 0.50\) region caused the collapse of the signal at \(\tau 7.63\) to a doublet with \(J_{10b,11} = 12\) cps, thereby confirming the previous assignment\(^92\). Irradiation of the \(\tau 5.5\) region collapsed the signal at \(\tau 7.63\) to a doublet (\(J = 4.5\) cps). The nmr spectrum confirms the trans stereochemistry of the C-10b and C-4b positions since the coupling constant, \(J_{10b,4b} = 12\) cps, is only consistent with diaxial coupling.

G. ALDOL CONDENSATION

Entry into the C-nor-D-homo steroid series was finally achieved by internal aldol condensation of the above ring-opened dialdehyde (60). This conversion was accomplished by reaction of the dialdehyde with sodium hydroxide in refluxing methanol solution. The resulting aldol product (67), mp 192°C, had the characteristic anisole ultraviolet spectrum (\(\lambda_{\text{max}} 284\) and 289 \(\mu\); \(\lambda_{\text{min}} 257\) \(\mu\)) while the infrared spectrum showed absorptions due to hydroxyl (3380 cm\(^{-1}\)) and saturated aldehyde carbonyl absorptions (1713, 1698 cm\(^{-1}\)).
The nmr spectrum showed the usual singlets at $\tau 8.91$ and $\tau 6.27$ attributed to the C-10a methyl and methoxyl protons. The former signal was displaced downfield while the latter was unaffected. The C-4b proton resonance appeared at $\tau 6.6$ as a well resolved quartet. Evidence for ring closure was available from the nmr spectrum of the compound. First of all the occurrence of a closely spaced doublet at low field ($\tau 4.6$ $J = 1.5$ cps) could be attributed to the C-11 proton. The same coupling occurs in the single aldehydic proton absorbing at $\tau 0.30$. It is to be noted that this proton is on a benzylic carbon atom, to which is attached a hydroxyl function and furthermore, the aldehydic function on the adjacent carbon is in close proximity to it. It is therefore not surprising that it occurs at low field. On the other hand, it should normally appear as a singlet and therefore some coupling, probably with the aldehydic proton is occurring ($J_{11, ald.} = 1.5$ cps). The appearance of this C-11 proton and the absence of the benzylic proton is ample evidence for ring closure. For some reason the C-8 proton appears upfield and is partially obscured by the methoxyl singlet. The aromatic protons occurred in the typical array, the only deviation being the superposition of the C-1 doublet spike onto the C-4 doublet spike.
H. ACETYLATION OF THE DIOL ALDEHYDE

The diacetate (68) of the above C-nor-D-homo compound (67) was crystalline mp 158.5-159.5°C. Its molecular formula, C_{24}H_{30}O_{6}, was established by mass spectrometry (found: C, 69.81; H, 7.40; O, 22.11, calculated: C, 69.54; H, 7.30; O, 23.16). Again the typical anisole ultraviolet spectrum was evident (λ_{max} 222, 286, and 291 μm; λ_{min} 252 μm) while the infrared spectrum indicated the disappearance of the hydroxyl absorption and the appearance of two new carbonyl absorptions (1720, 1703 cm\(^{-1}\)). The nmr spectrum of this diacetate aldehyde showed singlets at: \(\delta\) 9.02 (C-10a methyl); \(\delta\) 8.02 (C-8 acetate); 7.84 (C-11 acetate), and 6.35 (OCH\(_3\)). A quartet, which was assigned to the single C-4b benzylic proton appeared at \(\delta\) 6.58. Axial-axial as well as axial-equatorial couplings of 12 cps and 7 cps respectively, are observed between this proton and the pair of C-5 protons, giving rise to the above mentioned quartet. This confirms that the C-4b proton is ϒ oriented and thereby axial. The C-8 proton geminal to the acetate showed the usual multiplet at \(\tau\) 5.30 while the C-11 proton geminal to the acetate group due to its deshielding by the aromatic ring appears as a singlet amongst the aromatic protons at \(\tau\) 2.26. The aromatic protons appear at lower field than usual. A quartet registers at \(\tau\) 2.32, and a pair of doublets at \(\tau\) 2.51 and \(\tau\) 2.00. This is due to deshielding by the C-11 acetate carbonyl. The resonance of the aldehyde proton is seen as a singlet at \(\tau\) 0.10.

I. DEFORMYLATION

The desired C-nor-D-homo steroid series do not possess a C-10b aldehyde group. For this reason, efforts were made to deformylate the
C-nor-D-homo aldol product (67) synthesized in the above reaction. As mentioned in the beginning of the discussion, it was essential to develop a sequence in which it would be possible to retain the carbonyl in ring C of the C-nor-D-homo skeleton. This latter series would permit subsequent removal of this function leads to the veratramine series in which this function is lacking. Keeping this consideration in mind, several possible approaches were studied, two of which were developed.

One method developed in these laboratories utilized an oxidation of the C-11 hydroxyl (CrO₃ in acetone, Jones reagent) to a diketo aldehyde (69) and subsequent deformylation of the latter with 10% KOH solution in dioxane and water. The resultant product (70) was obtained in low yield, hence an elimination reaction involving loss of both the C-10b aldehyde and C-11 acetate to give the olefin (71) was considered.
Upon heating the C-nor-D-homo diacetate aldehyde (68) for eight days in a sodium acetate-acetic acid solution, an 80% yield of the olefin (71), mp 140-141°C, was obtained. The ultraviolet spectrum ($\lambda_{\text{max}}$ 227, 239, 263, 293, and 305 $\mu$m; $\lambda_{\text{min}}$ 248, 289, and 301 $\mu$m) was similar though not identical to the D-homo styrene compound (58) obtained earlier in the sequence. The infrared spectrum indicated the disappearance of one acetate and the aldehyde carbonyl leaving only the C-9 acetate carbonyl absorption (1731 cm$^{-1}$). The nmr spectrum showed a C-methyl singlet displaced downfield when compared with the spectrum of the trans-anti-trans acetate (42b) due to deshielding by the newly introduced double bond. Further evidence for the presence of a double bond was the presence of a very narrow singlet at $\tau$3.80. The methoxyl singlet was only slightly displaced downfield from $\tau$6.35 in the starting material to $\tau$6.27 while the signal for the remaining acetate function at C-8 was unaffected ($\tau$8.02).

The C-4b hydrogen appeared at $\tau$6.71 as a quartet. The C-5 $\alpha$ and $\beta$ hydrogens were evident at $\tau$9.1 and $\tau$7.61 respectively, as multiplets. A possible explanation for the deshielding of the C-5 methylenic hydrogen was provided in two separate studies. Nagata, studying the model tricyclic hydrophenanthrenes, observed a strong deshielding of the C-4 aromatic protons which varied directly with the amount of steric compression. If the compression of the C-4 proton electron cloud by that of the C-5 proton has a deshielding effect, then the C-5 proton in question should similarly be deshielded. In all the previously studied compounds, no C-5 proton resonance had been observed. In the C-nor-D-homo olefin case (71), the compressing C-5 proton is observed at $\tau$7.61 free of the methylenic envelope. It was proposed that the downfield shift was due only to the presence of an extended ring current. Studies by A. By of the D-homo-11,12-olefin (59) indicated that electronic contributions of the conjugated double bond were
not significant, hence any displacements of the C-4 proton would be due to a change in van der Waals compression.

To date the established range for $\Delta \tau_{1,4}$ has been 0.39-0.61, with the value of $\Delta \tau_{1,4} = 0.39$ for the case when no interaction is present. From figure 15, the $\Delta \tau_{1,4}$ for the C-nor-D-homo-olefin (71) was found to be $\Delta \tau_{1,4} = 0.38$ confirming that van der Waals compression was not responsible for the deshielding.

The shielding of the C-5 proton must be due to its position in the extended aromatic field. The fact that it is the C-5 proton that occurs at $\tau 9.1$ was confirmed in the decoupling studies performed to establish the stereochemistry of the C-4b proton (figure 16).

Irradiation at $\tau 6.71$ caused a collapse of the nine line multiplet at $\tau 7.61$ to a pair of triplets ($J_{5,5} = 13$ cps, $J_{6,5} = J_{6,6} = 3$ cps). Irradiation at $\tau 7.61$ caused a collapse of the quartet at $\tau 6.71$ to a doublet ($J = 12$ cps). In each of the above experiments changes were observed at $\tau 9.1$, thus establishing conclusively the identity of the proton resonating at $\tau 9.1$. As for the stereochemistry at C-4b the second experiment shows that a trans-trans coupling exists. This could only be possible if the C-4b proton was $\beta$ oriented.

This olefin would then be subjected to catalytic hydrogenation or some other reduction method, to yield the desired trans-anti-trans dihydro compound. In Johnson's series the wrong isomer was obtained when these reactions were performed. This result was rationalized by concluding that this was due to the steric hindrance C-7 and C-9 axial protons in ring A since the reactions performed by Johnson's collaborators were on the A/B cis compound.
J. CATALYTIC HYDROGENATION

When catalytic hydrogenation was performed on the olefin under study, it gave in good yield, a single sharp melting substance (mp 98.5-100°C) whose data allowed the assignment of structure (72a). The ultraviolet spectrum once again assumed the characteristic anisole type absorption (λ_max 207, 219, 282, and 288 μm; λ_min 214, 245, and 286 μm). The nmr spectrum recorded the usual singlets for the C-methyl and methoxyl protons. A quintet which appeared at τ7.00 was attributed to the C-4b axial proton split into a triplet (J = 6.5 cps) and then into a doublet (J = 12.5 cps). The models of the compounds show that the conformation of the olefin is not greatly changed by removal of the double bond. It may be concluded that the coupling constant between C-4b and C-10b protons is 6.5 cps, hence the C-10b proton must be β. The coupling constant between trans-diaxial protons is normally between 8 to 14 cps. Similarly, an ABX system was observed for the C-10b, C-11α and β protons in which the resonance for C-10b proton also appeared as a quintet. One line of this quintet was obscured by the C-8-acetate resonance. Nonetheless, this quintet is consistent with J_{10b,11α} = 12.5 cps, J_{10b,11β} = 6.5 cps, complementing the above conclusion about the C-10b stereochemistry.
K. BIRCH REDUCTION

Birch reduction of the olefin was undertaken, since this reaction tends to produce in most cases the thermodynamically most stable isomer. On carrying out this reaction on this compound, a substance identical with the product of catalytic hydrogenation (72) was obtained. None of the other isomer was detectable.

L. HYDROBORATION

Another alternative approach to the desired compound utilized the hydroboration of the olefin followed by a reductive or oxidative work-up. Hydroboration of the olefin in diglyme, followed by addition of propionic acid under reflux, gave a complex mixture. This mixture was simplified somewhat by hydrolysis of the acetate in aqueous methanolic potassium carbonate followed by reacetylation. Column chromatography followed by preparative T.L.C. gave a 14% yield of two acetates with an identical to that of the product of the preceding two reactions. The presence of these two compounds was also noted in the nmr spectrum where two signals for the methoxyl and C-10a angular methyl groups were noted. These signals were in the ratio 5:1 indicating a predominance of one isomer (72a).

M. BIRCH REDUCTION AND ISOMERIZATION

The previous discussion has considered the synthesis of C-nor-D-homo compound in which ring D is aromatic. It was now necessary to convert this ring system into one initially possessing a conjugated carbonyl function (73) as shown on page 52 and subsequently to introduce a methyl group into the α-position of the carbonyl system as required.
in (74). In a separate investigation by J. Cable\textsuperscript{58,59} of our laboratory, the latter substance (73) could be prepared from hecogenin (75) by the procedure of Johns\textsuperscript{58,59} and used for the total synthesis of verarine (76).

This compound (74), possessed the required trans-anti-trans "backbone" as well as a methyl group in the \(\alpha\) position of the \(\alpha\)-\(\beta\) unsaturated ketone. The most recent compound (73) synthesized in our sequence lacked the methyl substituent. In order to show that the stereochemistry of the above degradation product was indeed identical with that of the synthetic material, an \(\alpha\)-methylation of the synthetic material was necessary. To conserve the small amounts of C-nor-D-homo compound (67) available, the conditions of the Birch reduction and
methylation were developed on model D-homo-α,β-unsaturated ketones (77,78).

These latter substances were prepared from trans-anti-trans and trans-anti-cis alcohols (42a, 44) respectively, produced from the tetracyclic ketone (36), by Birch reduction (Section "A").

1. Birch Reduction of the Anisole Ring

(a) The trans-anti-trans compound

The trans-anti-trans alcohol (42a) in tetrahydrofuran was subjected to reduction using lithium metal in dry ammonia for 13 minutes. After destroying the excess lithium with ethanol the reaction mixture was worked up and recrystallized to give a product (79) melting at 124.5-127°C.

The compound, as expected, was transparent in the ultraviolet region above 210 μm. The nmr spectrum indicated that the methoxyl proton singlet was shifted upfield to δ6.5. The aromatic complex had disappeared in favour of an unresolved multiplet at δ5.40 which was attributed to
the single olefinic hydrogen at C-3. The vinylic hydrogen were not
discernable.

(b) The trans-anti-cis compound

The trans-anti-cis compound (43a) was subjected to similar reaction
conditions to give a good yield of the analogous reaction product (80)

\[
\begin{align*}
\text{HO} & \\
\text{OCH}_3 & \\
\text{H} & \\
\text{80} & \\
\end{align*}
\]

mp 129-130°C. Nagata\textsuperscript{97} quotes a melting point of 133-135°C for this
compound. Some of the spectral characteristics (UV and nmr) of this
compound were almost identical with those for the trans-anti-trans
product while the infrared spectrum differed only in the fingerprint region.

2. Enol Ether Hydrolysis and Isomerization

(a) The trans-anti-trans compound

The enol ether (79) was dissolved in an aqueous methanolic sulfuric
acid solution and was refluxed for one hour. Upon workup and column
chromatography a good yield of an \(\alpha,\beta\) unsaturated ketone (77) mp 182-
185.5°C, was obtained. The ultraviolet spectrum showed maxima at 239.5 μm and 308 μm with a minimum at 284.5 μm. The infrared spectrum indicated the characteristic "enone" absorption (1650 and 1670 cm⁻¹) as well as the hydroxyl absorption (3415 cm⁻¹). The nmr spectrum showed a broad singlet at τ4.22 due to the C-1 olefinic proton, as well as the usual resonances mentioned previously for the angular methyl protons, etc.

(b) The trans-anti-cis methyl ether cleavage and isomerization

Under the same hydrolytic conditions the trans-anti-cis compound yielded the compound (78), mp 199-202°C. The ultraviolet spectrum was superimposable with that of the previous isomer. The infrared spectrum showed minor variations in the fingerprint region. The broad olefinic singlet in the nmr spectrum was displaced slightly downfield to τ4.16. The C-10a methyl resonance showed a significant downfield shift to τ8.97 as compared with τ9.23 for the preceding isomer. The C-8 proton geminal to the hydroxyl function was shifted upfield to τ6.42 as compared with τ5.33 for the other isomers.

3. Birch Reduction, Hydrolysis and Isomerization of the C-nor-D-homo Trans-Acetate (72)

When this compound was subjected to the above described reactions,
a product (73) mp 178-180°C, was isolated in good yield. The ultra-
violet spectrum showed a maximum at 242 m\textmu completely consistent with
the calculated value of 244 m\textmu (Woodward's rules) for the anticipated
chromophore. The infrared spectrum showed the characteristic absorptions
for the hydroxyl (3475 cm\textsuperscript{-1}) as well as conjugated carbonyl functional
groups (1645, 1605 cm\textsuperscript{-1}). The broad singlet due to the olefinic proton
appeared downfield at \tau\textsubscript{4} 4.07. Similarly the C-10a methyl singlet was
shifted downfield to \tau 8.99 while the C-8 proton septet was shifted up-
field in a manner characteristic of a bent molecule. This compound will
be used as a more realistic model for the methylation reaction.

N. METHYLATION

The model compounds prepared in section "M", 1-3, were now used
to optimize the methylation procedure.

1. Studies on D-homo Compounds

(a) Stork\textsuperscript{98} had shown that a methyl group could be introduced
into simple cyclohexanones by the reaction of a magnesium bromide salt
of a Schiff's base with methyl iodide. For the simple system the yield
in this reaction exceeded that produced by the enamine alkylation.
When this reaction was attempted on the trans-anti-trans enone (77)
no crystalline compounds were isolated.
(b) **The enamine alkylation**

The pyrrolidine enamine of the trans-anti-trans enone was synthesized in good yield and its formation quickly established by ultraviolet spectroscopy ($\lambda_{\text{max}}$ 276 m\text{u}). Complete formation of this derivative was evident from the latter spectrum which never showed any evidence of the starting material ($\lambda_{\text{max}}$ 239 m\text{u}). On working up the reaction mixture (after 48 hours of reflux) only low yields of methylated material were obtained with recovery of 35-60\% of the starting material (77). The alkylated enone acetate (81), purified by preparative T.L.C., was identified by a disappearance of the olefinic proton singlet and appearance of a new singlet at $\tau$8.24 integrating for three protons and attributed to the olefinic methyl group.

![Chemical Structure](image)

The ultraviolet spectrum complemented this result by providing a maximum at 250 m\text{u}, in excellent agreement with the calculated value ($\lambda_{\text{max}}$ 249 m\text{u}). Mass spectrometry of the purified material gave a peak at m/e 344 as required by the monomethylated products.

(c) **Enolate trapping and methylation**

(A) **The trans-anti-cis isomer**

Due to repeated low yields in the enamine reaction, an alternative procedure was developed. Since the trans-anti-trans isomer was in
low supply it was decided to use the above mentioned trans-anti-cis isomer (78) as a substitute model for the reaction. On reacting this compound with lithium in ammonia under scrupulously dry conditions, then replacing the ammonia with tetrahydrofuran and/or methyl iodide under reflux, 25% of a dihydro methylated compound (82) was isolated.

This compound, upon bromination and dehydrobromination yielded a compound (83) with the correct molecular weight of 344 as established by mass spectrometry. Unfortunately this compound exhibited a maximum at 240 \( \mu \) in the ultraviolet spectrum rather than 250 \( \mu \) as mentioned above. Hence this compound, must be the result of enolate migration prior to methylation and the resultant attack of methyl iodide on the other side of the carbonyl group.

(B) The trans-anti-trans isomer

With the above evidence in hand, we turned to an investigation of the above reaction in the less readily available trans-anti-trans series. When the reaction was repeated on this isomer, a dihydro compound (84) was isolated at 40% yield. This compound had a very weak maximum at 280 \( \mu \) in the ultraviolet spectrum. The mass spectrum showed a parent peak of 304 in accordance with the required structure. The only revealing absorbance in the nmr spectrum was the presence of a doublet at \( \tau 9.02 \).
From the spectral evidence thus far it was impossible to determine whether the methylation had taken place in the correct direction. To determine the position of methylation the above product was brominated, then dehydrobromiated. The compound (85) resulting from this treatment showed (maxima) at 250 and 309 μ with the minimum at 287 μ in the ultraviolet region. The parent peak in the mass spectrum was decreased by two units to 302. This new data established unequivocally that the methylation proceeded in the proper position.
CONCLUSION

The enolate trapping-methylation sequence cleared the way for methylation of the trans-anti-trans-C-nor-D-homo compound (86) necessary for comparison with the relay substance (72) derived from hecogenin (73). This route will be possible after oxidation of the hydroboration product (87) to the C-11 ketone (88a) and epimerization of the C-10b position to produce the required stereochemistry (88b). The compound (90) required for methylation will be prepared by reduction of the C-11 ketone (88b) to the alcohol (89) under non-epimerizable conditions, and reducing the anisole ring using the conditions worked out above. Since John Cable of these laboratories has already synthesized verarine, a naturally occurring Veratrum alkaloid, using the above relay substance, the completion of the sequence described in this thesis would fill the last gap in the total synthesis of this Veratrum alkaloid.
EXPERIMENTAL

The melting points were determined on the Kofler block unless otherwise stated and are uncorrected. The ultraviolet spectra were recorded in methanol on a Cary 11 recording spectrophotometer and the infrared spectra were taken on a Perkin-Elmer Model 21 spectrophotometer as potassium bromide pellets unless otherwise stated. The nmr spectra were measured at 100 Mc/s on a Varian HA100 instrument using deuteriochloroform as solvent unless otherwise stated. The centres of gravity of the multiplets were recorded using the Tiers $\tau$ scale with tetramethylsilane as the internal standard. The proton types, multiplicity, half-height width ($W_{1/2}$) and the coupling constants, $J_{x,y}$ in cycles per second (cps) are indicated in parentheses. The microanalyses were performed by Mr. P. Borda, Microanalytical Laboratory, University of British Columbia. Every molecular weight quoted was determined mass spectrometrically on an AEI MS9 or the Atlas CH-4 mass spectrometer.

Birch Reduction of 2-methoxy-8-keto-10a-methyl 5,6,8,9,10,10a,11,12-octahydrochrysene (36)

Sodium metal (3.5 g) was added slowly to a mixture of anhydrous Analine (35 ml) and anhydrous ammonia (210 ml) contained in a flame dried apparatus. The former liquid was freshly distilled from sodium hydroxide pellets while the latter was distilled through a drying tube containing sodium hydroxide pellets. A solution of tetracyclic ketone (36), 3.5 g (74, 75, 76) in anhydrous tetrahydrofuran (70 ml) was added to the blue-bronze solvent mixture over a period of 7 minutes. Dry nitrogen was passed through the apparatus during the addition. The
mixture was stirred for a further 14 minutes. Ammonium chloride (8.5 g) was added in small portions to destroy the excess sodium. The ammonia was allowed to evaporate and the resulting residue was treated with water and extracted with ethyl ether. The organic phase was washed with dilute hydrochloric acid until the aqueous phase was no longer coloured. The organic phase was then washed with sodium bicarbonate, and finally with water until neutral. After drying over anhydrous magnesium sulphate, the solvent was removed and a yellow solid (3.24 g) was obtained. This solid was purified by chromatography on alumina (175 g - Grade III). Elution with benzene-ethyl ether (2:1) provided trans-anti-trans-2-methoxy-8-keto-10a-methyl-4b,5,6,6a,7,8,9,10,10a,10b,11,12-dodecahydro-chrysene (41, 773 mg). Several recrystallizations from ethanol provided a pure product (600 mg), mp 143-145.5°C, ultraviolet: $\lambda_{\text{max}}$ (log $\varepsilon$), 277 (3.20), 286 (3.17) μm, infrared: 1710, 1620, 1575, 1500 cm$^{-1}$, nmr: 8.97 (C-10a-angular methyl, 3H, singlet), 7.21 (C-12, C-12, 2H, quartet), 6.27 (CH$_3$O-, 3H, singlet), 3.43 (C-1, 1H, doublet $J_{1,3} = 21/2$ cps), 3.33 (C-3, 1H, quartet $J_{3,4} = 81/2$ cps), 2.82 (C-4, 1H, doublet $J_{1,4} = 0$ cps), found C, 80.77; H, 8.56; O, 10.93, calculated for C$_{20}$H$_{26}$O$_2$, C, 80.49; H, 8.78; O, 10.72, NW 298.4; empirical formula, C$_{20}$H$_{26}$O$_2$. Further elution with benzene-ethyl ether (1:2) provided trans-anti-trans-2-methoxyl-8β-hydroxy-10a-methyl-4b,5,6,6a,7,8,9,10,10a,10b,11,12-dodecahydrochrysene (42a, 2.193 g). This solid on recrystallization from ethyl ether or a mixture of benzene and petroleum ether (65-110°C) provided a pure sample of the alcohol (1.9 g) mp 156-158°C, ultraviolet: $\lambda_{\text{max}}$ 277 (log $\varepsilon$ 3.20) 286 (3.17) μm, infrared: 3405, 1615, 1575, 1500.
cm\(^{-1}\), nmr: 9.18 (C-10a angular methyl, 3H, singlet), 8.22 (C-8 hydroxyl proton removed by D\(_2\)O, 1H, singlet), 7.25 (C-12\(\alpha\)H, C-12\(\beta\)H, 2H, doublet), 6.42 (C-8 H, 1H, multiplet), 6.29 (methoxyl, 3H, singlet), 3.45 (C-1, 1H, singlet, \(J_{1,4} = 0\) cps), 3.35 (C-3, 1H, quartet, \(J_{1,3} = 3\) cps), 2.84 (C-4, 1H, doublet, \(J_{3,4} = 8\) cps), found: C, 80.32; H, 9.55; O, 10.60, calculated for C\(_{20}\)H\(_{28}\)O\(_2\): C, 79.95; H, 9.39; O, 10.65, MW 300.42 empirical formula C\(_{20}\)H\(_{28}\)O\(_2\), MS (atlas) parent peak 300, prominent peaks 147, 159, 160, 161, 173, 174, 187, 200, 213, 214.

The relative quantities of lactone and alcohol were found to vary unreproducibly especially if excesses of sodium were used. In general longer reaction times (greater than 30 minutes) gave rise to almost pure alcohol. This irreproducibility was due to traces of H\(_2\)O from incomplete drying of the ammonia.

Fractional crystallization of the oily mother liquors (35 g) gave rise to small amounts of other stereoisomers. A trans-anti-cis-2-methoxy-8\(\beta\)-hydroxy-10a-methyl-4\(\beta\),5,6,6\(\alpha\),7,8,9,10,10a,10b,11,12-dodecahydrochrysene (44a, 17g). This compound was identical with that characterized by Nagata.

Sodium Borohydride Reduction of trans-anti-trans-2-methoxy-8-keto-10a-methyl-4\(\beta\),5,6,6\(\alpha\),7,8,9,10,10a,10b,11,12-dodecahydrochrysene (41)

A solution of saturated ketone (2.66 g) in methanol (105 ml) was heated with a solution of sodium borohydride (1.37 g) in methanol and water (26 ml). The mixture was refluxed for 3 hours. The mixture was treated with concentrated hydrochloric acid (26 ml) and refluxed for
a further hour. The solution was concentrated in vacuo, water and ethyl ether were added and the ether layer was separated. The organic layer was washed with water and dried over anhydrous magnesium sulphate. On concentration a crystalline product was obtained, trans-anti-trans-2-methoxy-8-hydroxy-10a-methyl-4b,5,6,6a,7,8,9,10,10a,10b,11,12-dodecahydrochrysene (44a, 2.5g) mp 154-156°C, ultraviolet: 278 (3.22), 286 (3.17) μm, infrared: 3480, 3420, 1245 cm⁻¹, nmr: 9.19 (C-10a angular methyl, 3H, singlet), 6.28 (C-2 methoxyl, 3H, singlet), 5.98 (C-8β, 1H, multiplet-narrow), 3.1 (aromatic protons, 5H, multiplet), found: C, 80.08; H, 8.99; O, 10.97, calculated for C₂₀H₂₈O₂: C, 79.94; H, 9.41; O, 10.65, MW (MS-9) 300.209 empirical formula C₂₀H₂₈O₂. Another compound presented in the discussion remains uncharacterized, mp 135-138°C. This substance was shown by nmr to be a mixture of two isomers. The C-7 and C-8 olefin mixture was not characterized since the two compounds were also inseparable. This compound was identical with (42a), obtained in the Birch reduction.

Acetylation of trans-anti-trans-2-methoxy-8β-hydroxy-10a-methyl-4b,5,6,6a,7,8,9,10,10a,10b,11,12-dodecahydrochrysene (42a)

The crude alcohol (95 g) was dissolved in a 1:1 mixture of pyridine (120 ml) and acetic anhydride (120 ml). This mixture stood overnight at room temperature. After 22 hours the acetic anhydride was distilled off and the residue was treated with ice water. The mixture was then allowed to stand for 30 minutes after which time it was extracted with benzene. The organic phase was extracted with dilute hydrochloric acid, sodium bicarbonate and water. After drying the benzene over anhydrous
sodium sulphate, the solvent was removed to yield the crude acetate (100 g) (42b). This product was chromatographed on alumina (500 g - Grade II-III). Elution with petroleum ether (65-110°C) - benzene 2:1 provided a semi-pure acetate (42b) (91 g) while elution with chloroform-methanol - 1:1 provided a polar material (8 g). Rechromatography of semi-pure (42b) and recrystallization of the early fractions from petroleum ether (65-110°C) and ethyl ether yielded trans-anti-cis acetate (44b) (2.0 g) as needles mp 142-142.5°C, infrared: 1732, 1250 cm⁻¹, ultraviolet: λₘₐₓ 280 (3.27), 286 (3.24) μν, λₘᵡₐᵦₐₜ 247 (2.26), 284.5 (3.21 μν), nmr: 9.75 (C-10a angular methyl, 3H, singlet), 8.07 (C-8β acetate methyl, 3H, singlet), 6.31 (methoxyl, 3H, singlet), 5.35 (C-8β, 1H, multiplet-wide), 3.41 (C-1, 1H, doublet, J₁,₄ = 0), 3.36 (C-3, 1H, quartet, J₃,₁ - 3 cps), 2.96 (C-4, 1H, doublet, J₃,₄ = 8 cps), found: C, 77.06; H, 8.55; O, 14.15, calculated for C₂₂H₃₀O₃: C, 77.15; H, 8.83; O, 14.15, MW 342.46 empirical formula C₂₂H₃₀O₃, MS (atlas) parent peak 342, prominent peaks 147, 159, 160, 173, 174, 187, 200, 203, 225, 283.

Later fractions 84 g were recrystallized from ethanol or methyl cyclohexane to provide pure trans-anti-trans-2-methoxy-8β-acetoxycyclohexene (42b) mp 101°C, infrared: 1728, 1603, 1575, 1497, 1246 cm⁻¹, ultraviolet: λₘₐₓ 278 (3.18), 287 (3.14) μν, nmr: 9.15 (C-10a angular methyl, 3H, singlet), 8.01 (C-8β acetate, 3H, singlet), 7.25 (C-12α, C-12β, 2H, quartet, J₁ = 3 3/4, J₂ = 8 1/4 cps), 6.31 (methoxyl, 3H, singlet), 5.32 (C-8α, 1H, multiplet-broad), 3.47 (C-1, 1H, doublet, J₁₄ = 0 cps), 3.36 (C-3, 1H, quartet, J₁,₃ = 3 cps), 2.87 (C-4, 1H, doublet, J₃,₄ = 8 cps), found:
C, 77.06; H, 8.55; O, 14.15, calculated for \( C_{22}H_{30}O_3 \): C, 77.15; H, 8.83; O, 14.02, MW = 342.46; empirical formula, \( C_{22}H_{30}O_3 \), MS (atlas) parent peak 342, prominent peaks 147, 159, 160, 173, 174, 187, 199, 200, 213, 225, 239, 267, 282. The acetate of trans-anti-trans-2-methoxy-8\(\alpha\)-hydroxy-10\(\alpha\)-methyl-4\(\beta\),5,6,6\(\alpha\),7,8,9,10,10\(\alpha\),10\(\beta\),11,12-dodecahydrochrysene (45a) was prepared in the same manner mp 138-139.5°C, infrared: 1725, 1602, 1574, 1497, 1245 cm\(^{-1}\), ultraviolet: \( \lambda_{\text{max}} \) 223 (3.83), 279 (3.26), 287 (3.24), \( \lambda_{\text{min}} \) 247 (2.10), 285 (3.19) \( \mu \), nmr: 9.18 (C-10\(\alpha\) angular methyl, 3H, singlet), 8.00 (C-8\(\alpha\) acetate methyl, 3H, singlet), 7.24 (C-12\(\alpha\), C-12\(\beta\), 2H, quartet), 6.29 (methoxyl, 3H, singlet), 4.98 (C-8\(\beta\), 1H, narrow multiplet), 3.46 (C-1, 1H, doublet, \( J_{1,4} = 0 \) cps), 3.36 (C-3, 1H, quartet, \( J_{1,3} = 2.5 \) cps), 2.86 (C-4, 1H, doublet, \( J_{3,4} = 8 \) cps), found: C, 77.42; H, 9.01; O, 13.57, calculated for \( C_{22}H_{30}O_3 \): C, 77.15; H, 8.83; O, 14.02, MW 342.46, empirical formula, \( C_{22}H_{30}O_3 \), MS (atlas) parent peak 342, prominent peaks 147, 159, 160, 173, 174, 187, 200, 213, 225, 267, 282.

A mixture of two isomers was isolated mp 134.5-136°C, ultraviolet: \( \lambda_{\text{max}} \) 225 (3.76), 278 (3.34), 286 (3.31) \( \mu \), \( \lambda_{\text{min}} \) 246 (2.35), 284 (3.27) \( \mu \).

The elemental analysis was in good agreement with the empirical formula \( C_{22}H_{30}O_3 \), nmr: 9.02 (C-10\(\alpha\) angular methyl, 3H, singlet), 8.86 (C-10\(\alpha\) angular methyl, 3H, singlet), 8.01 (C-8\(\beta\) acetate methyl, 3H, singlet), 7.25 (C-12\(\alpha\), C-12\(\beta\), 2H, multiplet), 6.31 (methoxyl, 3H, singlet) 5.30, 5.08 (C-8\(\alpha\), 1H, overlapping septets), 3.3-3.5 (C-1, C-3; 2H, multiplet), 2.8-3.0 (C-4, 1H, doublets); the doubling in the
above spectrum conclusively proves the existence of at least two compounds.

A similar situation occurred in the olefinic mixture. A T.L.C. study showed that the C-8 axial alcohol was easily eliminated. Characterization of these mixtures was not pursued.

Oxidation of trans-anti-trans-2-methoxy-8-acetoxy-10a-methyl-4b,5,6,6a,7,8,9,10,10a,10b,11,12-dodecahydrochrysene (42b)

A solution of t-butyl chromate was prepared by the addition of chromium trioxide to t-butyl alcohol in the manner of Heusler and Wettstein except the final solution was concentrated to 600 ml rather than 100 ml as suggested. Aliquots were used for the various experiments.

The acetate (42b) (6.70 g) was dissolved in carbon tetrachloride (180 ml) and the t-butyl chromate solution (90 ml) was mixed with acetic anhydride (15 ml) before adding. The mixture was stirred under reflux for 4 hours and the excess oxidant was destroyed by stirring with a solution of oxalic acid (75 g in 100 ml water) for 2 hours. Frothing was controlled by emersion in ice water when necessary. The reaction mixture was partitioned between water and chloroform. The aqueous layer was extracted with chloroform. Incomplete decomposition of the oxidant was heralded by a yellow coloration of the chloroform extracts. It was found emulsions could be minimized by this type of a workup. The pooled organic phase was washed with water to remove inorganic salts, with sodium bicarbonate to remove residual acetic acid and finally with a 1:1 solution of saturated sodium bicarbonate and sodium carbonate,
to remove acidic reaction products. The faintly pink basic washings were extracted once with chloroform. The combined organic solutions were dried over anhydrous magnesium sulphate. After removal of the drying agent and evaporation of the solvent a crude neutral product (6.25 g) was obtained. The weight of acidic byproducts was negligible. The neutral material was chromatographed on Grade III alumina (300 g). Elution with benzene-petroleum ether (7:3) provided 56% recovery of starting material (42b, 3.74 g) and further elution with benzene-ethyl ether (1:1) yielded the desired crude keto acetate (4g) in 16% yield (1.16 g). After a more careful chromatography and recrystallization of the middle fractions from benzene-petroleum ether (65-110°C) colourless needles of the desired trans-anti-trans-2-methoxy-8a-acetoxy-12-keto-10a,methyl-4b,5,6,6a,7,8,9,10,10a,10b,11,12-dodecachydrochrysene (48) (0.73 g) was isolated with mp 145.5-147°C, infrared: 1803, 1672, 1600, 1565, 1491 cm⁻¹, ultraviolet: λ_max 222 (4.08), 254 (3.68), 322 (3.14 μ, nmr: 9.05 (C-10a angular methyl, 3H, singlet), 7.99 (C-8 acetoxy methyl, 3H, singlet), 7.70 (C-11β, 1H, quartet, J10b,11b = 14 cps), 7.24 (C-11α, 1H, quartet, J10b,11a = 3.5 cps), 6.22 (methoxyl, 3H, singlet), 5.32 (C-8α, 1H, septet, J8,7b = J8,9β = 5 cps), 2.97 (C-3, 1H, quartet, J1,3 = 3 cps), 2.72 (C-4,1H, doublet, J3,4 = 8.5 cps), 2.53 (C-1, 1H, doublet, J1,4 = 0 cps), found: C, 74.10; H, 7.76; O, 18.14, calculated for C_{22}H_{28}O_4: C, 74.13; H, 7.92; O, 17.96, MW 356.44, empirical formula C_{22}H_{28}O_4. MS (atlas) parent peak 356; prominent peaks 135, 161, 174, 175, 187, 188, 200, 201, 213, 214, 239, 242, 281, 296, 314, 341. If a crude sample of trans-anti-trans acetate (42b) was oxidized an
isomer of the 12-ketoacetate (49) was isolated in very small quantity. Ultraviolet absorption was almost identical with that of the trans-anti-trans isomer. The infrared differed slightly in fingerprint region, nmr: 8.88 (C-10a angular methyl, 3H, singlet) the other resonances were typical of this class of compound. This displacement of the C-10a methyl has become indicative of the trans-anti-cis isomer. The by products of this oxidation reaction were isolated and various modifications of functional groups were initiated to study the stereochemistry and reactivity of said molecules. The trans-anti-trans-12-keto acetate (49) was deacetylated to give trans-anti-trans-2-methoxy-8β-hydroxy-10a-methyl-12-keto-4b,5,6,6a,7,8,9,10,10a,10b-dodecahydrochrysene (50) mp 177°C, infrared: 3460, 1665, 1600, 1490 cm⁻¹, ultraviolet: \( \lambda_{\text{max}} \) 222 (4.39), 253 (3.99), 322 (3.54) \( \mu \), \( \lambda_{\text{min}} \) 238 (3.76), 279 (2.71) \( \mu \), nmr: 9.09 (C-10a angular methyl, 3H, singlet), 8.03 (C-8-OH, 1H, singlet removed by D₂O), 7.71 (C-11β, 1H, quartet, J₁₀b,₁₁β = 3.5 cps), 7.26 (C-11α, 1H, quartet, J₁₀b,₁₁α = 14 cps, J₁₁α,₁₁β = 16 cps), 6.40 (C-8α, 1H, septet, J₈,₉α = J₇,₈₁α, ₈₁β = J₈,₈₁β = 10 cps), 6.23 (methoxyl, 3H, singlet), 2.99 (C-3, 1H, quartet J₁,₃ = 3 cps), 2.73 (C-4, 1H, doublet, J₁,₄ = 0 cps), 2.55 (C-1, 1H, doublet, J₄,₃ = 8 cps), found: C, 76.54; H, 8.55; O, 14.91, calculated for C₂₀H₂₆O₃: C, 76.40; H, 8.34; O, 15.27, MW 314.41, empirical formula C₂₀H₂₆O₃, MS (atlas) parent peak 314, prominent peaks 135, 161, 174, 187, 188, 189, 201, 213, 257, 310. Under the conditions of deacetylation, ie 12-keto-acetate (1.4 g) in methanol (40 ml) and reflux with 10 ml 1.5 N K₂CO₃ for 2 hours some cleavage of the methoxyl group occurred. Reacetylation in the usual manner gave a
diacetate (56, 10 g) mp 240-243°C, infrared, 1762, 1724, 1672, 1603,
1492 cm$^{-1}$, ultraviolet: $\lambda_{\text{max}}$ 214 (4.37), 247 (4.02), 300 (3.41), $\lambda_{\text{min}}$
233 (3.86), 274 (3.16) $\mu\mu$, nmr: 9.07 (C-10a angular methyl, 3H, singlet),
8.03 (C-8$\beta$ acetoxy, 3H, singlet), 7.77 (aromatic acetate, 3H, singlet),
7.71 (C-11$\beta$, 1H, quartet, $J_{10a,11\beta} = 14$ cps), 7.25 (C-11$\alpha$, 1H, quartet,
$J_{11a,11\beta} = 16$ cps, $J_{10a,11\alpha} = 3.5$ cps), 5.35 (C-8$\alpha$, 1H, multiplet), 2.84
(C-3, 1H, quartet, $J_{1,3} = 2$ 1/2 cps), 2.62 (C-4, 1H, doublet, $J_{3,4} = 8$ 1/2 cps), 2.35 (C-1, 1H, doublet, $J_{1,4} = 0$ cps), found: C, 72.00;
H, 7.40, O, 20.60, calculated for C$_{23}$H$_{28}$O$_5$: C, 71.85; H, 7.34; O, 20.81,
MW 384.45, empirical formula C$_{23}$H$_{28}$O$_5$. MS (atlas) parent peak 384,
prominent peaks 140, 147, 173, 174, 199, 228, 267, 282, 342. This data
is consistent with the structure trans-anti-trans-2-acetoxy-8$\beta$-12 diacetoxy-
10a-methyl-4b,5,6,6a,7,8,9,10,10a,10b,11,12 dodecahydrochrysene (56).

One of the novel compounds (2.2 g) (54) isolated from the mother
liquors (23 g) proved to be remarkably stable. The data below is
consistent with the following compound, trans-anti-trans-2-methoxy-8$\beta$
acetoxy-4b-t-butyl peroxy-10a, methyl104b,5,6,6a,7,8,9,10,10a,10b,11,12
dodecahydrochrysene (54) mp 140°C, infrared: 1715, 16667, 1592, 1495
cm$^{-1}$, ultraviolet: $\lambda_{\text{max}}$ 206 (4.19), 224 (4.04), 273 (4.17), 285 (4.08),
298 (3.94), $\lambda_{\text{min}}$ 216 (3.95), 241 (3.23)$\mu\mu$, nmr: 8.74 (C-10a angular methyl, 3H, singlet), 8.54 (C-4b t-butyl, 9H, singlet), 8.02 (C-8 acetoxy, 3H, singlet), 7.10 (C-12, C-14, 2H, quartet), 6.21 (methoxy1, 3H, singlet),
5.40 (C-8d, 1H, septet), 3.41 (C-1, 1H, doublet), 3.29 (C-3, 1H, quartet),
2.15 (C-4, 1H, doublet) normal couplings value were observed.

The mother liquors of the t-butyl oxidation were treated with
Girard's "T" reagent, a compound which specifically derivatizes ketones
and makes them soluble in water. It was found that the 12-keto-acetate was five times more reactive than the corresponding naphthalenic-5-keto acetate (37). Girard's "T" reagent (60 g) was added to mother liquors (30 g) in methanol (750 ml) and a mixture of glacial acetic acid (75 ml) and acetic anhydride (2 ml) reflux was continued for 35 minutes after which the reaction mixture was extracted with water and ether. The aqueous phase was refluxed for one hour with concentrated sulphuric acid (10 ml) and re-extracted with ether. After drying the ether layer over anhydrous magnesium sulphate and the solvent an oil (8 g) was obtained enriched as described above in the two ketones. The process was repeated several times and after each repetition not more than 5% of the original weight remained unaccounted for. Fractional crystallization in the usual manner yielded two compounds. First, the compound of interest, 12-keto-acetate (49) (13 g) and second, the impurity trans-2-methoxy-5-keto-8g-acetoxy-10a methyl-5,6,6a,7,8,9,10,10a-octahydrochrysene (37) (4.5 g) mp 156-157.5°C, infrared: 1718, 1662, 1619, 1591 cm⁻¹, ultraviolet; \( \lambda_{\text{max}}^\text{max} \) 219.5 (4.66), 248 (4.43), 315 (3.79), 348 (3.48), \( \lambda_{\text{min}}^\text{min} \) 233 (4.23), 278 (3.02) mu, nmr: 8.81 (C-10a angular methyl, 3H, singlet), 7.99 (C-8β-acetoxy, 3H singlet), 7.44 (C-6α, C-6β, 2H, doublet, J₅,₆ = 9 cps), 6.18 (methoxyl, 3H, singlet), 5.30 (C-8α, 1H, septet, J₇,₈ = J₈,₉ = 11 cps, J₇,₈ = J₈,₉ = 5 1/2 cps (equatorial-equatorial)), 2.99 (C-1, 1H, doublet, J₁,₃ = 2 1/2 cps), 2.82 (C-3, 1H, quartet, J₃₄ = 9 1/2 cps), 2.62 (C-11, 1H, doublet, J₁₁,₁₂ = 8.5 cps), 2.22 (C-12, 1H, doublet), 0.96 (C-4, 1H, doublet, J₁,₄ = 0 cps), found: C, 75.10; H, 7.25; O, 17.82, calculated for \( \text{C}_{22}\text{H}_{24}\text{O}_{4} \): C, 74.97; H, 6.86, O, 18.16, MW 352.41, empirical formula \( \text{C}_{22}\text{H}_{24}\text{O}_{4} \), MS (atlas) parent peak 352,
prominent peaks 152, 153, 165, 171, 211, 249, 277, 292.

From the remaining underivatizable material fractional crystallization yielded two compounds. The first: trans-2-methoxy-8β-acetoxy-10a-methyl-5,6,6a,7,8,9,10,10a-octahydrochrysene (39, figure 10) mp 169-172.5°C, infrared: 1718, 1626, 1604, 1578 cm⁻¹, ultraviolet: \( \lambda_{\text{max}} \) 227 (4.74), 256 (3.55), 266 (3.64), 276 (3.66), 287 (3.44), 307 (2.97), 314 (3.04), 319 (3.18), 328 (3.10), 334 (3.27), \( \lambda_{\text{min}} \) 254 (3.52), 259 (3.54), 271 (3.60), 284 (3.47), 302 (2.91), 309 (2.97), 324 (3.06), 331 (2.10) μμ, found: C, 77.89; H, 7.69; O, 14.76, calculated for \( \text{C}_{22}\text{H}_{26}\text{O}_{3} \): C, 78.07; H, 7.74; O, 14.18, MW 338.43, empirical formula \( \text{C}_{22}\text{H}_{26}\text{O}_{3} \), MS (atlas) parent peak 338, prominent peaks 149, 165, 171, 178, 179, 185, 197, 207, 221, 263, 278, 323.

The second compound obtained from fractional crystallization was trans-2-methoxy-8β-acetoxy-10a-methyl-6a,7,8,9,10,10a-hexahydrochrysene (38, figure 10) (2.2 g) mp 158.5-160.5°C, ultraviolet: \( \lambda_{\text{max}} \) 244 (4.59), 276 (3.58), 288 (3.65), 301 (3.82), 314 (3.90), \( \lambda_{\text{min}} \) 273 (3.56), 281 (3.55), 293 (3.64), 307 (3.73), 327 (3.38), 342 (3.41) μμ, found: C, 78.55; H, 7.67; O, 13.64, calculated for \( \text{C}_{22}\text{H}_{24}\text{O}_{3} \): C, 78.54; H, 7.19; O, 14.27, MW 336.41 empirical formula \( \text{C}_{22}\text{H}_{24}\text{O}_{3} \), MS (atlas) parent peak 336, prominent peaks 115, 128, 158, 159, 165, 171, 172, 173, 178, 179, 221, 235, 246, 261, 276.

In order to study lead tetraacetate in pyridine as a selective oxidizing agent for bifunctional secondary alcohol, one of which is benzylic, the 5 keto acetate (37) was dissolved in methanol and refluxed with a 1.5 N aqueous solution of potassium carbonate in the usual manner to give trans-2-methoxy-5-keto-8β-hydroxy-10a-methyl-6,6a,7,8,9,10,10a-
heptahydrochrysene (52) (75% yield), mp 135.5-137°C, infrared: $\lambda_{max}$ 221 (4.70), 248 (4.46), 315 (3.87), 355 (3.60), $\lambda_{min}$ 233 (4.27), 278 (3.40) $\mu \mu$, nmr: 8.81 (C-10a angular methyl, 3H, singlet), 7.81 (C-8β-hydroxyl, 1H, singlet, removed with $D_2O$), 7.41 (C-6α, D-6β, 2H, doublet, $J_{5α,6α} = J_{5α,6β} = 9$ cps), 6.35 (C-8α, 1H, multiplet), 6.18 (methoxyl, 3H, singlet), 2.99 (C-1, 1H, doublet), 2.81 (C-3, 1H, quartet, $J = 21/2$ cps), 2.61 (C-11, 1H, doublet, $J_{11,12} = 8.5$ cps), 2.21 (C-12, 1H, doublet, 0.96 (C-4, 1H, doublet), found: C, 77.17; H, 7.32; O, 15.31, calculated for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14; O, 15.47, MW, 310.38 empirical formula $C_{20}H_{22}O_3$, MS (atlas) parent peak 310, prominent peaks 140, 152, 165, 211, 225, 235, 249, 251, 277, 290, 308.

The above compound (1.4 g) was reduced in methanol (140 ml) with sodium borohydride (4 g) in water (15 ml) by refluxing for four hours. The mixture was poured into water and filtered recrystallization from ethyl acetate gave an analytical sample of trans-2-methoxy-5α,8β-dihydroxy-10a-methyl-5,6,6a,7,8,9,10,10a-octahydrochrysene (53) mp 207.5-208.5°C, infrared: 3300, 1623, 1600, 1506, 860, 836, 785 $\text{cm}^{-1}$, ultraviolet: $\lambda_{max}$ 333.5 (3.36), 327 (3.23), 319 (3.27), 306 (3.01), 285 (3.57), 275 (3.73), 265 (3.70), 255 (3.60), 232 (4.95), $\lambda_{min}$ 324 (3.20), 299 (2.90), 282 (3.56), 269 (3.66), 258 (3.59), 252 (3.58) $\mu \mu$, nmr: (in Pyridine - $D_2O$), 8.80 (C-10a methyl, 3H, singlet), 6.24 (methoxyl, 3H, singlet), 6.2 (C-8α, 1H, multiplet) (other resonances obscured by solvent) 4.39 (C-5β, 1H, triplet, $J_{6β,7β} = J_{6α,7β} = 8$ cps), found: C, 76.66; H, 7.86; O, 15.39, calculated for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74; O, 15.37, MW 312.39, empirical formula $C_{20}H_{24}O_3$, MS (atlas) parent peak 312,
prominent peaks 139, 165, 167, 200, 221, 235, 246, 261, 279, 294.

The above diol (53, 930 mg) was reacted with lead tetra-acetate (1.18 g) in anhydrous pyridine (15 ml) at room temperature overnight. The mixture was poured into dilute hydrochloric acid and extracted with ethyl ether. After drying and evaporating the ethyl ether the gum (304 mg) was chromatographed on Grade III alumina (30 g). In addition to recovered starting material and a mixture of ketols, major product was found to be trans-2-methoxy-5,8-diketo-6,6a,7,9,10,10a-hexahydrochrysene (52) mp 193°C, infrared: 1700, 1670, 1620, 1590, 1502 cm\(^{-1}\), ultraviolet: \(\lambda_{\text{max}}\) 221 (4.70), 249 (4.46), 316 (3.88), 356 (3.60), \(\lambda_{\text{min}}\) 233 (4.27), 279 (3.41)\(\mu\)m, nmr: 8.63 (C-10a methyl, 3H, singlet), 6.18 (methoxy1, 3H, singlet), 2.99 (C-1, 1H, doublet, \(J_{1,3} = 2\ 1/2\) cps), 2.82 (C-3, 1H, quartet, \(J_{3,4} = 9\ 1/2\) cps), 2.62 (C-11, 1H, doublet, \(J_{11,12} = 8\ 1/2\) cps), 2.19 (C-12, 1H, doublet), 0.94 (C-4, 1H, doublet, \(J_{4,1} = 0\) cps), found: C, 78.17; H, 6.68; O, 15.50, calculated for \(C_{20}H_{20}O_3\): C, 77.90; H, 6.54; O, 15.57, MW 308.36, empirical formula \(C_{20}H_{20}O_3\), MS (atlas) parent peak 308, prominent peaks 175, 209, 211, 223, 225, 237, 239, 251, 265, 293.

Further study of the oxidation products of this diol (53) was abandoned.

**Synthesis of trans-anti-trans-2-methoxy-8β-acetoxy-10a-methyl-12-hydroxy-4b,5,6,6a,7,8,9,10,10a,10b,11,12-dodecahydrochrysene (55)**

The 12 keto acetate (49) (3.2 g) was dissolved in methanol (400 ml) and a solution of sodium borohydride (1.0 g) in methanol (400 ml) and water (20 ml) was added. The mixture was stirred at room temperature
for 3.5 hours. Acetic acid (15 ml) was added and the solution was stirred for a further 1/2 hour. The reaction mixture was partitioned between water and ethyl ether then washed with sodium bicarbonate solution and water. After drying the organic layer over magnesium sulphate (anhydrous) and removal of the liquid, a gum (3.2 g) was isolated. On T.L.C., two spots of ratio 2:1 were observed. The slower major product was crystallized from ethanol or benzene - high boiling petroleum ether gave an analytical sample of trans-anti-trans-20methoxy-8β-acetoxy-10a-methyl-12β-hydroxy-4b,5,6,6a,7,8,9,10,10a,10b, 11,12-dodecahydrochrysene (55) mp 147.5-149°C, infrared: 3503, 1703, 1609, 1504 cm\(^{-1}\), ultraviolet: \(\lambda_{\text{max}}\) 226 (3.86), 281 (3.33), 288 (3.31), \(\lambda_{\text{min}}\) 247 (2.77), 286 (3.27)\(\mu\), nmr: 9.15 (C-10a methyl, 3H, singlet), 8.03 (C-8acetoxy, 3H, singlet), 7.93 (C-12β hydroxy, 3H, singlet) removed by D\(_2\)O exchange), 6.29 (C-2 methoxyl, 3H, singlet), 5.3 (C-8α, C-12d-2H, multiplet), 3.30 (C-3, 1H, quartet, J\(_{1,3}\) = 3 cps), 2.96 (C-1, 1H, doublet, J\(_{1,4}\) = 0 cps), 2.90 (C-4, 1H, doublet, J\(_{3,4}\) = 9 cps), found: C, 73.91; H, 8.31; O, 17.70, calculated for C\(_{22}\)H\(_{30}\)O\(_4\): C, 73.71; H, 8.44; O, 17.85, MW 358.46, empirical formula C\(_{22}\)H\(_{30}\)O\(_4\). MS (atlas) parent peak 358, prominent peaks 158, 159, 171, 172, 173, 174, 185, 265, 280, 296, 298, 316, 340, 342, 356.

If the above sodium borohydride reaction mixture was refluxed for as little as one hour the major product is a mixture of C-12 epimeric diols (57) trans-anti-trans-2-methoxy-8β,12β-dihydroxy-10a-methyl-4b, 5,6,6a,7,8,9,10,10a,10b,11,12-dodecahydrochrysene (57) mp 190°C, infrared: 5370, 3310, 1615, 1572, 1495, 887 cm\(^{-1}\), ultraviolet: \(\lambda_{\text{max}}\) 224 (3.81), 280 (3.24), 288 (3.21), \(\lambda_{\text{min}}\) 247 (2.05), 286 (3.18)\(\mu\), nmr: (in Pyridine)
9.22 (C-10a methyl, 3H, singlet), 6.38 (C-2 methoxyl, 3H, singlet),
6.24 (C-8a, 1H, septet, \( J_{7,8} = J_{8,9} = 5 \) 1/2 cps - axial:equatorial,
\( J_{7,8} = J_{8,9} = 11 \) cps - axial:axial), 5.00 (Cl2a, 1H, quartet, \( J_{11\beta,12\alpha} = 10 \) cps, \( J_{11\alpha,12\alpha} = 5 \) cps). The other resonance were obscured by the
solvent, found: C, 76.02; H, 8.97; O, 15.16, calculated for \( \text{C}_{20}\text{H}_{28}\text{O}_{3} \):
C, 75.91; H, 8.92; O, 15.17, MW 316.42, empirical formula \( \text{C}_{20}\text{H}_{28}\text{O}_{3} \),
MS (atlas) parent peak 316, prominent peaks 298, 185, 175, 174, 173,
159, 158, 150, 149.

The diacetate (56) of the above compound was synthesized in the
usual manner, trans-anti-trans-2-methoxy-8β,12α-diacetoxy-10α-methyl,
4β,5,6,6α,7,8,9,10,10α,10β,11,12-dodecahydrochrysene (56) mp 175°C,
infrared: 1730, 1720, 1608, 1506, 1378 cm\(^{-1}\), ultraviolet: \( \lambda_{\text{max}} \) 226
(3.84), 281 (3.33), 288 (3.30), \( \lambda_{\text{min}} \) 246 (2.18), 286 (3.28)\(_{\text{mu}}\), nmr: 9.16
(C-10a methyl, 3H, singlet), 8.03 (C-8β acetoxyl, 3H, singlet), 7.92
(C-12β acetoxyl, 3H, singlet), 6.30 (C-2 methoxyl, 3H, singlet), 5.35
(C-8α, 1H, septet, \( J_{7e,8} = J_{8,9e} = 5 \) cps, \( J_{7a,8} = J_{8,9a} = 10 \) cps), 4.09
(C-12α, 1H, quartet, \( J_{11e,12a} = 6 \) cps, \( J_{11a,12a} = 9 \) cps), 3.35 (C-1,
1H, doublet, \( J_{1,4} = 0 \) cps), 3.28 (C-3,1H, quartet, \( J_{1,3} = 3 \) cps), 2.86
(C-4, 1H, doublet, \( J_{3,4} = 8 \) 1/2 cps), found: C, 71.72; H, 7.91; O,
20.20, calculated for \( \text{C}_{24}\text{H}_{32}\text{O}_{5} \): C, 71.91; H, 8.05; O, 19.98, MW 400.50,
empirical formula \( \text{C}_{24}\text{H}_{32}\text{O}_{5} \), MS (atlas) parent peak 400, prominent peaks
158, 159, 171, 172, 173, 174, 184, 185, 265, 280, 325, 340, 358.

Selective oxidation of the epimeric diol (54)

The diol (3.7 g) was oxidized with lead tetra-acetate (5.5 g-1.0 mole)
in anhydrous purified pyridine (70 ml). After several minutes the solution
became warm. This solution was worked up after 12 hours and chromatographed on Grade III alumina (150 g). Elution with benzene gave trans-anti-tran.-2-methoxy-8,12-diketo 10a-methyl-4b,5,6,6a,7,8,9,10,10a,10b, 11,12-dodecahydrochrysene (58) (0.34 g - 9.3%) mp 170-172°C, infrared: 1706, 1672, 1605, 1497 cm⁻¹, ultraviolet: λ max 224 (4.23), 253 (3.92), 320 (3.49) μ, λ min 233 (3.71), 2.79 (2.69) μ, nmr: 8.90 (C-10a methyl, 3H, singlet), 7.21 (C-11α, 1H, quartet, J 10b,11 = 3 1/2 cps, J 11α,11β = 16 cps), 6.24 (methoxyl, 3H, singlet), 2.98 (C-3, 1H quartet, J 1,3 = 3 cps), 2.72 (C-4, 1H, doublet, J 3,4 = 8 cps), 2.55 (C-1, 1H, doublet), found: C, 76.67; H, 7.91; O, 15.51, calculated for C 20 H 24 O 3 : C, 76.89; H, 7.74; O, 15.37, MW 312,39, empirical formula C 20 H 24 O 3 , MS (atlas) parent peak 312, prominent peaks 149, 161, 174, 187, 255, 270, 297.

Elution with benzene-ethyl acetate (9:1) gave 74.3% of the product as a mixture of ketols recrystallization of these fractions from ethanol gave a compound identical with the above characterized ketol (50) (2.39 g - 65%) obtained by deacetylation of 13 keto acetate (49). Further elution with ethyl acetate:methanol (1:1) gave unchanged diol (0.47 g - 12.7%).

Dehydration of the crude alcohol (54)

The crude alcohol (3.2 g) was dissolved in anhydrous benzene (150 ml) and phosphorus pentoxide (3.2 g) was added. After 2 hours of reflux the reaction mixture was cooled in ice water then decanted into another flask. A small amount of ice was added and the yellow-green fluorescent solution was swirled occasionally while most of the residue
in the reaction flask was dissolved in ice water. To the suspension in the reaction flask ethyl ether and saturated sodium chloride solution were added. Sodium bicarbonate was added in small portions until the solution became basic. At this point it was as difficult to destroy the emulsions formed as it was to completely dissolve the residue. The aqueous layer was extracted several times with ether and pooled with the decanted solution. The pooled organic phase was washed with sodium bicarbonate, water, and dried over magnesium sulphate. On removal of solvent the crude material (2.7 g) was isolated. Purification by column chromatography on alumina (Grade III, 100 g) gave the desired olefin (59) (2.2 g) with benzene-petroleum ether (1:1).

Recrystallization from ethanol gave pure trans-anti-trans-2-methoxy-8β-acetoxy-10α-methyl-4β,5,6,6a,7,8,9,10,10a,10b-decahydrochrysene (59). mp 105-106.5°C, infrared: 1725, 1628, 1600, 1565, 1485 cm⁻¹, ultraviolet: λ_max 221 (4.44), 262.5 (3.84), 270 (3.88), 302 (3.51), 312 (3.40) μm, λ_min 247 (3.83), 284 (3.48) μm, nmr: 9.11 (C-10α methyl, 3H, singlet), 8.15 (C-10αα, 1H, multiplet), 8.04 (C-8 acetoxy1, 3H, singlet), 6.32 (CO2 methoxy1, 3H, singlet), 5.33 (C-8α, 1H, septet, J_7e,8a = J_8a,9e = 5 1/2 cps, J_7a,8a = J_8a,9a = 11 cps), 4.11 (C-12, 1H, quartet, J_10aa,12 = 2 cps), 3.67 (C-11, 1H, quartet, J_11,12 = 10 cps, J_10bα,11 = 3 cps), 3.49 (C-1, 1H, doublet, J_1,4 = 0 cps), 3.39 (C-3, 1H, quartet, J_1,3 = 2 1/2 cps, J_3,4 = 8 cps), 2.98 (C-4, 1H, doublet), found: C, 77.48; H, 8.23; O, 14.44, calculated for C_{22}H_{28}O_3: C, 77.61; H, 8.29; O, 14.10, MW 340.44, empirical formula C_{22}H_{28}O_3, MS (atlas) parent peak 340, prominent peaks 158, 159, 160, 161, 171, 172, 173, 184, 185, 197, 263, 265, 280, 325, 338.
Synthesis of the diol (61) by osmic acid oxidation

The olefin (59) characterized above (600 mg), was dissolved in dry ethyl ether (10 ml). Osmium tetroxide (500 mg, 12% excess) was dissolved in dry ethyl ether (10 ml) and latter and former solutions were rapidly mixed. The osmium tetroxide container was rinsed with more ether (10 ml) and added. The solution was allowed to stand at room temperature in the dark for 57 hours. The dark precipitate which separated was treated with methanol (6 ml) and water (1 ml). Hydrogen sulphide gas was passed into the solution for 5 minutes, the solution was stirred for a further 5 minutes and the precipitate filtered in a sintered glass funnel. The precipitate was washed with methanol then removed and subjected to the hydrogen sulphide treatment twice more to insure decomposition of the osmate ester. When for some unknown reason the osmium sulphide did not aggregate sufficiently and was passed through the sintered glass funnel it was found that only centrifugation was able to remove this impurity. When the solvent was removed from the filtrate solution a crude solid product (0.688 g) was obtained. This substance was refrigerated until purified by chromatography.

Elution of the trans-anti-trans-2-methoxy-8g acetoxy-11,12-dihydroxy-10a-methyl-4b,5,6,6a,7,8,9,10,10a,10b,11,12-dodecahydrochrysene (61, 590 mg), from Woelm silica gel was accomplished with 5% methanol in chloroform. T.L.C. showed two isomers with \( R_f \) values 0.17 and 0.13 the latter being the major constituent. Recrystallization of the polar fractions from chloroform and petroleum ether (65-110°C) produced an analytical sample mp 225-226°C, infrared: 3450, 1705, 1610, 1585, 1500 cm\(^{-1}\), ultraviolet: \( \lambda_{\text{max}} \) 276 (3.21), 282 (3.19) m\( \mu \), \( \lambda_{\text{min}} \) 244.5
(2.13), 280 (3.16) \text{\textmu} \text{m}, \text{nmr: } 9.05 \text{ (C-10a methyl, 3H, singlet), } 8.48 \text{ (C-11 or 12 hydroxy1, 1H, doublet - removed by D}_2\text{O exchange), } 8.02 \text{ (C-88 acetoxyl, 3H, singlet), } 7.22 \text{ (C-11 or 12 hydroxy1, 1H, doublet-removed by D}_2\text{O exchange), } 6.24 \text{ (C-2 methoxy1, 3H, singlet), } 5.94 \text{ (C-11, 1H, multiplet, to triplet on D}_2\text{O addition), } 5.60 \text{ (C-12, 1H, quartet, to doublet on D}_2\text{O addition), } 5.3 \text{ (C-8, 1H, multiplet), } 3.25 \text{ (C-3, 1H, quartet, } J_{c,1} = 2 \text{ 1/2 cps), } 2.94 \text{ (C-4, 1H, doublet, } J_{3,4} = 8 \text{ 1/2 cps), } 290 \text{ (C-1, 1H, doublet), found: } C, 70.18; H, 7.99; O, 21.83, \text{ calculated for } C_{22}H_{30}O_5: C, 70.56; H, 8.08; O, 21.36, MW 374.46, empirical formula C_{22}H_{30}O_5, \text{ MS (atlas) parent peak 374.}

**Acetylation of the diol**

The above diol acetate (61) was acetylated in the usual manner to give the triacetate trans-anti-trans-2-methoxy-8a,11,12-triacetoxy-10a-methyl-4b,5,6,6a,7,8,9,10,10a,10b,11,12-dodecahydrochrysene (62) mp 194-195.5, infrared: 1732, 1612, 1497 \text{cm}^{-1}, \text{ ultraviolet: } \lambda_{\text{max}} 283 (3.32), 277 (3.33), 225 (3.88), \lambda_{\text{min}} 280 (3.30), 243 (2.48) \text{\mu} \text{m}, \text{nmr: } 8.95 \text{ (C-10a methyl, 3H, singlet), } 8.11 \text{ (C-11 acetoxyl, 3H, singlet), } 8.00 \text{ (C-88 acetoxyl, 3H, singlet), } 7.87 \text{ (C-12 acetoxyl, 3H, singlet), } 6.22 \text{ (C-2 methoxy1, 3H, singlet), } 5.33 \text{ (C8a, 1H, septet), } 4.33 \text{ (C-11, C-12, 2H, multiplet), } 3.19 \text{ (C-3, 1H, quartet), } 3.13 \text{ (C-1, 1H, doublet), } 2.87 \text{ (C-4, 1H, doublet), found: } C, 68.89; H, 7.24; O, 23.87, \text{ calculated for } C_{26}H_{34}O_7: C, 68.10; H, 7.47; O, 24.43, MW 438.53, empirical formula C_{26}H_{34}O_7, \text{ MS (atlas) parent peak 458, prominent peaks 149, 159, 161, 171, 174, 175, 176, 187, 188, 230, 263, 279, 296, 313, 338, 356, 372, 383, 398, 416, 443.
Periodate cleavage of the diol (61)

The above diol mixture (166.7 μg) was dissolved in methanol (77.5 ml) and a solution of periodic acid in water (24 ml, 0.0219 M in acid) was added to the reaction mixture. A 10% increase of temperature was noted. The reaction, which was followed by ultraviolet spectroscopy proceeded rapidly. After two hours in the dark at room temperature ethylene glycol (0.39 ml) was added and mixed. On standing for one hour the reaction mixture was partitioned between aqueous sodium bicarbonate and benzene washed with water and dried over anhydrous sodium sulphate. After removing the solvent the expected acetoxy dialdehyde (60) 173.4 mg) was obtained. T.L.C. showed one spot. Recrystallization from benzene-petroleum ether (65-110°C) produced an analytical sample of trans-anti-trans-11,12-seco-2-methoxy-8β-acetoxy-10a-methyl-11,12-diformyl-4β,5,6,6a,7,8,9,10,10a,10b,11,12-dodecahydrochrysene (60) mp 135-137°C, infrared: 2750, 1730, 1715, 1678, 1602, 1501 cm⁻¹, ultraviolet: λ_max 225 (4.33), 255.5 (3.86), 321 (3.50) μm, λ_min 242.5 (3.75), 281 (2.70) μm, nmr: 8.87 (C-10a methyl, 3H, singlet), 8.01 (C-8 acetoxyl, 3H, singlet), 7.63 (C-10b, 1H, quartet, J₁₀b,₁₁ = 6 1/2 cps, J₁₀b,₄b = 12 cps), 6.23 (C-2 methoxyl, 3H, singlet), 5.5 (C-4b, 1H, multiplet), 5.3 (C-8, 1H, multiplet), 2.98 (C-3, 1H, quartet, J₁,₃ = 2 1/2 cps), 2.74 (C-1, 1H, doublet), 2.74 (C-4, 1H, doublet, J₃,₄ = 9 cps), 0.50 (C-11, 1H, doublet, J₁₀b,₁₁ = 6 1/2 cps), -0.27 (C-12, 1H, singlet), found: C, 70.96; H, 7.46; O, 21.84, calculated for C₂₂H₂₈O₅: C, 70.94; H, 7.58; O, 21.44, MW 327.44, empirical formula C₂₂H₂₈O₅.

Since chromatography of this compound gave a very poor recovery it
was used directly for the next reaction, both these reactions being carried out on the same day.

**Aldol condensation of the dialdehyde (60)**

A solution of crude dialdehyde (60) (480 mg) in methanol (110 ml) was added to a solution of sodium hydroxide (100 mg in 1.4 ml water). Reflux was continued for three hours, after which time the reaction mixture was partitioned between chloroform and water several times. After drying over sodium sulphate and removing the solvent, a crude orange reaction product (67) 397 mg), T.L.C. showed an intense orange fluorescent spot when sprayed with antimony trichloride-acetic acid (1:1) and heated in the oven. Recrystallization from benzene-petroleum ether (65-110°C) gave an analytical sample of C-nor-2-methoxy-8β,11-dihydroxy-10a-methyl-10b-formyl-4β,5,6,6a,7,8,9,10,10a,10b,11-undecahydrachrysene (67) mp 192°C, infrared: 3380, 2740, 1713, 1697, 1616, 1588, 1482 cm⁻¹, ultraviolet: \( \lambda_{max} \) 284 (3.36), 2.89 (3.32) μm, \( \lambda_{min} \) 257 (2.74) μm, nmr: 8.91 (C-10a methyl, 3H, singlet), 6.6 (C-4b, 1H, quartet), 6.35 (C-8α, 1H, multiplet - obscured), 6.27 (C-2 methoxyl, 3H, singlet), 4.6 (C-11, 1H, doublet), 3.32 (C-3, 1H, quartet), 3.08 (C-4, 1H, doublet - overlaps with C-1), 3.02 (C-1, 1H, doublet), 0.30 (C-10b formyl, 1H, doublet), found: C, 72.66; H, 7.85; O, 19.49, calculated for \( C_{20}H_{26}O_4 \): C, 72.70; H, 7.93; O, 19.37, MW 330.41, empirical formula \( C_{20}H_{26}O_4 \), MS (atlas) parent peak 330, prominent peaks 158, 171, 172, 173, 174, 175, 186, 204, 213, 225, 235, 251, 269, 279, 284, 297, 312, 328.
Acetylation of the dihydroxy aldehyde (67)

Upon acetylang the analytical sample of the above C-nor-dihydroxy aldehyde under the usual conditions a 85% yield of C-nor-2-methoxyl-11-diacetoxy-10a-methyl-10b formyl-4b,5,6,6a,7,8,9,10, 10a,10b,11-undecahydrochrysene (68) was obtained, mp 158.5-159.5°C, ultraviolet: \( \lambda_{\text{max}} \) 222 (3.91), 286 (3.50), 291 (3.44) \( \mu \), \( \lambda_{\text{min}} \) 252 (2.57) \( \mu \), nmr: 9.02 (C-10a methyl, 3H, singlet), 8.02 (C-8B acetoxyl, 3H, singlet), 7.84 (C-11 acetoxyl, 3H, singlet), 6.58 (C-4b, 1H, quartet, \( J_{4b,5a} = 7 \) cps, \( J_{4b,5b} = 12 \) cps), 6.35 (C-2 methoxyl, 3H, singlet), 5.30 (C-8a, 1H, multiplet), 2.51 (C-1, 1H, doublet), 2.32 (C-3, 1H, quartet), 2.26 (C-11, 1H, singlet), 2.00 (C-4, 1H, doublet), 0.10 (C-10b formyl, 1H, singlet), Found: C, 69.81; H, 7.40; O, 22.79, calculated for \( \text{C}_{24}\text{H}_{30}\text{O}_{6} \): C, 69.54; H, 7.30; O, 23.16, MW 414.48 empirical formula \( \text{C}_{24}\text{H}_{30}\text{O}_{6} \), MS (atlas) parent peak - not visible, prominent peaks 158, 172, 251, 266, 211, 324, 326, 356.

Deacetyl-deformylation of the diacetate aldehyde (68)

The diacetate (68) was dissolved in glacial acetic acid (15.0 ml) containing sodium acetate (50 g - 4 molar) and acetic anhydride (3 ml) and refluxed for 20 hours. The reaction mixture was poured into water, partitioned between aqueous sodium bicarbonate-benzene, washed with water and dried over sodium sulphate. After removal of the solvent the crude product was chromatographed on 50 g of alumina. Elution with benzene-hexane (1:9) gave the olefin (71) (621 mg, 57.6% yield). Elution with chloroform gave a polar material (521 mg) which was reacted once more and worked up in the above manner to give more
olefin (71) (293 mg). The overall yield was 84.8%. Crystallization of this compound from hexane-benzene gave an analytical sample of large plates which was trans-C-nor-2-methoxy-8β-acetoxy-10a-methyl-4b,5,6,6a,7,8,9,10,10a,monahydrochrysene (71), mp 140-141°C, infrared: 1731, 1609, 1573, 1480, 1470, 1447 cm⁻¹, ultraviolet: λmax 227 (4.41), 239 (4.21), 263 (3.88), 293 (3.54), 305 (3.51) μm, λmin 248 (3.75), 289 (3.47), 301 (3.42) μm, nmr: 9.11 (C-5α, 1H, multiplet - by spin decoupling), 8.89 (C-10a methyl, 3H, singlet), 8.02 (C-8β acetoxy, 3H, singlet), 7.61 (C-5β, 1H, multiplet, J5α,5β = 13 cps, J4b,5β = 6 1/2 cps, J5β,6β = J5β,6α = 3 cps), 6.72 (C-4b, 1H, quartet, J4b,5β = 6 1/2 cps, J4b,5α = 12 1/2 cps), 6.27 (C-2 methoxy, 3H, singlet), 3.80 (C-11, 1H, singlet), 3.40 (C-3, 1H, quartet), 3.19 (C-1, 1H, doublet), 2.86 (C-4, 1H, doublet), found: C, 77.55; H, 7.97; O, 14.48, calculated for C21H26O3: C, 77.27; H, 8.03; O, 14.71, MW 326.42, empirical formula C21H26O3, MS (atlas) parent peak 326, prominent peaks 158, 172, 249, 251, 311, 324.

Catalytic hydrogenation of the olefin (71)

The olefin (71) (47 mg) was dissolved in ethanol (10 ml) was hydrogenated over palladium on charcoal (100 mg) at slightly over one atmosphere for 24 hours. The reaction mixture was diluted with ethanol (40 ml) and filtered. The filtrate was evaporated and the residue dissolved in chloroform and filtered again to leave a clear gum. The nmr spectrum showed that no olefinic proton was present. On crystallization from methanol an analytic sample of trans-syn-cis-C-nor-2-methoxy-8β-acetoxy-10a-methyl-4b,5,6,6a,7,8,9,10,10a,10b,11-
undecahydrochrysene (72), mp 98.5-100°C, infrared: 1727, 1620, 1586, 1490, 1475 cm⁻¹, ultraviolet: \(\lambda_{\text{max}}\) 207 (3.97), 219 (3.88), 282 (3.45), 288 (3.41) mu, \(\lambda_{\text{min}}\) 214 (3.86), 245 (2.11), 286 (3.38) mu, nmr: 8.99 (C-10a methyl, 3H, singlet), 8.03 (C-8 beta acetoxy, 3H, singlet), 7.89 (C-10 beta, 1H, quintet, \(J_{10a,1l} = 7\) 1/2 cps, \(J_{10b,1l} = 12\) cps), 7.43 (C-11 beta, 1H, quartet, \(J_{11a,1l} = 15\) cps), 7.26 (C-11 alpha, 1H, quartet), 7.00 (C-4 beta, 1H, quintet, \(J_{4b,10b} = J_{4b,5a} = 6\) cps, \(J_{4b,5a} = 12\) cps), 6.31 (C-2 methoxyl, 3H, singlet), 5.33 (C-8 alpha, 1H, multiplet), 3.43 (C-3, 1H, quartet), 3.29 (C-4, 1H, doublet), 3.05 (C-1, 1H, doublet), found: C, 76.52; H, 8.81; O, 14.67, calculated for \(C_{21}H_{28}O_3\): C, 76.79; H, 8.59; O, 14.61, MW 328.44, empirical formula \(C_{21}H_{28}O_3\), MS (atlas) parent peak 328, prominent peaks 146, 158, 159, 160, 173, 186, 197, 214, 225, 227, 253, 268.

**Birch reduction of the olefin (71)**

The olefin (71) (272 mg) was dissolved in t-butanol (20 ml) and tetrahydrofuran (25 ml) in a three necked flask. Ammonia (190 ml) was condensed in and lithium (2 g) was added. After stirring under reflux for 40 minutes the blue colour disappeared. The ammonia was evaporated in a stream of nitrogen. The residue was partitioned between benzene-ethyl ether and water. The benzene layer was washed with water and dried over sodium sulphate. On removal of the solvent a partly crystalline material (317 mg) was obtained. Chromatography on alumina (35 g, Grade III) after a one and one-half hour reflux in methanol (50 ml) and 12 N hydrochloric acid (2.5 ml). Elution with benzene-ethyl acetate (9:1) gave four fractions (183 mg). The first
(29 mg) fraction showed two similar coloured spots on antimony trichloride-acetic acid (1:1) sprayed silica TLC plate. The remaining three fractions (154 mg - 66%) appeared to consist of only one of these substances. The first fraction (29 mg) was not further investigated.

**Reductive hydroboration of the olefin (71)**

Diborane generated by the slow addition of sodium borohydride (0.6 g) in diglyme (30 ml) to boron trifluoride etherate (5 ml) in diglyme (20 ml) was passed in a stream of nitrogen into a solution of the olefin (71) (225 mg) in diglyme (30 ml). Generation of the diborane took two hours and the solution of olefin was allowed to stand overnight in contact with the gas. One drop of water was added followed by propionic acid (7 ml) and the mixture was heated under reflux for five hours, poured into water and extracted with ethyl ether. The ether extract was washed with dilute aqueous alkalic sodium chloride solution and dried over magnesium sulphate. The solvent was removed to give a brown gum (290 mg). This material showed several blue spots on TLC when sprayed with antimony trichloride. This material (290 mg) was dissolved in a mixture of methanol (35 ml) water (15 ml) and potassium carbonate (1 g). Reflux was maintained for two hours. The product was partitioned between chloroform and water and dried over sodium sulphate. The residue was reacetylated in the usual manner. The usual workup gave an oil (236 mg) which was chromatographed on alumina (50 g, Grade III). Elution with hexane-benzene (17:3)
gave (69 mg) a material with \( R_F \) comparable to that of the two birch reduction products of the reaction immediately above. Further elution with he:ane-benzene (3:1) gave a complex mixture (121 mg) not further investigated. The major product (32 mg, 14%) after two preparative TLC's of the first fractions was submitted to nmr. The product appeared to consist of two isomers in a ratio of 5:1 in favour of what appears to be the trans-syn-cis-C-nor-2-methoxy-8β-acetoxy-10α-methyl-4β,5,6,6a,7,8,9,10,10a,10b,11-undecahydrochrysene (72a). The ratio was estimated from the doubling of the methoxyl acetoxy and methyl peaks, the C-ring protons appeared to be identical.

Oxidative hydroboration of the olefin (71)

The olefin (130 mg) and the ethyl ether adduct of boron trifluoride (0.5 ml) were dissolved in ethyl ether (10 ml) and stirred under nitrogen at 0°C. Lithium aluminum hydride (130 mg) in ether (15 ml) was added gradually over forty-five minutes. Stirring was continued for two hours during which time the temperature was allowed to rise to 20°C. The solution was worked up in the usual manner and 70% ethanol (10 ml) containing sodium hydroxide (0.25 g) was added to the residue. Hydrogen peroxide solution (3 ml, 20%) was added dropwise. When effervescence subsided the solution was heated to 70°C. Further effervescence was observed for ten minutes. The solution was cooled, diluted, and neutralized with acid. This solution was partitioned between water and chloroform. The product (125 mg) was purified by preparative TLC on silica gel "GF", 0.5 mm thick, developed with ethyl acetate:petroleum ether (2:1). Bands
were located by water spray. The main band was removed and extracted to give a 52% yield (68 mg) of trans-anti-trans-C-nor-2-methoxy-88-dihydroxy-10a-methyl-4b,5,6,6a,7,8,9,10,10a,10b,11-undecahydrochrysene (72b) mp 180-181°C, nmr: 8.97 (C-10a-methyl, 3H, singlet), 8.39 (C-8,11 hydroxyls, 2H, singlets - removed by D₂O exchange), 6.86 (C-4b, 1H, quintet, J₀b,10b = 12 1/2 cps, J₄b,5a = J₄b,5β = 6 1/4 cps), 6.3 (C-8a, 1H, multiplet), 6.24 (C-2 methoxyl, 3H, singlet), 4.91 (C-11, 1H, doublet, J₁₀a,11 = 10 cps), 3.27 (C-3, 1H, quartet, J₁,3 = 2 1/2 cps), 3.07 (C-1, 1H, doublet, J₃,4 = 8 cps), 2.98 (C-4, 1H, doublet).

Birch Reduction of Anisole Compounds

Reduction and hydrolysis of the trans-anti-cis acetate (44b)

The trans-anti-cis acetate (9.4 g) was dissolved in t-butanol (120 ml) and tetrahydrofuran (150 ml) in a three necked flask which had been flame dried and fitted with a dry ice condenser. Dry ammonia (400 ml) was condensed into the flask. Lithium (6 g) was added and the mixture stirred for six hours. Addition of ethanol destroyed the excess lithium. After removal of the ammonia in a stream of nitrogen the residue was poured into water and the butanol and tetrahydrofuran were distilled. The mixture was cooled to room temperature and filtered. The white solid (8.7 g) was crystallized from hexane to give an analytical sample of trans-anti-cis-2-methoxy 88-hydroxy-10a-methyl-1,4,4b,5,6,6a,7,8,9,10,10a,10b,11,12-tetra-decahydrochrysene (80) mp 129-130°C, nmr: 9.14 (C-10a methyl, 3H, singlet), 8.23 (C-8 hydroxyl, 1H, singlet - removed with D₂O), 6.50
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(C-2 methoxyl, 3H, singlet), 6.10 (C-8α, 1H, unresolved multiplet),

found:  C, 80.21; H, 10.21; 0, 9.53, calculated for C_{20}H_{30}O_{2}:  C, 79.42; H, 10.00; 0, 10.58, MW 302.44, empirical formula C_{20}H_{30}O_{2}, MS (atlas) parent peak 302, prominent peaks 140, 147, 159, 160, 161, 173, 175, 176, 177, 187, 213, 215, 283, 298, 300.

The crude enol (80) (8.7 g) from the preceding reaction was dissolved in methanol (500 ml) and 6-N hydrochloric acid (50 ml) followed by reflux for twelve hours. After partitioning between chloroform-water, drying over sodium sulphate, and evaporating the solvent gave the crude product (8.1 g). Chromatography on alumina (400 g, Grade III) gave a complex mixture (1.4 g) in the first fractions were the eluent was benzene-chloroform (9:1). The latter fractions with the same eluent consisted of a white solid (0.79 g) which on crystallization from hexane-acetone gave an analytical sample of trans-anti-cis-2-keto-8 hydroxy-10α-methyl-1,3,4,4b,5,6,6a,7,8,9,10,10α,10b,11,12-hydrochrysene, mp decomposed >140°C, ultraviolet: \( \lambda_{\text{max}} \) 208 (3.38), 286 (1.59) μm, \( \lambda_{\text{min}} \) 274 (1.56) μm, nmr: 9.15 (C-10α methyl, 3H, singlet), 8.36 (C-8β, 1H, singlet - removed by D_{2}O), 7.28 (C-1, 2H, broad singlet), 6.43 (C-8, 1H, septet), found:  C, 79.38; H, 9.88; 0, 11.86, calculated for C_{19}H_{28}O_{2}:  C, 79.12; H, 9.79; 0, 11.10, MW 288.41, empirical formula C_{19}H_{28}O_{2}, MS (atlas) parent peak 288, prominent peaks 145, 146, 147, 158, 159, 160, 161, 162, 172, 173, 179, 186, 199, 249, 251, 268, 270, 286.

The desired material (4.6 g) was eluted with benzene-chloroform (4:1). Recrystallization from hexane-acetone gave an analytical sample of trans-anti-cis-2-keto-8-hydroxy-10α-methyl-3,4,4a,4b,5,6,6a,7,8,9,10,10α,10b,11,12-pentadecahydrochrysene (78). This compound was
characterized by Nagata\textsuperscript{96}, mp 199-202°C, nmr: 8.97 (C-10a methyl, 3H, singlet), 8.04 (C-8 hydroxyl, 1H, singlet, removed with D\textsubscript{2}O), 6.42 (C-8a, 1H, septet), 4.16 (C-1, 1H, singlet), found: C, 78.91; H, 9.52; O, 11.57, calculated for C\textsubscript{19}H\textsubscript{28}O\textsubscript{2}: C, 79.12; H, 9.79; O, 11.10, MW 283.41, empirical formula C\textsubscript{19}H\textsubscript{28}O\textsubscript{2}.

Reduction and hydrolysis of the trans-anti-trans alcohol (42a)

A solution of trans-anti-trans alcohol (1.63 g) in dry t-butanol (25 ml) and dry tetrahydrofuran (30 ml) was added to dry ammonia (80 ml). Lithium (1.1 g) was added and the mixture stirred under reflux for six hours. Addition of ethanol destroyed the excess lithium and the ammonia was evaporated under a stream of nitrogen. The residue was partitioned between benzene and water. Removal of the solvent after drying left a white solid (1.67 g). Crystallization from benzene-hexane provided an analytical sample of trans-anti-trans-2-methoxy-8B-hydroxy-10a-methyl-1,4,4b,5,6,6a,7,8,9,10,10a,10b,11,12-tetradecahydrochrysene (77) mp 124.5-127°C, infrared: 3238, 1696, 1668, 1228 cm\textsuperscript{-1}, nmr: 9.24 (C-10a methyl, 3H, singlet), 8.02 (C-8 hydroxyl, 1H, removed with D\textsubscript{2}O), 6.54 (C-2 methoxy, 3H, singlet), 5.44 (C-3, 1H, multiplet), found: C, 79.54; H, 9.80; O, 10.66, calculated for C\textsubscript{20}H\textsubscript{30}O\textsubscript{2}: C, 79.42; H, 10.00; O, 10.58, MW 302.44, empirical formula C\textsubscript{20}H\textsubscript{30}O\textsubscript{2}, MS (atlas) parent peak 302, prominent peaks 140, 147, 161, 173, 174, 175, 176, 186, 188, 213, 215, 285, 287, 300.

The methyl enol (77) (4.4 g) was dissolved in méthanol (100 ml) and 12-N-hydrochloric acid (10 ml). Reflux was continued for three hours after which the reaction mixture was partitioned between
ethyl ether and water. Upon removal of solvent, to give a white solid (3.7 g). Several crystallizations from hexane-benzene gave an analytical sample of trans-anti-trans-2-keto-8β-hydroxy-10a-methyl-3,4,4a,4b,5,6,6a,7,8,9,10,10a,10b,11,12-pentadecahydrochrysene (77), mp 182-183°C, infrared: (nujol) 3425, 3350, 1671, 1652, 1623, 1617 cm\(^{-1}\), ultraviolet: \(\lambda_{\text{max}}\) 239.5 (4.23), 308 (1.91) \(\mu\), nmr: 9.24 (C-10a methyl, 3H, singlet), 7.86 (C-8 hydroxyl, 1H, singlet removed by D2O), 6.41 (C-8a, 1H, septet), 4.22 (C-1, 1H, singlet), found: C, 79.21; H, 10.01; O, 10.78; calculated for C\(_{19}\)H\(_{28}\)O\(_2\): C, 79.12; H, 9.79; O, 11.10, MW 288.41, empirical formula C\(_{19}\)H\(_{28}\)O\(_2\), MS (atlas) parent peak 288, prominent peaks 110, 134, 147, 160, 165, 179, 228, 246, 260, 270.

Birch reduction of the C-nor-D-homo olefin (71)

The olefin (350 mg) was dissolved in t-butanol (15 ml) and tetrahydrofuran (20 ml). Dry ammonia was condensed into the three-necked flask and lithium (1 g) was added. After refluxing for five hours the blue colour disappeared. The ammonia was evaporated in a stream of nitrogen. The residue was partitioned between benzene and water. The dry solvent was evaporated to give a crystalline product. The product was dissolved in methanol (100 ml) and 12-N-hydrochloric acid (5 ml). The mixture was refluxed for three hours before the usual simple workup. Chromatography on alumina (30 g, Grade III) gave a mixture (2.48 mg) when the eluent was benzene-ethyl acetate (9:1). Several crystallizations gave an analytical simple of trans-2-keto-8β-hydroxy-10a-methyl-3,4,4a,4b,5,6,6a,7,8,9,10,10a,
10β,11-tetradecahydrochrysene (73), mp 178-180°C, infrared: 1727, 1620, 1586, 1490, 1475 cm\(^{-1}\), ultraviolet: \(\lambda_{\text{max}}\) 242 (4.19) μm, nmr: 8.99 (C-10α methyl, 3H, singlet), 7.78 (C-8 hydroxyl, 1H, singlet - removed by D\(_2\)O), 6.45 (C-8α, 1H, septet), 4.07 (C-1, 1H, broad singlet), found: C, 78.51; H, 9.58; O, 11.91, calculated for C\(_{18}\)H\(_{26}\)O\(_2\): C, 78.79; H, 9.55; O, 11.66, MW 214.39, empirical formula C\(_{18}\)H\(_{26}\)O\(_2\).

**Enamine Alkylation of trans-anti-trans-α,β-unsaturated ketone (77)**

The conjugated ketone (260 mg) was dissolved in a mixture of benzene (11 ml) and pyraolidine (0.5 ml) before refluxing for three hours during which time water was removed by azeotropic distillation. The ultraviolet of the residue spectrum showed a strong peak at 276 μm and no significant absorption at 239 μm. This indicated that the yield of dienamine was quantitative. Dry methanol (6 ml) and dry methyl iodide (1 ml) where added to the residue and the solution was refluxed for 56 hours. The solvent was removed and replaced with methanol (4 ml), water (1 ml), acetic acid (0.4 ml) and sodium acetate (0.5 g anhydrous). This solution was refluxed for 250 minutes. The reaction mixture was partitioned between water and chloroform. The organic layer was dried over sodium sulphate. The removal of the dry solvent after filtration left an oily residue (350 mg). Column chromatography on alumina (20 g, Grade II-III) gave five fractions, the first containing the methylated material. Preparative TLC gave a semi crystalline oil (18 mg) which crystallized to give a compound melting over a seven degree range. The ultraviolet spectrum had the following absorbances: \(\lambda_{\text{max}}\) 250, 309 μm; \(\lambda_{\text{min}}\) 287 μm, MS (atlas)
parent peak 302, prominent peaks 99, 123, 124, 136, 147, 149, 161, 175, 176, 177, 260, 284, MW 302.44, empirical formula $C_{20}H_{30}O_2$.

The acetate of this compound was prepared but so far has not been crystallized. The ultraviolet of this compound as expected is superimpossable with that of the alcohol, MW 344.48, MS (atlas) parent peak 344, prominent peaks, 145, 147, 149, 161, 171, 177, 183, 218, 257, 269, 272, 284, 302. 50% of the crude starting material (130 mg) was recovered in the remaining four fractions.

Enolate Trapping and methylation birch reduction of the trans-anti-cis-α,β-unsaturated ketone (78)

A solution of the ketone (1.44 g) in dry tetrahydrofuran (80 ml) was added dropwise to a scrupulously dry ammonia solution (150 ml) of lithium (160 mg). The solution was stirred for twenty minutes after which time the dry ice condenser was replaced by a dry water condenser. The ammonia was removed in a stream of dry nitrogen while more tetrahydrofuran (120 ml) was added. The solution was refluxed for twelve minutes to remove the last traces of ammonia. Methyl iodide (20 ml) was added and the solution was refluxed for three hours. The mixture was poured into water and extracted with benzene. The benzene extract was washed with water dried and evaporated to yield an oil (1.63 g). This oil, when chromatographed on alumina (200 g, Grade III). The eluent was benzene with increasing amounts of chloroform. The volumes of each fraction collected was 200 ml. The first two fractions (98 mg, 208 mg respectively) were a complex mixture and were not further investigated. The third fraction
(700 mg) contained one major component. This fraction was subjected to 0.19 M bromine (10 ml) after being dissolved in acetic acid (5 ml). This mixture was refluxed for one hour with magnesium oxide (3 g) in dimethyl formamide (30 ml). The crude product was chromatographed on alumina (35 g, Grade III). Eluting with light petroleum ether-benzene (4:1), the first six fractions were a complex mixture while the next seven contained 281 mg of a pure compound. Sublimation of this material gave an analytical sample of trans-anti-cis-2-keto-3-methyl-8β acetoxy-10α-methyl-4,4a,4b,5,6,6a,7,8,9,10,10α,10b,11,12,13-heptadecahydrochrysene (73), mp 188-189°C, infrared: 1731, 1670, 1482 cm⁻¹, ultraviolet: λmax 240 (3.98) μm, nmr: 8.77 (C-10α methyl, 3H, singlet), 8.23 (C-3 methyl, 3H, quartet, J3,4 = 1.4 cps, J3,4a = 2.2 cps), 7.89 (C-1β, 1H, quartet, J1α,1β = 16 cps, J1α,13 = 315 cps, J18,13 = 12 cps), 7.56 (C-1α, 1H, quartet), 5.33 (C-8, 1H, septet), 3.19 (C-4, 1H, broad singlet), found: C, 76.90; H, 9.42; O, 13.68, calculated for C22H32O3: C, 76.70; H, 9.36; O, 13.93, MW 344.48, empirical formula C22H32O3, MS (atlas) parent peak 344, prominent peaks 145, 147, 149, 159, 161, 174, 185, 200, 214, 260, 269, 274, 284, 316, 342.

Enolate synthesis and methylation of the trans-anti-trans-α,β-unsaturated ketone (77)

The tetrahydropyran of the ketone was prepared by dissolving the ketone (624 mg) in freshly distilled tetrahydropyran (10 ml) along with several milligrams of toluene-p-sulfonic acid. After sixteen hours powdered potassium carbonate was added. Stirring was continued
for six hours. The mixture was diluted with ether filtered and the filtrate evaporated to leave a gum (1040 mg) [some loss at this point]. A solution containing most of the tetrahydropyranyl ether ketone in dry tetrahydrofuran (25 ml) was added to scrupulously dry solution of ammonia (50 ml) containing lithium (49 mg) a further amount of lithium (20 mg) was added to maintain the blue colour. The solution was allowed to evaporate slowly while more tetrahydrofuran (50 ml) was added. When the ammonia was completely removed methyl iodide (20 ml), which had been freshly distilled was added and the solution refluxed for three hours. Most of the solvent was distilled off and the rest partitioned between benzene and water. The dried benzene layer was evaporated and replaced with 3% aqueous oxalic acid (20 ml) in ethanol (25 ml). After the usual workup the residue (890 mg) was chromatographed on alumina (85 g, Grade III). Benzene-chloroform (4:1) gave a ketone fraction (393 mg). This fraction was rechromatographed on alumina (60 g, Grade III). The center fractions (278 mg) were crystalline. Recrystallization from acetone-hexane gave an analytical sample (65 mg) of trans-anti-trans-l-methyl-2-keto-8-hydroxy-10a-methyl-1,3,4,4a,4b,5,6,6a,7,8,9,10,10a,10b,11,12,13-heptadecahydrochrysene (84) mp 182-183°C, ultraviolet: $\lambda_{max}$ 280 μm (very weak), nmr: 9.26 (C-10a methyl, 3H, singlet), 9.02 (C-1 methyl, 3H, doublet), 8.24 (C-8 hydroxyl, 1H, singlet removed by D₂O), 6.43 (C-8α, 1H, septet), MS (atlas) parent peak 304, prominent peaks 149, 232, 247, 271, 272, 286, 290.

This crude ketone (213 mg) was acetylated in the usual manner. The acetate was treated with 0.19 M bromine in acidic acid (4.4 ml)
after the acetate was dissolved in acetic acid (7 ml). The product was refluxed with magnesium oxide (2 g) in dimethyl formamide (25 ml) for one hour. The product, which was a complex mixture, was chromatographed on alumina (35 g, Grade III). Elution was with light petroleum ether containing increasing concentrations of benzene. Early fractions contained the starting material (85 mg). Later fractions contained $\alpha,\beta$ unsaturated material (79 mg). In these fractions small amounts of the wrong isomer were detected by ultraviolet spectroscopy. Preparative TLC isolated the required material (12 mg). This compound was identical with the acetylated compound isolated from enamine alkylation.
BIBLIOGRAPHY


(83) A. By, Unpublished Results.


(86) W.A.C. Gladstone. Unpublished Results.


