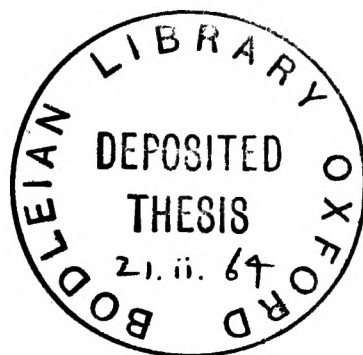


STUDIES IN THE SYNTHESIS
OF THE HIGHER TERPENES

A Thesis submitted for the Degree of
Doctor of Philosophy

by

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INTRODUCTION

The triterpenes form a group of natural products generally containing thirty carbon atoms, representing a multiple of a basic C_5 isopentane (isoprene) unit. The structural relationship of the triterpenes is given by the biogenetic isoprene rule^(1,2) which states that the combination of the basic isoprene unit leads to the formation of aliphatic molecules such as geraniol (1), farnesol (2), geronyl-geraniol (3) and squalene (4) which by cyclisation and rearrangement give rise to mono- (C_{10}) , sesqui- (C_{15}) , di- (C_{20}) , tri- (C_{30}) , tetra- (C_{40}) and polyisoprenoid terpenes ($n C_5$).

The triterpenes are widely distributed in the vegetable kingdom but are present to only a limited extent in the animal kingdom, molecules such as lanosterol (5) and agnosterol (6) which are present in wool fat do not conform to the isoprenoid ruling but still tend to be considered as terpenes rather than steroids.

Many reviews of the chemistry and biogenesis of triterpenes have been made in recent years.^(3,4,5,6) Because of the tremendous expansion in the volume of literature on terpenes, and also the particular nature of this thesis, only the triterpenes will be mentioned in detail in this introduction. The triterpenes can be separated into two major groups, the squalenoid and non-squalenoid. The

former is only a small group containing molecules related to squalene⁽⁷⁾ by varying degrees of cyclisation. Examples are hydroxyhopanone (7),^(8,9) the dammarene diols (8),⁽¹⁰⁾ α -onocerin (9)⁽¹¹⁾ and ambrein (10).⁽¹²⁾

The non-squalenoid molecules, derived from squalene by cyclisation and molecular rearrangements include tetracycles and pentacycles. Variations in stereochemistry in the former at C₁₃, C₁₄, C₁₇ and C₂₀ give rise to many isomeric compounds with very different physical properties, lanosterol (5),⁽¹³⁾ tirucallol (11b),⁽¹⁴⁾ euphol (11a)⁽¹⁵⁾ being typical examples. Also the ergostane-cholestane relationship of the steroid series is repeated in the triterpenes with molecules such as eburicoic acid (12) and the polyporenic acids A and C (13,14),^(16,17) the extra carbon atom being located at C₂₄ and often existing as a methylene group.

By far the largest group of triterpenes, the pentacyclics, are derived from six fundamental carbon skeletons. These are oleanane (15), ursane (16), lupane (17), taraxastane (18), taraxerane (19) and friedelane (20).

Because of its importance, the biogenetic formation of triterpenes is illustrated by reference to the formation of the dammarene diols (8). This will serve to show many of the major theoretical points and also to throw light on the origin of one of the major raw materials used in section A of the experimental work which follows. The sequence to

be described is drawn out on plate III.

The biosynthesis of squalene is believed to involve the intermediates, acetate, mevalonate, isopentenyl pyrophosphate (23), geranyl pyrophosphate (1a) and farnesyl pyrophosphate (2a). Mevalonic acid is built up from acetate using acetyl coenzyme A as the donor of two carbon atoms. The next major step is the phosphorylation of mevalonic acid, (18,19,20,21,22) which leads via elimination and decarboxylation to isopentenyl pyrophosphate. (23) Successive condensations of the pyrophosphate intermediates then lead to the formation of all-trans-squalene. The cyclisation of squalene was initially of interest in relation to the formation of cholesterol (26) and lanosterol (5). With the knowledge of the origin of all the carbon atoms in the cholesterol nucleus (27), (29) Woodward and Bloch (24) and Dauben et al. (25) showed that the cyclisation followed the route shown (28) with subsequent 1,2-shifts of the marked methyl groups, (26,27) to give lanosterol (5) which was then converted to cholesterol (29). (30) It has in fact been demonstrated that lanosterol can be biosynthesised from squalene. (28)

The importance of lanosterol (31) in this scheme led Ruzicka (1,2) to postulate a similar sequence for the formation of all triterpenes. He assumed that squalene would take up potential chair and boat conformations in space and that a species such as OH^+ would initiate a concerted pattern

of ring closures^(32,33) obeying antiplanar, cationic 1,2-addition, 1,2-rearrangement and 1,2-elimination. The cation intermediates were represented as bridge structures as in (25 a and b). In particular the chair, chair, chair boat conformation in (24) will give rise to the cations (25 a and b) from which the dammarene diols (3) can arise by the addition of OH^- .

Variations in conformation of squalene or its partially cyclised cationic intermediates can give rise to the whole range of tetracyclic and pentacyclic triterpenes.

The triterpenes have few reactive centres and consequently the elucidation of their structures has been extremely difficult. The difficulties have also been enhanced by the fact that many of the triterpenes form only a minor part of the natural product under investigation and hence are isolated in only minute quantities. Their investigation has, therefore, necessarily involved the utilisation of new techniques for analysis and detection of functional components of the molecule. Physical methods⁽³⁴⁾ such as infra-red and ultra-violet spectroscopy, molecular rotation differences, optical rotatory dispersion, nuclear magnetic resonance, gas-liquid chromatography, adsorption chromatography and even mass spectrometry are being used constantly. A knowledge of the geometry of the molecules has become increasingly important in explaining many of the

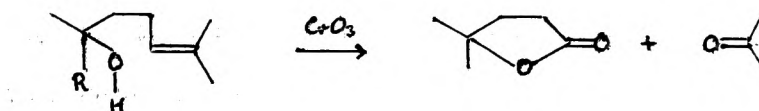
chemical reactions which occur, for example the contraction of ring A in tirucallenol when the β -hydroxyl group is treated with phosphorus pentachloride.

The determination of a few key structures led to the identification of many others and the classical methods, particularly of complete degradation were rapidly replaced by interconversions and comparisons of the physical properties described above. The investigation into the structure of the dammarene diols (8)^(10,40) will serve as a useful illustration of the methods now being applied to determine the structure of such molecules.

Molecular weight determinations and analysis showed the diols to be $C_{30}H_{52}O_2$ typical of many of the tetracyclic triterpene diols already known. Titration with perbenzoic acid showed the presence of one double bond and after hydrogenation the molecule was saturated to tetranitromethane. An ultra-violet spectrum showed no appreciable end absorption so characteristic of molecules such as lanosterol (5) and euphol (11a) containing an endocyclic tetrasubstituted double bond. An infra-red spectrum showed strong hydroxyl absorptions and absorptions were still present at 3620 cm.^{-1} after acetylation with acetic anhydride and pyridine suggesting the possibility of a tertiary hydroxyl group. Molecular rotation differences⁽³⁶⁾ indicated the presence of a 3β -hydroxyl group, an observation which was

substantiated both by the mode of formation of the diols⁽³⁷⁾ and also by the fact that the closely related dammaradienone (30a) showed a band at 1711 cm.^{-1} characteristic of a six-membered ring ketone and also gave a positive Zimmerman test, a reaction shown by Barton and de Mayo⁽³⁸⁾ to be specific for terpenes having a 3-oxo group.

Oxidation with chromium trioxide gave acetone and two isomeric compounds of molecular formula $\text{C}_{27}\text{H}_{42}\text{O}_3$ showing a saturated γ -lactone carbonyl absorption at 1785 cm.^{-1} . This suggested the presence of an isopropylidene group and conceivably the γ -lactone was formed by a cyclisation in the way illustrated if it was assumed a lanosterol type side chain was present.



Dehydration of both diol monoacetates with phosphorus oxychloride and pyridine led to compounds identical with dammaradienyl acetate (30b) and dehydration using the method of Christen *et al.*,⁽³⁹⁾ led to the formation of isotirucall-enyl and isoeuphenyl acetates. Ozonolysis of the products from the phosphorus oxychloride dehydrations led to the isolation of formaldehyde and both nor and hexakisnor ketones (31 and 32). The results of the oxidations, dehydrations and ozonolyses therefore indicated the presence of a C_{20} tertiary hydroxyl group and the existence of two diols was

explained by two differing configurations at C₂₀.

The transformation into isotirucallenyl and isoeuphenyl acetates determined the form and stereochemistry of the major part of the molecule apart from the configuration of the C₁₃ and C₁₇ hydrogen atoms, and the absolute orientation of the C₂₀ hydroxyls. Application of Ruzicka's biogenetic arguments^(1,2) favoured the presence of 13 β - and 17 α -hydrogens, this also appeared to be substantiated by the fact that the hexakisnor and norketones (32,31) were stable to prolonged strong alkali treatment.⁽⁴⁰⁾ The problem of C₁₃ and C₁₇ was solved by Ourisson and co-workers.^(41,42) Ourisson degraded Millis's hexakisnor and norketones (32,31) with peroxytrifluoro acetic acid to obtain the octakisnor derivative (33). By an elegant series of potential epimerisation and elimination reactions he demonstrated that the C₁₇ substituent was in its most stable orientation. He also derived the C₁₇ epimer for comparison purposes. The formation of two C₁₇ oxo-derivatives one with a C₁₃ α -proton and one with a C₁₃ β -proton and use of molecular rotation differences followed by optical rotatory dispersion techniques determined the absolute configurations of the octakisnor compounds which were directly related to the dammarene diols. It was therefore concluded that a 13 β -H and 17 α -H were present in the dammarene diols.

No convincing argument has been evolved for the absolute orientation of the C₂₀ hydroxyl.^(41,42) Nuclear magnetic

resonance studies have recently been carried out by Lehn.⁽⁸⁶⁾

Synthesis of Triterpenes.

Very few total syntheses of triterpenes have been recorded, and much of the early work was directed towards molecules which possessed elements of symmetry and were therefore relatively simple. X-ray analysis of the thiourea clathrate complex of squalene had shown it to have the all-trans-configuration⁽⁴³⁾ and it has been synthesised by Isler et al.⁽⁴⁴⁾ and by Cornforth, Cornforth and Mathew^(7,45) utilising 3,5-dichloropentan-2-one as the major carbon source.

The first total synthesis of a polycyclic triterpene is a further example of the interrelation and correlation of the tetracyclic molecules and lies in the conversion of the already synthesised cholesterol (29)^(46,47) to lanosterol (5), its 24,25-dihydro derivative and the two corresponding $\Delta^{7,9}$ (11) compounds⁽¹³⁾ by methylating suitably placed $\alpha\beta$ -unsaturated ketones and degrading and rebuilding the side chain. This constitutes a total synthesis not only of lanosterol but also of dihydrolanosterol, agnosterol (6) and dihydroagnosterol.

The synthesis of the more complex pentacyclic triterpenes has not followed the general steroid theme⁽⁴⁸⁾ of gradually building up the molecule from small units, but has laid emphasis on the fabrication of bulky units each having the correct stereochemistry, these units being then coupled and

cyclised. The reason for this type of synthetic approach is that difficulties are encountered in ensuring that the C_8 , C_{10} , C_{14} and C_{17} angular substituents, which are generally methyl, have the correct configuration, a factor which is more easily resolved in the coupling of two AB and DE or ABC and E units. Also the cyclisation of the symmetrical α -onocerin (9a) to the pentacyclic γ -onocerin (34a)⁽⁴⁹⁾ gave grounds for believing that acid induced ring closures of coupled AB, DE tetracycles, possessing similar centres for protonation would lead to the naturally occurring pentacyclic conformation in every case.

The synthesis of pentacyclic triterpenes has been approached by the following general procedures.

- 1) The cyclisation of squalene and its derivatives.
- 2) The linking of two bicyclic units representing rings AB and DE in the final molecule.
- 3) Procedures involving the use of a tricyclic intermediate to serve as a basis for rings ABC and also procedures where a tricyclic intermediate is a source of rings BCD.

The work on the cyclisation of squalene has been aimed chiefly at the synthesis of pentacyclosqualenes with the onocerane skeleton (35). By acid induced cyclisations Heilbron and co-workers⁽⁵⁰⁾ obtained what was probably a mixture of isomeric tetracyclosqualenes (36). Barton and

Overton⁽⁴⁹⁾ have shown that an analogous compound α -onocera-diendione (9b) gives β -onoceradiendione (37) under mildly acid conditions and γ -onocerenedione (34b) under strongly acid conditions. Pentacyclosqualene can be obtained by Wolf-Kishner reduction of the dione.

Attempts have been made to apply the Schenk photosensitised oxidation of olefins^(51,52) to introduce an oxygen function into a terminal isopropylidene group of the squalene molecule before cyclising but complex mixtures were obtained and simple model experiments indicated that the inserted hydroxyl group caused difficulties in cyclisation under the conditions used.

The combination of two bicyclic moieties representing AB and DE was first discussed by Halsall and Thomas.⁽⁵³⁾ Their attempt to carry out such a synthesis was, however, unsuccessful. The feasibility of such a route has nevertheless been demonstrated in the synthesis of olean-11,13-diene (41) by Corey and co-workers⁽⁵⁴⁾ and also by Barltrop, Littlehales and Rogers.⁽⁵⁵⁾ The latter workers derived the halide (42) of correct configuration by a degradative/synthetic process from sclareol (43) and used it to alkylate the racemic octalone (44) thereby obtaining the epimeric ketones (45). Reduction with lithium in liquid ammonia gave the mixture of trans- β -decalones (46a and 47a) which without further separation was treated with lithium methyl

to give the alcohols (46b and 47b). Cyclodehydration using aluminium chloride in nitromethane/ether gave after gas-liquid chromatographic purification a product identical in all respects with the mixed crystals of olean-13(18)-ene (48) and 18- α -olean-12-ene (49).

Corey and Sauers⁽⁵⁶⁾ electrolytically coupled the hydroxy-acid derived from the (-) lactone (50) to obtain the tetracyclic diol (51) which on treatment with phosphoryl chloride in pyridine gave γ -onocerene (52). The (-) lactone⁽⁵⁷⁾ was prepared by acid catalysed isomerisation of the (+)lactone (53) obtained from sclareol (43). In a similar manner Stork and co-workers⁽⁵⁸⁾ synthesised α -onocerin (9a) via the intermediate (54), which has also been independently synthesised by Church, Ireland and Marshall.⁽⁵⁹⁾

α -Onocerin (9a) was cyclised to give γ -onocerin (52b)⁽⁴⁹⁾ and the latter was converted to hopenone-I (55)⁽⁶⁰⁾ a product of dehydration and isomerisation⁽⁸⁾ of hydroxyhopenone (7). This constitutes a close approach to the synthesis of a pentacyclic triterpene.

Most other attempts to prepare (54) have relied on the alkylation of the decalone (56). This decalone was prepared by Halsall, Rodewald and Willis⁽⁶¹⁾ and by Woodward and his co-workers.⁽⁶²⁾ The former workers introduced the keto function by base-catalysed isomerisation of the epidioxide (57) produced by the addition of oxygen to the diene (58).⁽⁶³⁾

Unfortunately attempts to alkylate the blocked ketone (56) were unsuccessful.

Attempts to prepare the decalone (56) by Robinson ring extension of the ketone (59) by Willis,⁽⁶¹⁾ Sondheimer and Elad⁽⁶⁴⁾ and by Stork and Czruskovicz⁽⁶⁵⁾ have proved unsuccessful, Sondheimer and Elad reporting a yield of 2%.

Ireland and Marshall⁽⁶⁶⁾ have developed a very useful bicyclic intermediate (60) in good yield. Benzoquinone is condensed with butadiene and the trans-isomer is isolated via the diethylene ketal (61). After removing the ketal groups with dilute acid, lithium tri-t-butoxy aluminium hydride⁽⁶⁷⁾ is used to reduce one of the carbonyls and the other is removed by a Wolf-Kishner reduction. Oxidising the product (61a) with chromium trioxide in pyridine and protecting the active CH₂ next to the carbonyl with an n-butylthiomethylene group gave (62). Angular methylation was accomplished using methyl iodide and potassium t-butoxide,⁽¹⁾ the reaction giving preferentially the β -methylated product. Sodium borohydride reduction and an acid-catalysed rearrangement gave the unsaturated aldehyde (63), supposedly by initial formation of the hemithioacetal and its hydrolysis. The aldehyde (63) was reduced and the primary allyl alcohol was equilibrated⁽⁶⁸⁾ with ethyl vinyl ether to give (64), which on pyrolysis gave (60). This could be reduced to the alcohol with sodium borohydride or oxidised to the corresponding acid. The pyrolysis was stereospecific placing the

substituent into the unnatural α -orientation. This would not matter if the synthesis were completed by the Corey technique, for the acidic conditions of the cyclisation would epimerise this centre.

The same workers also showed that the formation of the epoxide of ^{*the ketone derived from the oxidation of (61a)*} (63) with perbenzoic acid and reduction with lithium aluminium hydride led to the introduction of the 3 β -hydroxyl group characteristic of triterpenes. The gem-dimethyl group at C₄, however, still remains to be inserted.

The acid from (60) can clearly be utilised in Kolbe coupling procedures and also simple operations can convert it into a derivative useful for the alkylation of a suitable bicyclic DE intermediate.

Acetylenic coupling has been investigated by Sondheimer and his co-workers.⁽⁷⁰⁾ The source of rings A and B was the ketone (65) which was subsequently converted into the ketone (66) by Cocker and Halsall⁽⁶⁹⁾ and by Sondheimer and Elad.⁽⁶⁴⁾ The latter workers condensed two molecules of the trans-decalone (66) and one of acetylene bis-magnesium bromide to obtain a mixture of meso (67) and racemic (68) tetracyclic diols. The racemic diol was converted into racemic dinoronocerane (69). The successful preparation⁽⁷¹⁾ of the acetylenic hydroxybenzoate (70) from the decalone (71) shows that the method is applicable to decalones containing methyl and protected hydroxyl substituents. It has been proposed⁽⁷¹⁾ to couple this acetylenic derivative with a

decalone such as (72a) as the first stage in the synthesis of a 3-hydroxylated oleanane system. Sondheimer and Rosenthal⁽⁷²⁾ prepared the cis- and trans-decalones (73) as a model for the DE rings by isomerising the 1,9-epoxy-10-methyl-decalin. This work was continued by Sondheimer and Wolfe⁽⁷³⁾ in the 7,7,10-trimethyl- Δ^1 ⁽⁹⁾-octalin system. The oxygen function was introduced by a Brown hydroboration⁽⁷⁴⁾ and the derived alcohol was oxidised to the cis- and trans-decalones (72b).

Diels-Alder coupling has been little used but one example is of interest. The tetracyclic diketone (74) has been synthesised⁽⁷⁵⁾ by reduction of the adduct (75) obtained from two molecules of the α -methylene ketone (76) which was itself obtained by cyclising farnesic acid. Attempts have been made to couple differing ketones (76 and 77)⁽⁷⁶⁾ in order to obtain precursors for the oleanane skeleton but as yet no definite product has been identified.

In a somewhat unusual attack on the triterpene molecule Ireland et al.⁽⁸²⁾ have also synthesised a potentially useful CD intermediate (94). The readily available keto alcohol (95)⁽⁸³⁾ gave the ketone ketal (96) by the following successive reactions:- catalytic reduction to the cis-decalin system, ketalisation of the saturated ketone and oxidation of the alcohol with Jones' reagent.⁽⁸⁴⁾ Treatment of (96) with methyl lithium gave a tertiary alcohol which was dehydrated with iodine and the resultant olefin was hydrated using the

Brown et al.⁽⁸⁵⁾ procedure of hydroboration. Further oxidation with Jones' reagent⁽⁸⁴⁾ gave (94).

Tricyclic intermediates have not been very much in vogue until recently. Johnson and Ireland⁽⁷⁷⁾ have recently synthesised the intermediate (73) which it is hoped will provide the basis for further elaboration to pentacyclic triterpenes such as siarasinolic acid (79). It is conceivable that this work is related to Ireland's⁽⁷⁸⁾ researches into the synthesis of (+)-sandaracopimaradiene (80) and (+)-pimaradiene (81). In the initial stages of this latter synthesis the tetralone (32) was converted into the tricyclic ketone (83) by the Cornforth, Robinson procedure⁽⁷⁹⁾ and then dimethylated using the Woodward technique.⁽¹³⁾ Conversion of the desoxy-methyl ether to the free phenol and reduction of the aromatic ring by ruthenium and hydrogen⁽⁸⁰⁾ gave (84) which was oxidised by Jones' reagent to the trans-anti-cis tricyclic ketone converted by filtration through alumina to the trans-anti-trans ketone(85).

Halsall and Mellor⁽⁸⁷⁾ have worked on the synthesis of a tricyclic BCD intermediate (36) via the bicyclic diene (87) with the intention of using the keto groups as active sites for the addition of rings A and E. The model compound (88) has been successfully prepared.

Ryback⁽⁸¹⁾ transformed elemadienolic and elemadienonic acids (90 and 91) into isotirucalleryl acetate (92) by a

route discussed in more detail later in this thesis. This compound was oxidised to the unsaturated ketone (93) with the object of obtaining by ozonolysis the tricyclic intermediate (39) from which tetra and pentacyclic triterpenes should be readily available.

The work described in this thesis is concerned firstly with the possible development and extension of the partial synthesis implicit in the Ryback⁽⁸¹⁾ approach. Secondly in continuation of the work of Littlehailes,⁽⁵⁵⁾ described earlier on p.10, attempts are described to synthesise a hydroxylated bicyclic AB intermediate related to (42) which is to be used in a similar approach to the pentacyclic system to give a triterpene containing the naturally occurring β -hydroxyl group.

REFERENCES TO INTRODUCTION

1. Ruzicka, Experientia, 1953, 9, 357.
2. Ruzicka, Proc.Chem.Soc., 1959, 341.
3. Simonsen and Owen, 'The Terpenes', Vols.I and II, (1947), Vol.III, (1952), Vols. IV and V, (1957), University Press, Cambridge.
4. de Mayo, 'The Chemistry of Natural Products', Vols. II and III. Interscience, New York-London, 1959.
5. Barltrop and Rodgers, Progress in Organic Chemistry, 1961, 5, 96.
6. Wagner and Folkers, Endeavour, 1961, 20, 177.
7. Cornforth, Cornforth and Mathew, J., 1959, 112 and 2539.
8. Fazakerley, Halsall and Jones, J., 1959, 1877.
9. Baddeley, Halsall and Jones, J., 1960, 1715.
10. Mills, J., 1956, 2196.
11. Barton and Overton, J., 1955, 2639.
12. Dietrich and Lederer, Helv.Chim.Acta, 1952, 35, 1148.
13. Woodward, Patchett, Barton, Ives and Kelly, J., 1957, 1131.
14. Arigoni, Jeger and Ruzicka, Helv.Chim.Acta, 1955, 38, 222.
15. Arigoni, Viterbo, Dunnenberger, Jeger and Ruzicka, Helv.Chim.Acta, 1954, 37, 2306.
16. Holker, Powell, Robertson, Simes, Wright and Gascoigne, J., 1953, 2422.
17. Halsall and Hodges, J., 1954, 2385.
18. Markley and Smallman, Federation Proc., 1960, 19, 240.
19. Loomis and Sattaile, Federation Proc., 1960, 19, 240.
20. Tchen. J.Biol.Chem., 1958, 233, 1100-3.

21. Levy and Popjak, Biochem.J., 1960, 75, 417.
22. Cornforth, Fletcher, Heillic and Popjak, Nature, 1960, 185, 923.
23. Chaykin, Law, Phillips, Tchen and Bloch, Proc.Acad.Sci. U.S.A., 1958, 44, 998.
24. Woodward and Bloch, J.Amer.Chem.Soc., 1953, 75, 2023.
25. Dauben, Abraham, Hotta, Chaikoff, Bradlow and Soloway, J.Amer.Chem.Soc., 1953, 75, 3038.
26. Cornforth, Cornforth, Pelter, Horning and Popjak, Proc.Chem.Soc., 1958, 112; Tetrahedron, 1959, 5, 311.
27. Maudgel, Tchen and Bloch, J.Amer.Chem.Soc., 1958, 80, 2589.
28. Bloch, Vitamins and Hormones, 1957, 15, 119.
29. Bloch, Helv.Chim.Acta, 1953, 36, 1611.
30. Alexander and Schwenk, Arch.Biochem.Biophys., 1957, 66, 381.
31. Clayton and Bloch, Federation Proc., 1955, 14, 194..
Tchen and Bloch, J.Amer.Chem.Soc., 1955, 77, 6085.
32. Tchen and Bloch, J.Amer.Chem.Soc., 1956, 78, 1516.
33. Tchen and Bloch, J.Biol.Chem., 1957, 226, 931.
34. Pinder, Chem.and Ind., 1961, 753, 1130.
35. Birch, Ann.Rep.Chem.Soc., 1950, 199.
36. Klyne, J., 1954, 1979.
37. Barton, Experientia, 1950, 6, 316.
38. Barton and de Mayo, J., 1954, ~~1979~~ 887
39. Christen, Dunnenberger, Roth, Heusser and Jeger, Helv.Chim.Acta, 1952, 35, 1756.
40. Mills and Werner, J., (1955), 3132.

41. Crabbe, Ourisson and Takanashi, Tetrahedron, 1958, 3, 279.
42. Biellmann, Crabbe and Ourisson, Tetrahedron, 1953, 3, 303.
43. Nicolaides and Laves, J.Amer.Chem.Soc., 1954, 76, 2596.
44. Isler, Ruegg, Chapard-dit-Jean, Wagner, and Bernhard, Helv.Chim.Acta, 1956, 39, 897.
45. Barltrop and Rogers, Quarterly Reviews, 1962, 16.
46. Cardwell, Cornforth, Duff, Holtermann, and Robinson, J., 1953, 361.
47. Woodward, Sondheimer, Taub, Heusler and McLamore, J.Amer.Chem.Soc., 1952, 74, 4223.
48. Fieser and Fieser "Steroids", Reinhold, New York.
49. Barton and Overton, J., 1955, 2639.
50. Heilbron, Owens and Simpson, J., 1929, 873.
51. Schenk, Angew.Chem., 1957, 69, 579.
52. Telfer, Part II. Thesis, Oxford, 1960.
53. Halsall and Thomas, J., 1956, 2431.
54. Corey, Hess and Proskow, J.Amer.Chem.Soc., 1959, 81, 5258.
55. Barltrop, Rogers and Littlehales, Tetrahedron Letters, 1962, No.10, 429.
56. Corey and Bauers, J.Amer.Chem.Soc., 1957, 79, 3925;
ibid., 1959, 81, 1757.
57. Ruzicka and Janat. Helv.Chim.Acta, 1931, 14, 645.
58. Stork, Davies and Meisels, J.Amer.Chem.Soc., 1959, 81, 5516.
59. Church, Ireland and Marshall, Tetrahedron Letters, 1961, No.1, 34.
60. Schaffner, Cagliotti, Arigoni and Jeger, Helv.Chim.Acta, 1958, 41, 152.

61. Halsall, Rodewald, and Willis, J., 1959, 2798;
Willis, D.Phil.Thesis, Oxford, 1957.
62. Woodward and co-workers, unpublished results.
63. Eschenmoser, Shreiber and Julia, Helv.Chim.Acta,
1953, 36, 482.
64. Sondheimer and Elad, J.Amer.Chem.Soc., 1957, 79, 5542.
65. Lynen, Eggerer, Henning and Kessell, Angew.Chemie,
1958, 70, 738. see footnote 24.
66. Ireland and Marshall, J.Org.Chem., 1962, 27, 1620.
67. Brown and McFarlin, J.Amer.Chem.Soc., 1958, 80, 5372.
68. Watenabe and Canlon, J.Amer.Chem.Soc., 1957, 79, 2828.
69. Cocker and Halsall, J., 1957, 3441.
70. Sondheimer and Elad, Proc.Chem.Soc., 1957, 206.
71. Sondheimer and Elad, J.Amer.Chem.Soc., 1958, 80, 1967.
72. Sondheimer and Rosenthal, J.Amer.Chem.Soc., 1958, 80, 3995.
73. Sondheimer and Wolfe, Canad.J.Chem., 1959, 37, 1870.
74. Brown and Rao, J.Org.Chem., 1957, 22, 1136.
75. Romann, Frey, Stadler and Eschenmoser, Helv.Chim.Acta,
1957, 40, 1900.
76. Romann, Ph.D. Thesis, Zurich, 1960.
77. Johnson, Niata International Congress of Pure and
Applied Chemistry, Abstracts, 1963, 16.
78. Ireland and Schiess, J.Org.Chem., 1963, 28, 6.
79. Cornforth and Robinson, J., 1949, 1855.
80. Johnson, Rogier, Ackermann, J.Amer.Chem.Soc., 78, 1956, 6322.
81. Ryback, D.Phil.Thesis, Oxford, 1962.

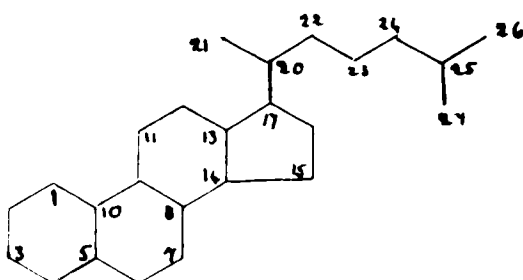
82. Church, Ireland and Shridhar, J.Org.Chem., 1962, 27, ⁷⁰⁷~~1952~~.
83. Boyce, Whitehurst, J., 1960, 2680.
84. Bowdon, Heilbron, Jones, Weedon, J., 1946, 39.
85. Brown, Murray, Murray, Snover, Zweifel, J.Amer.Chem.Soc.,
1960, 82, 4233.
86. Lehn, Bull.Soc.Chim.France, 1962, 1832.
87. Mellor, D.Phil.Thesis, Oxford, 1962.

NOMENCLATURE

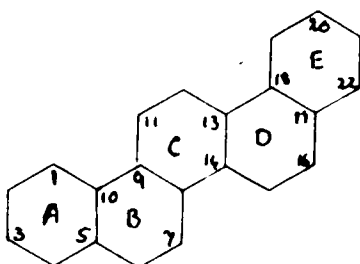
(See also p 45)

NOMENCLATURE

(See also p. 45)

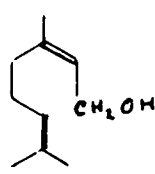


TETRACYCLIC

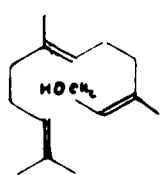


PENTACYCLIC

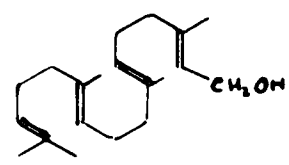
PLATE I (1-12)



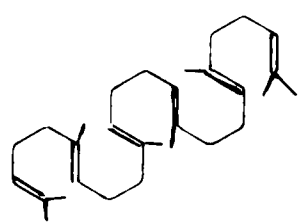
1



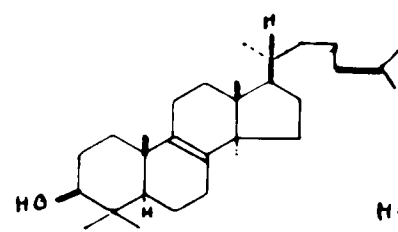
2



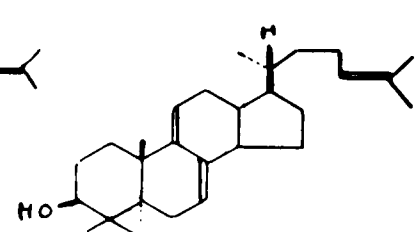
3



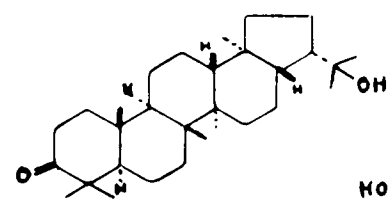
4



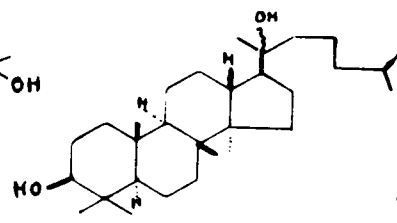
5



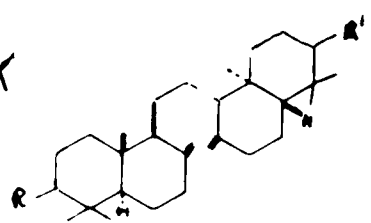
6



7



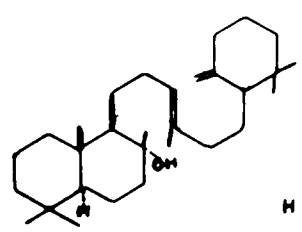
8



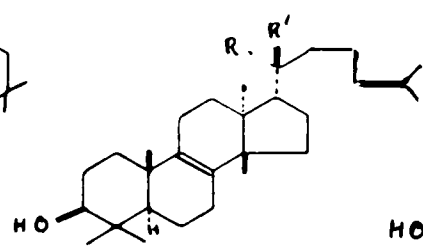
9

(a) $R = \beta OH$, $R' = \alpha OH$

(b) $R = R' = \text{ketone}$



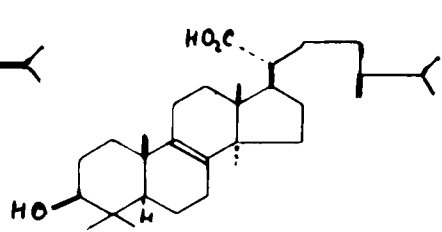
10



11

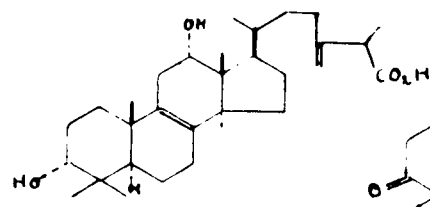
(a) $R = Me$, $R' = H$

(b) $R = H$, $R' = Me$

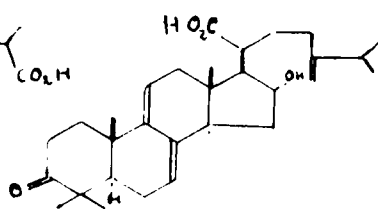


12

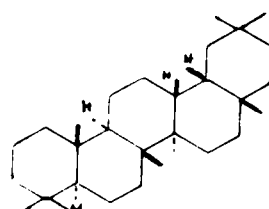
PLATE II (13 → 20)



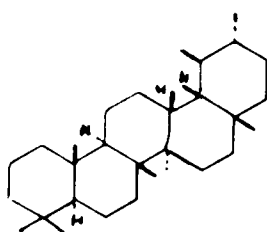
13



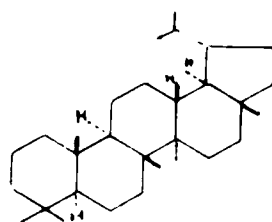
14



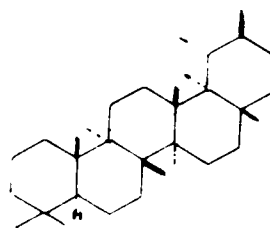
15



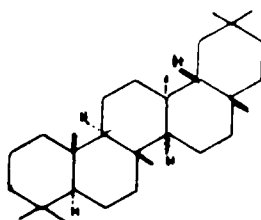
16



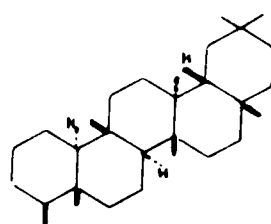
17



18



19



20

PLATE III (21 → 26)

III

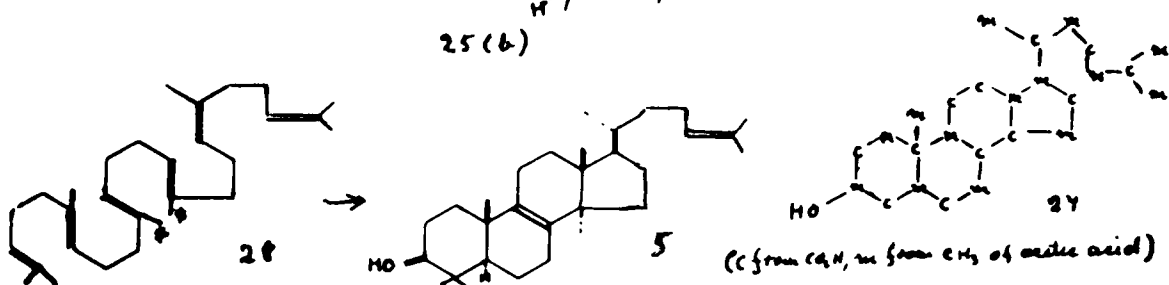
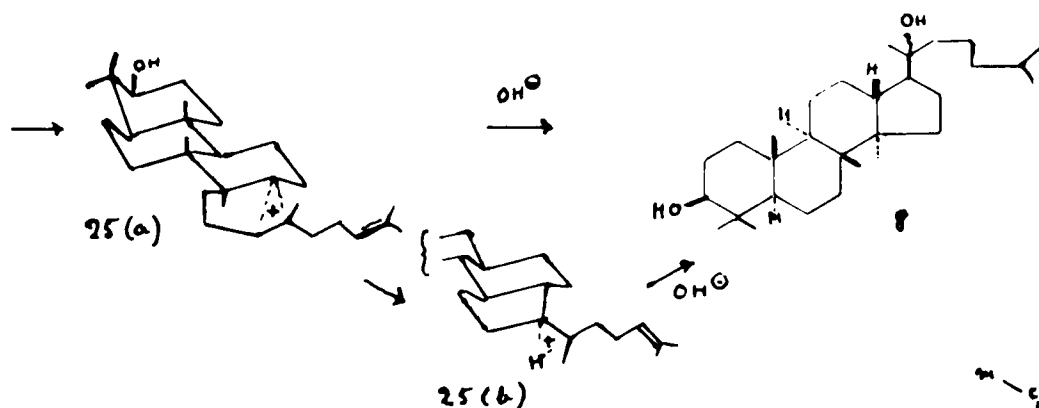
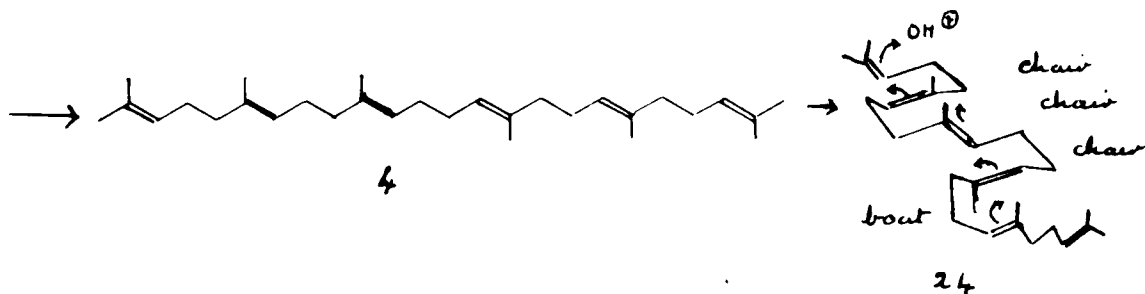
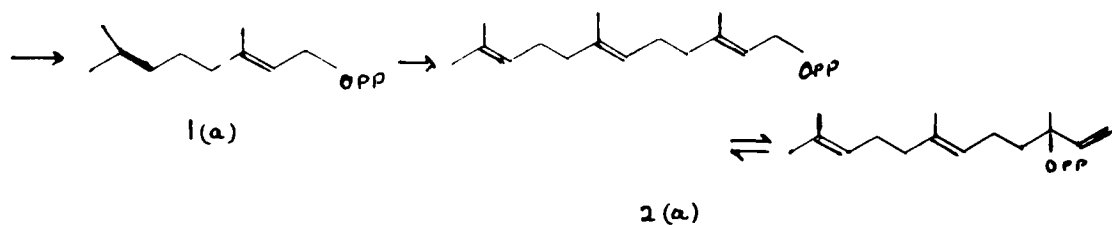
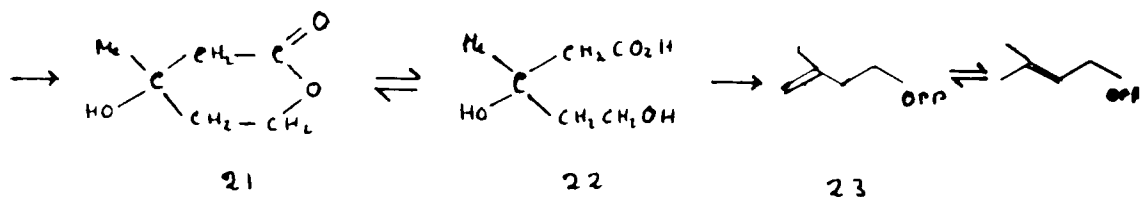
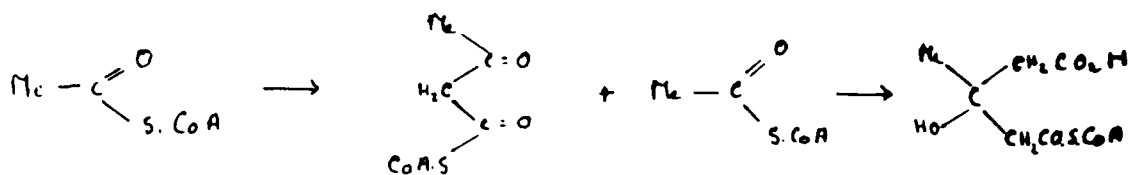
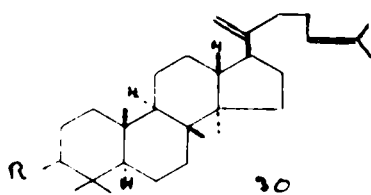
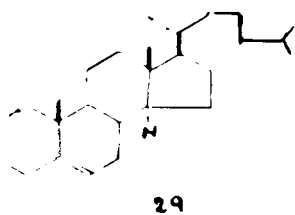
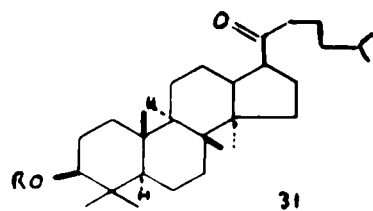


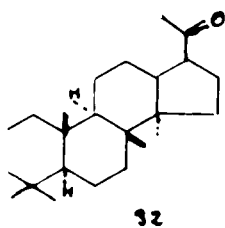
PLATE IV (29 → 40)



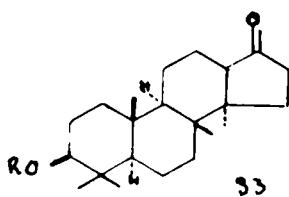
- (a) $R = \text{ketone}$
(b) $R = \beta \text{OAc}$



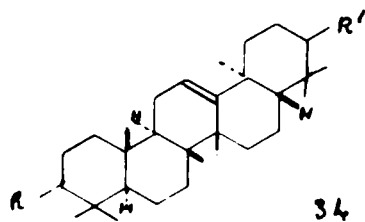
- (a) $R = \text{Ac}$
(b) $R = \text{H}$



- $R = \text{Ac}$
 $R = \text{H}$



- (a) $R = \text{Ac}$
(b) $R = \text{H}$



- (a) $R = \beta \text{OH}, R' = \alpha \text{OH}$
(b) $R = R' = \text{ketone}$

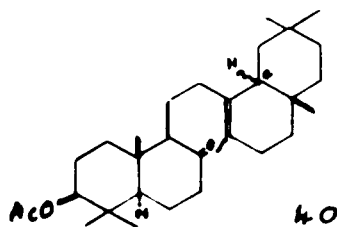
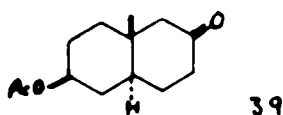
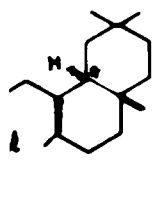
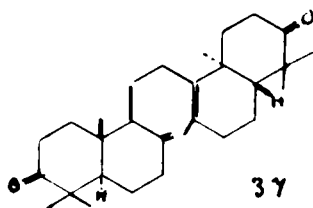
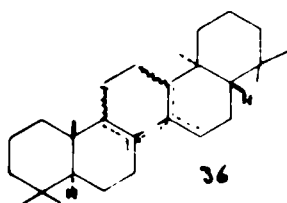
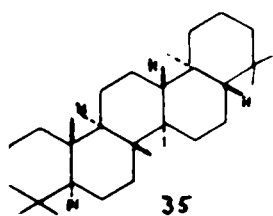
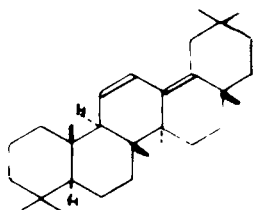
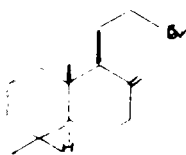


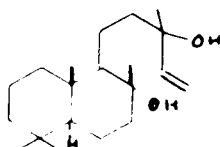
PLATE V (41 → 52)



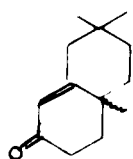
41



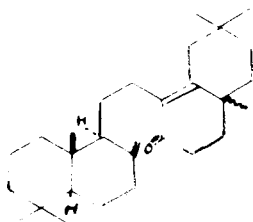
42



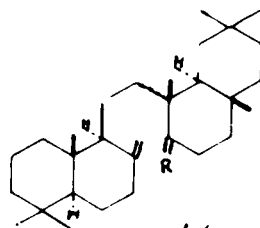
43



44



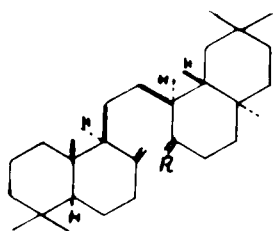
45



46

(a) R = isobutane

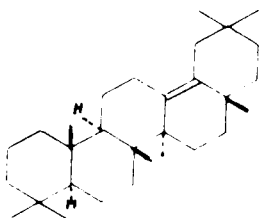
(b) R = $\begin{matrix} \text{OH} \\ \diagup \\ \text{C} \\ \diagdown \\ \text{Me} \end{matrix}$



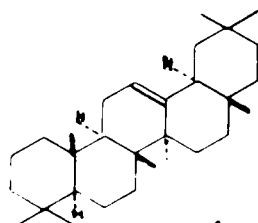
47

(a) R = isobutane

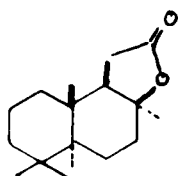
(b) R = $\begin{matrix} \text{OH} \\ \diagup \\ \text{C} \\ \diagdown \\ \text{Me} \end{matrix}$



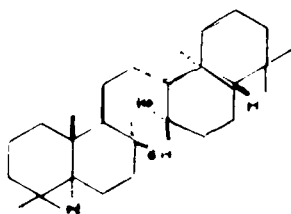
48



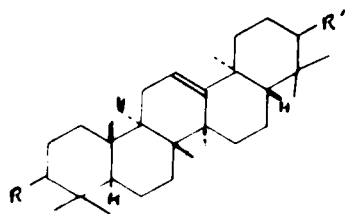
49



50



51

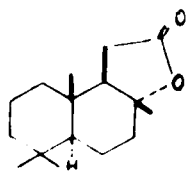


52

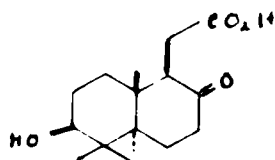
(a) R = R' = H

(b) R = β OH, R' = α OH

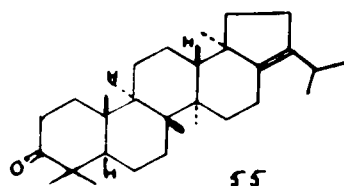
PLATE VI (53 → 66)



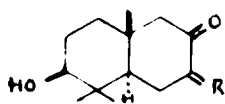
53



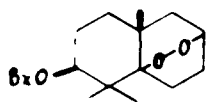
54



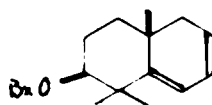
55



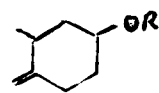
56



57

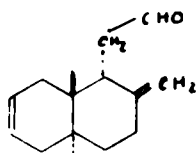


58

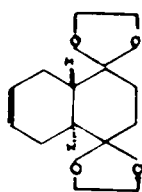


59

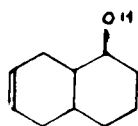
R, blocking group



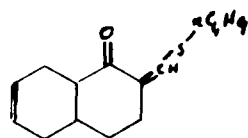
60



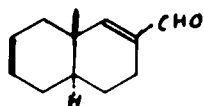
61



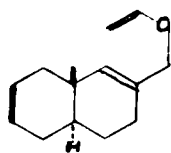
61a



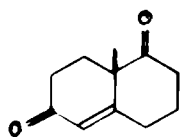
62



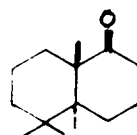
63



64

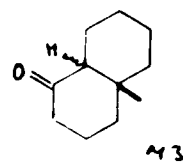
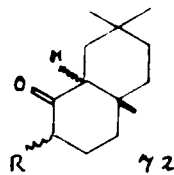
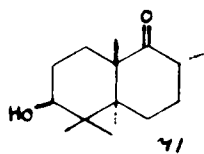
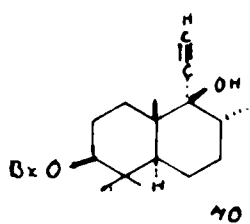
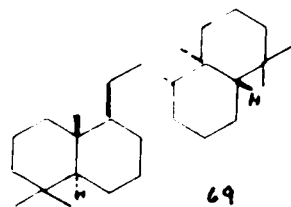
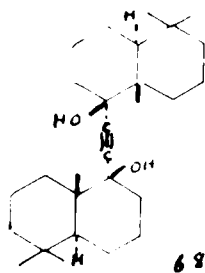
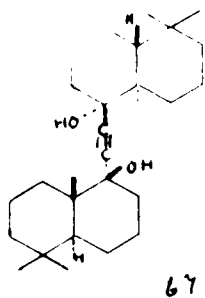


65



66

PLATE III (67 → 79)



(a) $R = Me$

(b) $R = H$

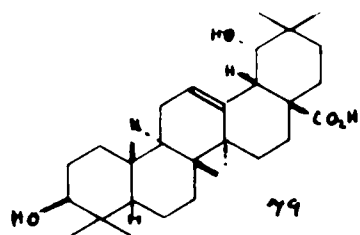
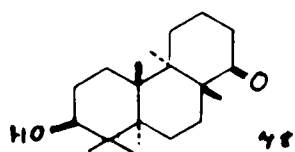
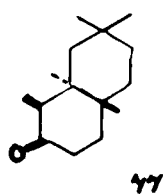
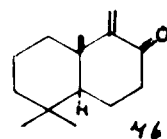
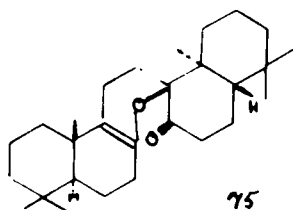
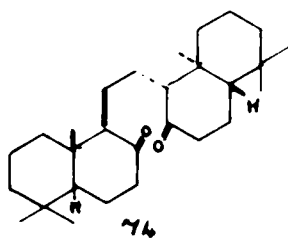
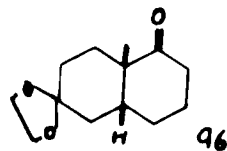
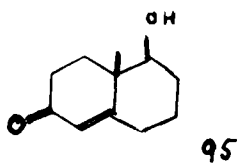
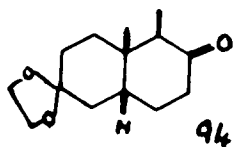
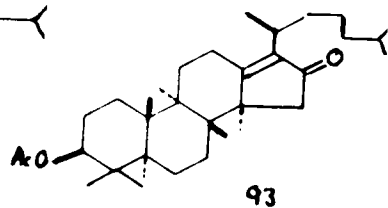
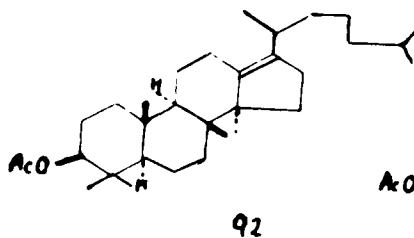
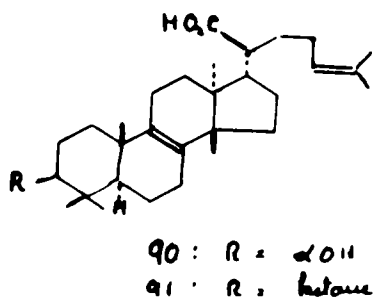
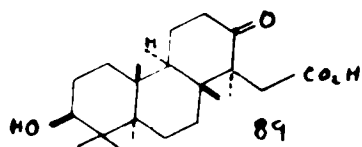
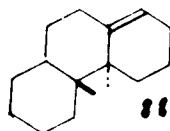
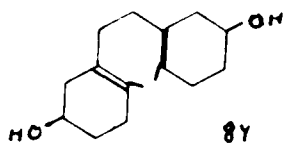
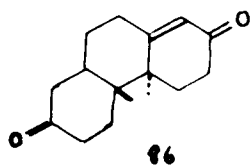
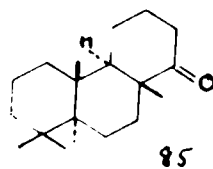
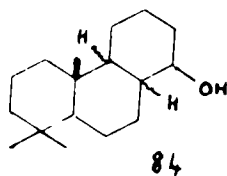
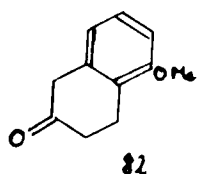
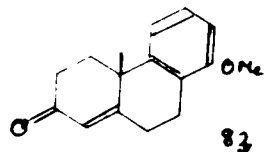
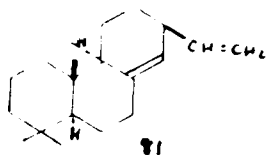
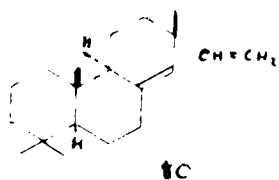


PLATE VIII (80 → 96)



DISCUSSION

Section A.

THE EFFICIENT ISOLATION OF THE TRICYCLIC INTERMEDIATE (A22) AND ITS USE IN THE SYNTHESIS OF PENTACYCLIC TRITERPENES.

Investigations by Ruzicka and co-workers^(1,5,14) into the nature and structural relationships of tirucallenol (A5), euphenol (A45) and the elemi acids led Ryback⁽²⁾ to suppose that a practicable route could be devised which would make the tricyclic acetoxy-keto ester (A22) readily available for partial syntheses of other triterpenes. He extracted elemadienolic acid (A39) from Manila elemi resin in 6-10% yield.^(84,85) The acid obtained in this way was contaminated with up to 15% elemadienonic acid (A40)^(86,89) and a small amount (3%) of dienic impurities (A41, A42)⁽⁸⁴⁾ indicated by their characteristic ultra-violet absorption at 232, 239 and 247 mμ. Attempts failed to isomerise (A39) or any of its derivatives under acid conditions into isotirucalleryl derivatives (A6). This substantiated the results of previous workers.⁽⁸⁴⁾

He therefore decided to convert (A39) to elemenonic acid (A44) and then follow the stereospecific conversion of (A44) to tirucallenol (A5) in the manner worked out by the Zurich school.⁽¹⁾ Hydrogenation using Adams catalyst removed the $\Delta^{24(25)}$ side chain double bond, and the

3 α -hydroxyl group was converted into ketone by chromic acid in acetone.⁽⁸⁸⁾ Certain difficulties were encountered in obtaining a pure sample of elemenonic acid (A44), several recrystallisations being necessary.

It would now appear that the difficulties encountered were caused by the presence of some $\Delta^{7(8)}$ isomer, described by Birch and his co-workers⁽⁸⁹⁾ as a result of an investigation into the structure of flindissol (A46). However, these results do not affect the use of the elemi acids in the manner described by Ryback, as acid will induce isomerisation of the $\Delta^{7(8)}$ isomer to the $\Delta^{8(9)}$ (A44).

The purified keto acid (A44) was esterified with diazomethane and then reduced with lithium aluminium hydride to tirucallenediol (Ala)⁽¹⁾ containing a 3 β -hydroxyl group.⁽⁹⁰⁾ Acetylation of (Ala) gave the diacetate which was hydrolysed to give the 3-monoacetate (A2) in variable yields, isolation being by fractional recrystallisation from benzene or chromatography on deactivated alumina. The 21-hydroxyl group was removed by lithium aluminium hydride reduction of the methane-sulphonyloxy derivative (A3) giving tirucallenol (A5). The acetate of (A5) was isomerised by boiling with acetic acid containing some aqueous hydrochloric or sulphuric acids to give (A6). This, in turn, was oxidised with t-butyl chromate to give (A7) which was ozonised to give the tricyclic acetoxy-keto-ester (A22). However no yield is quoted by Ryback⁽²⁾

nor by Ruzicka⁽⁵⁾ in this final stage and the indications in the former case are that sufficient material was isolated for a melting point only.

It was unclear at this stage whether the process worked out by Ryback was satisfactory for the simple and reproducible production of reasonable quantities of the tricyclic intermediate (A22), and in particular the yield in the ozonolysis of the α/β -unsaturated ketone (A7) was unknown.

Our initial investigations were concerned with obtaining answers to these questions. As samples of tirucallenediol (A1a) were at hand the investigation began here. Immediately difficulties were encountered. Acetylation of the diol gave the diacetate in high yield but semihydrolysis of the latter with one equivalent of potassium hydroxide in dry ethanol/benzene gave anything from 10 to 50% yields of the monoacetate (A2). Attempts to get around this undesirable sequence by the formation of the $C_{(21)}$ monotoluene-*p*-sulphonate or monomethanesulphonate and their reduction to tirucallenol (A5) proved abortive. It therefore became apparent that the laborious cycle of diacetylation, semihydrolysis with poor yields, fractional recrystallisation and reacetylation of mixed hydrolysis products could not be avoided.

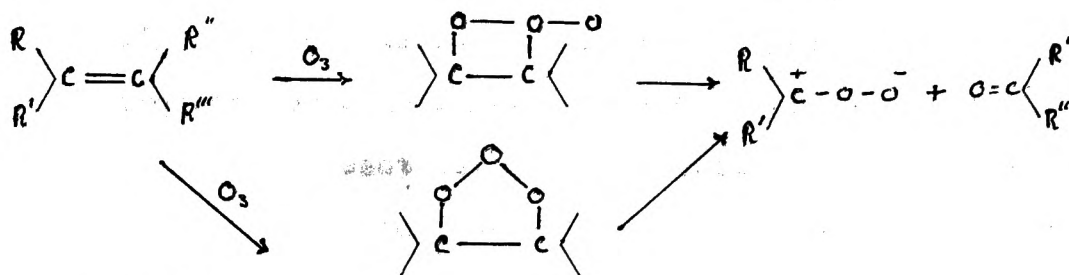
The 3 β -monoacetate (A2) so obtained, when converted into its $C_{(21)}$ methanesulphonyl derivative, reduced with lithium aluminium hydride and isomerised gave isotirucallenyl acetate (A6), in high yield.

The oxidation of isotirucallenyl acetate (A6) with *t*-butyl chromate had been well worked out by Ruzicka et al. (5). He had shown that many of the possible oxidation products from isotirucallenyl acetate (A6) were in fact obtained e.g. the 12-oxo (A16) and the desired 16-oxo (A7) derivatives together with their respective epoxides. Moreover he had shown that (A7) could be isolated by chromatography and indeed it was found in the present work that a consistent yield of up to 50% (A7) could be obtained.

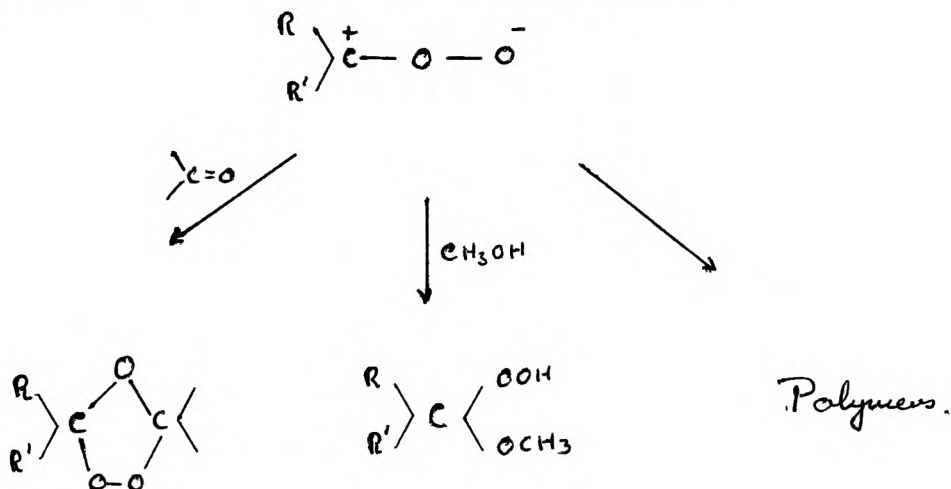
The conversion of the $\alpha\beta$ -unsaturated ketone (A7) into the tricyclic keto-ester (A22) was first attempted by ozonolysis in ethyl acetate at -70° . (5) It led to the isolation of (A22) in a 20% yield.

The neutral products remaining after ozonolysis were shown by gas-liquid chromatography and infra-red spectroscopy to contain approximately 30% starting material and a complex mixture of breakdown products.

In a series of papers, Bailey and other workers (92,93,94,95,9) have carried out an intensive investigation into the mechanism of ozonolysis and the various factors governing the products to be expected and their respective yields. It appears that ozone makes an electrophilic attack on the olefinic bond to form a primary ozonide, both four and five membered ring intermediates being postulated which rapidly break down to a zwitterion and a carbonyl compound.



The more stable of the two ^{possible} zwitterions is usually that which can more easily accommodate polarisation. The zwitterion may react in any one of several different ways: with itself to form a dimeric or polymeric peroxide, with a carbonyl compound to form an ozonide with the classical five membered cyclic structure, with a compound having an active hydrogen or it may undergo rearrangement.



Pryde and Andrews⁽⁹⁷⁾ using results derived from the ozonolysis of methyl oleate state that better yields of aldehydic products were obtained when an active solvent (i.e. one which will react with the zwitterionic intermediate such as methanol or glacial acetic acid were used rather than inactive solvents such as heptane or ethyl acetate. However, the application of these results to the ozonolysis of the $\alpha\beta$ -unsaturated ketone (A7) gave little significant variation in the yield of acid products. In fact, the use of methanol as solvent was positively detrimental.

Researches by Criegee and Gunther⁽²⁹⁾ indicated that the poor yields of the desired carbonyl function could be caused by the formation of epoxides. They attempted to counteract this by having one equivalent of tetracyanoethylen present with the olefin to be fissioned during the passage of ozone, and in the simple cases which they examined, high yields of aldehydes and ketones were reported. However, when this modification was applied to the ozonolysis of the $\alpha\beta$ -unsaturated ketone (A7) only a poor yield of acidic products was obtained. Spectroscopic analysis showed that the whole of the tetracyanoethylene had been destroyed presumably by conversion to the epoxide. Criegee had previously shown that the epoxide was formed in such ozonolyses

A table combining the results of the ozonolyses of the $\alpha\beta$ -unsaturated ketone (A7) is given on p. 62 .

It would appear from this series of ozonolyses that the poor yields stem from an inability of the ozone molecule to get at the $\Delta^{13(17)}$ double bond in (A7). A possible reason for the slow attack on (A7) could be that the olefinic bond is deactivated to electrophilic attack by the electron withdrawing character of the conjugated carbonyl. However, numerous examples of the attack of ozone on $\alpha\beta$ -unsaturated ketones are known, a particular example being the ozonolysis of cholest-4-ene-3-one (A47)⁽²⁶⁾ where good yields of the keto-acid (A48) were obtained.

An alternative and more likely reason is that ozone finds difficulty in attacking the double bond in (A7) for structural reasons, in particular the side chain must block access to the $\Delta^{13(17)}$ bond. If one could assume that the initiating step in the ozone molecule's quest for a double bond were reversible and also rate determining then it is possible that in the case of (A7) restrictions would be placed on the free rotation of the side chain about the 17,20 carbon-carbon bond by the proximity of a bulky ozone molecule and this may be sufficient to prevent the easy formation of the ozone/olefin complex, whatever its form, necessary to the initiation of reaction. The rather better yields of acid products obtained when a large excess of ozone is used may be evidence of this.

Other methods of fissioning olefins were also tried out.

Reaction with an equivalent quantity of osmium tetroxide gave no reaction, the usual working up procedure of reduction with lithium aluminium hydride and cleavage of the supposed glycol led only to the isolation of tirucall-15-ene-3 β ,16-diol (A31) in almost quantitative yield. Alkaline 30% hydrogen peroxide used so successfully by Plattner et al.⁽³³⁾ also did not touch the $\Delta^{13(17)}$ bond, hydrolysis of the 3 β -acetate grouping being the only reaction.

The electronic deactivating effect of the carbonyl on the olefinic bond is again not sufficient to explain the complete absence of attack therefore it would appear that steric features are again important. Moreover it is described later on p.38 how the cleavage of the double bond in isotirucallenyl acetate (A6) takes place in high yield with osmium tetroxide and lead tetraacetate. This would indicate that the carbonyl group in addition to its electronic effect must also exercise some steric influence on the course of the reaction.

Edward et al.⁽³⁴⁾ had shown that application of the Lemieux reagent⁽³⁵⁾ to the oxidation of cholest-4-ene-3-one (A47) gave between 30 and 90% cleavage of the double bond in ring A with formation of the keto acid (A48). The identical conditions applied to (A7) gave unchanged starting material.

It was therefore concluded from the above series of reactions that only ozonolysis offered a means of attacking

the olefinic bond in (A7) and that this could only be induced to give a 20% yield.

Four weaknesses in the route from the elemi resin to the tricyclic intermediate (A22) had now become apparent:

(i) Isolation of a pure sample of elemenonic acid (A44) required several difficult recrystallisations to remove impurities.

(ii) The yields from the semihydrolysis of the diacetate (A1) were not reproducible and a laborious recycling procedure was necessary.

(iii) Only a 20% yield could be obtained in the ozonolysis of (A7).

(iv) Excluding acetylations, ten operations were necessary to get from the crude elemi acid extract to the tricyclic intermediate (A22).

The development of another route to the tricyclic intermediate was clearly of great importance. In 1955 and 56, Mills and Werner^(8,9) had published two papers containing the results of an investigation into the Dammare resins and they had shown that the neutral extract from the resin contained a high percentage of hydroxylic and ketonic materials which they later showed to be the dammarene diols (A8,A9) and the related ketonic alcohols (A8a,A9a). One of the main features of their structural determination was their conversion by dehydration to tirucallanol (A4) and euphenol (A5). Clearly here lay the basis of an alternative

route to the $\alpha\beta$ -unsaturated ketone (A22) which deserved further consideration.

Mills examined the neutral extract using adsorption chromatography on deactivated alumina. Unfortunately his alumina was deactivated by a non-specific method and his elution technique did not lend itself to the practical isolation of large quantities of useful intermediates. It was later found that one of the components of the neutral fraction, hydroxyhopanone (A49), could be removed by crystallisation⁽¹⁰⁾ prior to chromatography. This latter fact coupled with suitable adjustment of the eluting solvents and deactivation of the alumina in the way described on p.44, however, enabled the separation of the neutral resin constituents to be standardised in such a way that a consistent 50% recovery of the required hydroxylic and ketonic materials (A8,A9,A8a,A9a) could be made.

The combined mixture of hydroxylic and ketonic materials was reduced with lithium aluminium hydride and the product was identified with an authentic sample of mixed C₍₂₀₎epimeric dammarene diols (A8,A9) by a comparison of retention times on gas-liquid chromatography. The authentic sample was kindly provided by J. S. Mills. Although the gas-liquid chromatographic column could not resolve the two epimers a slight broadening of the recorded peak was observed and the retention time was slightly different to that recorded for each epimer alone.

The mixture of epimeric diols was acetylated at C₍₃₎ and dehydrated by boiling with glacial acetic acid containing dilute sulphuric acid to give a mixture of isotirucallenyl and isoeuphenyl acetates (A6,A14) as the major product. This mixture of acetates was purified by chromatography, this process also serving to separate the two epimers. Isotirucallenyl acetate (A6) was eluted first followed successively by an intermediate mixed fraction and isoeuphenyl acetate(A14). The physical constants of each acetate were identical with the values recorded in the literature.

Further conversions to the tricyclic intermediate (A22) using the epimeric mixture gave identical results to those already discussed for isotirucallenyl acetate (A6) alone. Although this route to (A22) contains the rather tricky ozonolysis stage it is very much superior to the one described earlier. Every stage is reproducible and has in fact been carried out five times on scales varying from 1 to 30 g. of the initial neutral extract. At no stage is a yield obtained of less than 45% except of course for the breakdown of the $\alpha\beta$ -unsaturated ketone and it should also be noted there are only four major stages. Thus even allowing for the awkward final stage a highly successful route to (A22) has been worked out.

Two monocyclic precursors for ring E have also been synthesised. Following the directions of Nalsall et al. (48)

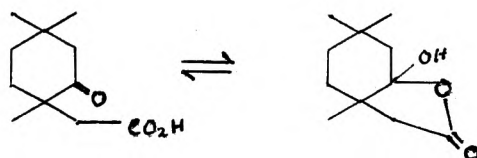
dimedone was converted to the enol chloride (A32) which was then hydrogenated to give the cyclohexanone derivative (A33). The overall yield from this reaction was very variable. The slightest trace of moisture in the chloroform solvent used in the first stage appeared to give rise to compounds which effectively poisoned the catalyst in the second stage, a very large excess of catalyst being necessary to cause an appreciable hydrogen uptake. Carbethoxylation was carried out using ethyl oxalate and sodium ethoxide, the substituent being introduced to the carbonyl on the side away from the gem-dimethyl group. Distillation from broken glass plus iron filings caused elimination of carbon monoxide and the formation of the keto ester (A34).⁽⁵²⁾

The preparation of the second keto ester (A26) presented a more difficult problem. Dimedone was again the starting material. The lability of the protons on the methylene group between the carbonyls under basic conditions led to the introduction of both methyl and ethoxycarbonylmethyl groups, the former via methyl iodide and the latter via ethyl bromoacetate, sodium ethoxide being the base in each case.

One of the carbonyl groups was removed by reacting with one equivalent of ethane dithiol⁽⁵³⁾ and reduction of the resultant thioketal (A36) with freshly prepared Raney nickel. It was found that despite the use of equivalent quantities of reagents a considerable portion (up to 20%) of the bis-thioketal (A37) was formed, making necessary a careful

chromatographic separation on alumina. The mono and disubstituted derivatives (A37,A38) did not separate easily and investigation of the fractions by taking infra-red spectra and observing the carbonyl stretching region was necessary to indicate where the mono-substituted derivative was becoming the preponderant component of the eluted material. After separation, both products were readily crystallisable solids with sharp melting points.

The desulphurisation of the monothioketal (A38) went without difficulty giving a high yield of the cyclohexanone derivative (A26a) which in turn was hydrolysed to give the acid (A26). A novel feature of the acid was its reluctance to crystallise and the presence of an absorption peak in the infra-red at 1780 cm.^{-1} . As the acid analysed correctly and the ethyl ester prior to hydrolysis had all the expected physical properties, it was assumed that an equilibrium must exist between the keto-acid (A26) and a γ -lactone in the manner illustrated.⁽¹³³⁾



Several reports of the successful synthesis of polycyclic molecules by electrolytic coupling had been made.^(98,99,102) With this in mind it was decided to attempt to couple the tricyclic acid (A25) with the monocyclic acid (A26). None of the previous syntheses, however,

were entirely analogous. The synthesis of pentacyclosqualene by Corey and his group⁽⁹⁸⁾ had a certain simplicity, namely that the two acids involved were identical. Many examples of mixed couplings do exist though, in other fields⁽¹³²⁾ and large variations in size of the two components can be tolerated. In cases such as this it is common practice to use an excess of the acid which is more readily available.⁽³⁹⁾

The use of methanol as a solvent has very much widened the scope of the Kolbe reaction, less restriction being placed on the necessity for a high concentration of carboxylate ions or for a high anode current density. Neither the temperature nor pH of the reaction remain such critical factors as in aqueous media.^(100,101) Also the increased solvating power of methanol for organic materials is a tremendous advantage. Beside these advantages methanol also cuts down many of the side reactions common in aqueous media such as the formation of the non-coupled paraffin, its related alcohol, olefin or ester.^(103,104)

Possible disadvantages are the high resistance methanol offers to the passage of a current with the consequent large dissipation of heat. Also some esterification can occur. Solubility and heat dissipation were two factors of prime importance in the attempted coupling of the tricyclic and monocyclic intermediates (A25 and A26). One of the more noticeable features of (A26) was its very poor solubility in any organic solvents other than chloroform or

dichloromethane. However it did dissolve in hot methanol if the solution was sufficiently dilute, but as electrolyses usually give better results with higher concentrations a saturated solution was used with a consequent preceipitation of (A25) if the solution was cooled. The heat generated during the electrolysis was sufficient to boil the small scale cell dry (contained 3 ml. of solution) in a very short time, therefore cooling was very important. As a result of these two factors a fine balance of solubility and heat dissipation had to be carefully observed.

The electrolytic vessel used was a 0.5 in. diameter pyrex test tube, 4 in. long. The electrodes were of platinum, 0.75 sq.in. in area and were set parallel and approximately 0.1 in. apart. External cooling was applied in the form of an ice brine bath, which was sufficient to cause the methanol to reflux on the walls of the vessel provided that the current was not greater than 0.20 amps.

A trial experiment using myristic acid approximately 2% neutralised by sodium led to an almost quantitative recovery of the coupled product n-hexacosane. In the first attempt to couple the two acids (A25) and (A26) the latter was present in a four molar excess and sufficient sodium was added to neutralise approximately 3% of the acids. The maximum current consistent with gentle boiling of the methanol solvent was passed. The only products identified, however,

were the unchanged tricyclic intermediate (A22) and the bis-cyclohexylethane derivative (A27).

To try and prevent this preponderant coupling of the monocyclic keto acid (A26), the reaction was repeated but in this case (A26), in solution in methanol, was slowly dropped into the reaction vessel during the course of the electrolysis, thus attempting to ensure an excess of the tricyclic intermediate (A22) was always present. Again, however, the only coupled product identified was that derived from the monocyclic keto ester.

It is known that the cross-coupling of differing acids quite often leads to only a small yield of the mixed product, so that on the scale of the above reaction it would be very difficult to detect mixed coupling if in fact it did occur. Examination of the esterified products by gas-liquid chromatography, however, did not show the presence of any higher molecular weight material in the regions where it would be expected and therefore a negative result must be accepted. During the course of other experiments on the cleavage of the double bond in isotirucallenyl acetate (A6) it was found that the resultant 1,5-diketone (A21) was decomposed on the gas-liquid chromatographic column giving no sharp peak so that conceivably the 1,6-diketone (A50) expected from the coupling would not be stable to this type of investigation. A thin plate chromatogram, however, did not clarify this point.

Further electrolytic experiments were therefore suspended both to allow a build up of the tricyclic intermediate (A22) and also to allow consideration of other synthetic procedures which were being developed.

In anticipation of the synthesis of the 1,6-diketone (A50) attempts were made to fission the $\Delta^{13(13)}$ double bond in δ -amyrin (A28). β -Amyrin (A30) was isolated from a mixture of α - and β -amyrins by fractional recrystallisation of the benzoates. Selenium dioxide dehydrogenation of the acetate (A29) gave β -amyradiene acetate (A51) and hydrogenation of the disubstituted double bond gave δ -amyrin acetate (A32). Ozonolysis of (A32) gave only unchanged starting material and prolonged treatment with osmium tetroxide in boiling pyridine showed no attack of the double bond, substantiating the results of Halsall et al.⁽⁴⁶⁾ who attempted the hydroxylation of a mixture of δ -amyrin acetate (A32) and ψ -taraxasterol acetate (A52) under milder conditions showing that only the latter compound was attacked.

A further course of experiments was carried out with relation to the 1,5-diketones obtainable from the fission of the olefinic bond in both isotirucallenyl and isoeuphenyl acetates (A6,A14). As was reported by Ruzicka and his group^(5,14,15) either of the two compounds (A6,A14) could be converted via the glycols (A19a,A19) to the 1,5-diketones (A21,A20) using osmium tetroxide and lead tetraacetate. It was found

difficult to obtain analytically pure samples of the glycols, the best solvent for recrystallisation being methanol and the results of analysis always showed that (A19a) and (A19) were deposited with methanol of crystallisation the last traces of which could not be removed. However, direct conversion of the crude hydroxylated products with lead tetraacetate to the diketones (A20,A21) in high yield removed any necessity to isolate the intermediate diols.

The diketones (A20,A21) were prepared in order to carry out model experiments on the ring closure of diketones using a pinacolic type reduction procedure. The coupling of many different types of ketones in this way had already been reported. Perkin, Ray and Robinson⁽¹⁰⁵⁾ coupled two ketones to obtain the pinacol from trimethyl brazilone (A53) using zinc dust and glacial acetic acid, a reaction also utilised by Mehr, Becker and Spaerri⁽¹⁰⁶⁾ to obtain (A54) from the related diketone. However, in both these instances intermediates would be stabilised by the presence of the aromatic rings. Pinacolic reductions of non-aromatic systems have tended to use reagents such as sodium in moist ether, or di- and trivalent metals such as magnesium or aluminium, these being used in conjunction with mercuric chloride to ensure that an active surface is given to the metal. Solvents such as dry benzene or propanol/acetic acid mixtures are used.^(20,24,25) The application of procedures such as these to the 1,5-diketones (A20,A21) led only to the recovery

of unchanged starting materials.

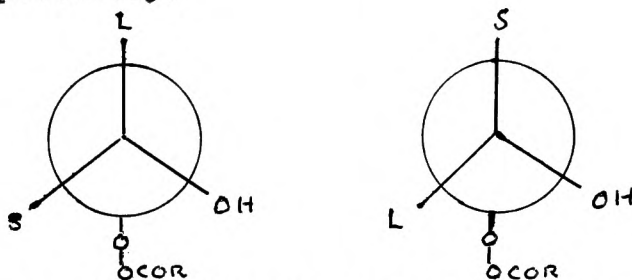
The formation of an acyloin from an ester or acid chloride^(22,23) is a combination reduction/condensation reaction that occurs in the presence of molten sodium and an inert high boiling solvent such as toluene or xylene with the initial formation of a diketone. Further reduction of this diketone by the metal yields the sodium salt of the ene-diol form of the acyloin.⁽¹⁰⁷⁾ This reaction has had considerable prominence because of its success in the synthesis of macrocyclic acyloins.⁽²³⁾

The similarity of the acyloin reaction to the pinacolic reduction suggested that the application of the conditions of the former to either of the 1,5-diketones (A20,A21) might result in the desired ring closure. The use of such reaction conditions did in fact meet with a certain amount of success. The reaction was carried out under dry oxygen-free nitrogen and its course was followed by the extraction of samples at intervals and subjecting them to infra-red analysis. Observation of the carbonyl absorption region indicated that the acetoxy group was quickly lost and that this was slowly followed by a diminution in the ketone carbonyl band. A solid product was isolated, albeit in poor yield, which was attributed the structure (A55) from its mode of preparation and the physical data obtained. Its melting point and infra-red spectrum showed it to be different from the

previously obtained glycol (A19a). However further investigation will be necessary before any definite conclusions to its precise structure can be made.

Before the development of the extremely dependable route to the tricyclic relay (A22) described on p.30-32, attempts were made to apply the Baeyer-Villiger oxidation,⁽¹⁰⁸⁾ using peroxytrifluoroacetic acid,⁽¹⁹⁾ to the 1,5-diketone (A21) in the hope that isolation of a useful tricyclic intermediate might be possible from the reaction products.

The rearrangement involved in the Baeyer-Villiger reaction has both electronic and steric driving forces.^(17,109,110) The electronic forces favour rearrangement of the group which can most easily stabilise a positive charge. For example, in nearly all cases of the oxidation of methyl alkyl ketones it is the alkyl group which migrates. The type of steric or conformational driving force which can occur is illustrated in the diagram, where S and L stand for small and large groups respectively.



The favoured orientation occurs when the S and OH groups lie about the bulky per-acid group. The application of these principles to the 1,5-diketone (A21) leaves very much an open

question which group can be considered large or small and also whether electronic or steric factors will have the most effect. As there was also the possibility that the ring ketone would react, a definite forecast of the reaction products to be expected could not be made.

In fact in carrying out this reaction on the diketone(A21) the major product was found to be unchanged starting material. The concurrent development of the previously mentioned route to the tricyclic keto-ester (A22) rendered further researches into the Baeyer-Villiger reaction unnecessary.

The simplest way of utilising the tricyclic intermediate (A22) would appear to be by reducing it to the triol (A56) with lithium aluminium hydride and then mono-mesylating or tosylating the one primary alcohol group which is present. In this form or as the corresponding halide a suitably protected version of the molecule could then be used to alkylate the already synthesised monocyclic keto-ester (A34) to give the tetracyclic intermediate (A57). Use could then be made of the ester group to achieve resolution, remembering of course that it is β to a ketone group which must be protected before hydrolysing the ester. Ring closure could then be achieved by oxidising the hydroxyl groups to ketone and boiling with sodium in xylene. Possibly a better cyclisation process may stem from reducing the ketone in the potential ring E to the alcohol and dehydrating the

resultant tetracyclic triol followed by ring closure with acid. The acid ring closure would no doubt give several isomers. If Ireland's method⁽¹¹¹⁾ of reintroducing the 3β -hydroxyl group, lost in the dehydration stage, into ring A is to be used, it is probable that the fairly inert $\Delta^{13(18)}$ isomer would be the most favourable case to use.

The basis of another route to the pentacyclic triterpenes would be by the preparation of a lithium alkenyl such as (A58)⁽¹¹²⁾ followed by attack on the 14-keto group contained in the tricyclic intermediate (A22). Hydrolysis and acid ring closure of the resulting tetracyclic carboxylic acid (A59) would give a racemic pentacyclic triterpene with a keto-group in ring D.

EXPERIMENTALSECTION A.Notes:

(a) Melting points were taken both in open capillaries and on a Kofler microscope hot-stage, the latter are marked (Kofler).

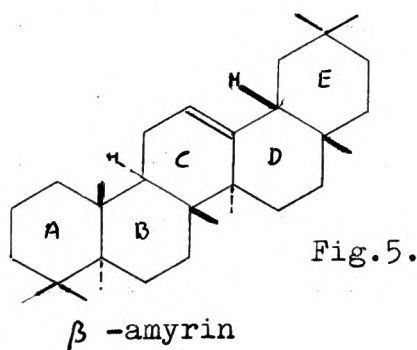
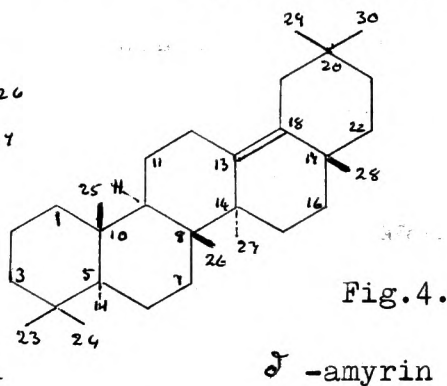
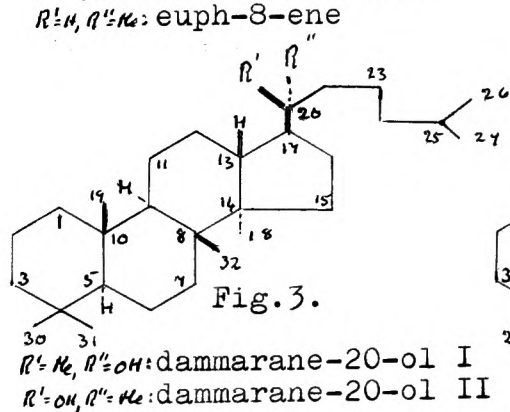
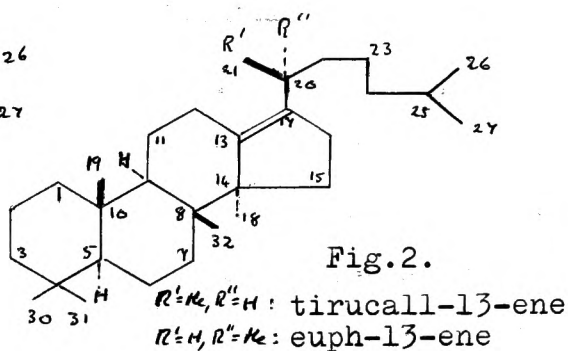
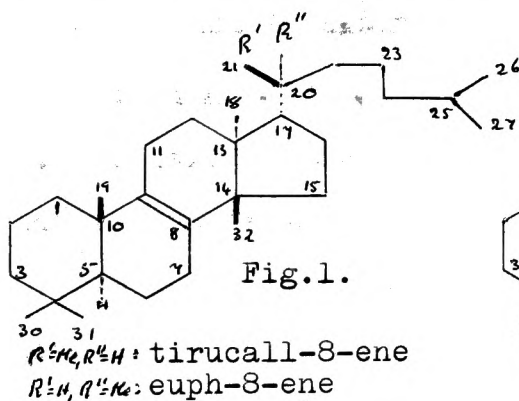
(b) Unless otherwise stated, Peter Spence and Son Ltd., Type 'H' alumina, deactivated with 5% by weight of 10% aqueous acetic acid, was used for chromatography.

Light petroleum refers to that fraction of b.p. 40-60°.

(c) In this section gas-liquid chromatograms were obtained using a Pye Argon machine with β -ray ionisation detector employing the following conditions; column temperature 220°, a gas inlet pressure of 10 lb./sq.in., amplifier gain 3, detector voltage 1250 v. The column consisted of E301, 1½% on kieselguhr, and the samples were injected in benzene solution. The ratio of retention time to that of tirucall-13-ene-3 β -ol-3-acetate is denoted by R_t .

(d) Infrared measurements were recorded on a Perkin-Elmer 137 and/or 237 (Infrared) spectrophotometer. A Cary 14 recording spectrophotometer was used for measurements in the ultra-violet. Optical rotations were measured in chloroform.

e) Nomenclature: The name and numbering of the carbon skeletons of the tetracyclic and pentacyclic triterpenes described in the following section will be as indicated in the diagrams below. Fig. 5 also depicts the lettering to be adopted for each ring. The standard convention of representing the orientation of substituent groups by dotted (α) and heavy (β) lines is used.



Tirucall-8-ene-3 β ,21-diol diacetate (A1)

Tirucall-8-ene-3 β ,21-diol⁽¹⁾ (4.00 g., 0.009 mol.) was acetylated with acetic anhydride and pyridine to give the diacetate (3.32 g., 70%). m.p. 125-7° after two recrystallisations from chloroform/methanol (Found: C, 77.2; H, 10.9. Calc. for C₃₄H₅₆O₄: C, 77.3; H, 10.7%). Lit.⁽²⁾ m.p. 120-1°.

Tirucall-8-ene-3 β ,21-diol 3-acetate (A2)⁽¹⁾

Tirucall-8-ene-3 β ,21-diol diacetate (2.45 g., 0.0046 mol.) in dry benzene (40 ml.) was hydrolysed by the addition of a solution of potassium hydroxide (0.130 g., 0.0023 mol.) in dry ethanol (14 ml.) and allowing the mixture to stand at room temperature for 24 hours. The products were worked up in the usual manner to give a solid residue from which fractional recrystallisation in methanol/chloroform gave tirucall-8-ene-3 β ,21-diol 3-acetate (0.651 g., 29%), m.p. 178-9°, as the first fraction. Lit.⁽¹⁾ m.p. 177-9°. Evaporation of the mother liquors left a mixture of mono and di-acetylated diol. This was recycled.

Tirucall-8-ene-3 β ,21-diol 3-acetate-21-methanesulphonate(A3)⁽²⁾

Tirucall-8-ene-3 β ,21-diol 3-acetate (3.19 g., 0.0066 mol.) and methane sulphonyl chloride (1.55 g., 0.013 mol.) were dissolved in dry pyridine at 0° and allowed to stand at room temperature for 24 hours. Iso-

lation of the product and two recrystallisations from methanol gave tirucall-8-ene-3 β ,21-diol 3-acetate-21-methanesulphonate (2.50 g., 67%), m.p. 115-7°, ν_{max} . (CCl₄), 1735, 1360, 1250, 1160 cm.⁻¹, R_t = 1.29. (Found: C, 69.7; H, 9.98; S, 5.34. Calc. for C₃₃H₅₆O₅S: C, 70.2; H, 9.99; S, 5.50%). Lit.⁽²⁾ m.p. 118-9°.

Tirucall-8-ene-3 β -ol acetate (A4)

Tirucall-8-ene-3 β ,21-diol 3-acetate-21-methanesulphonate (2.50 g., 0.0044 mol.) was reduced with lithium aluminium hydride in dry boiling ether to give, after 6 hours and the usual working up, tirucall-8-ene-3 β -ol (A5) (2.03 g., quant.), m.p. 147-9° after recrystallisation from methanol. ν_{max} . (nujol), 3360 cm.⁻¹, R_t = 1.03, (Found: C, 83.8; H, 12.3. Calc. for C₃₀H₅₂O: C, 84.0; H, 12.2%). Lit.^(1,3) m.p. 150-151° and 141.5-.42.5°.

Acetylation was carried out with acetic anhydride and pyridine⁽⁴⁾ to give tirucall-8-ene-3 β -ol acetate (2.01 g., 90%), which after recrystallisation twice from chloroform/methanol and once from ethanol showed m.p. 144-5°, ν_{max} . (CHCl₃), 1735, 1250, R_t = 1.06, (Found: C, 81.7; H, 11.55. Calc. for C₃₂H₅₄O₂: C, 81.5; H, 11.6%). Lit.⁽³⁾ m.p. 147-9°.

Tirucall-13-ene-3 β -ol acetate (isotirucallienyl acetate) (A6)⁽⁵⁾

Tirucall-8-ene-3 β -ol acetate (1.34 g., 0.0028 mol.) was isomerised by heating with glacial acetic acid (20 ml.)

and concentrated hydrochloric acid (0.8 ml.) at 100° for 4 hours. The product, after two recrystallisations from ethanol, gave tirucall-13-ene-3 β -ol acetate (0.801 g., 60%), m.p. $94-6^{\circ}$, $R_f = 1.00$, mixed melting point with authentic tirucall-13-ene-3 β -ol acetate gave m.p. 94° . (Found: C, 81.5; H, 11.6. Calc. for $C_{32}H_{54}O_2$: C, 81.5; H, 11.6%). Lit.⁽⁶⁾ m.p. $94-6^{\circ}$. (7.22)

16-Oxotirucall-13-ene-3 β -ol acetate (A7)⁽⁵⁾

Tirucall-13-ene-3 β -ol acetate (0.727 g., 0.0015 mol.) was oxidised with *t*-butyl chromate in carbon tetrachloride⁽⁷⁾ (15 ml. containing 2.1 g. of chromium trioxide) in the manner described for the epimeric mixture on page 52. 16-oxotirucall-13-ene-3 β -ol acetate was isolated as a gum (0.371 g., 50%) which slowly solidified, $R_f = 1.75$, $\nu_{\max.}$ ($CHCl_3$), 1730, 1690, 1630 cm^{-1} , $\lambda_{\max.}$ (EtOH) = 243 μ , $\epsilon = 13,800$. Lit.⁽⁵⁾ $\lambda_{\max.}$ (EtOH) = 243 μ , $\epsilon = 13,000$.

Chromatographic investigation of the neutral constituents of dammar resin.^(8,9)

A sample of the neutral dammar resin material (15.25 g.) from which the hydroxyhopanone had been extracted according to the directions of Dunstan, Fazakerley, Halsall and Jones,⁽¹⁰⁾ was chromatographed on alumina (750 g.). Elution with (1:1) light petroleum/benzene (8.25 L.) and benzene (0.75 L.) afforded a yellow gum (3.29 g.), $\nu_{\max.}$ ($CHCl_3$), 1705 cm^{-1} (saturated ketone C = O). Further elution with

benzene (6.75 L.) and (9:1) benzene/ether (6 L.) gave another gum (7.22 g.), $\nu_{\max.}(\text{CHCl}_3)$, 3300-3700 cm^{-1} (broad -OH absorption) and 1705 cm^{-1} . Elution with ether (2 L.) gave material (1.17 g.) which was not characterised.

Gas liquid chromatograms showed the middle fraction to be made up of two major components $R_t = 1.61$ and 1.19. This fraction (7.22 g.) in dry ether (30 ml.) was slowly added to a stirred suspension of lithium aluminium hydride (2 g.) in dry ether (100 ml.), and then heated under reflux for 12 hours. The resulting complex and the excess of hydride were decomposed with wet ether, water and dilute hydrochloric acid. The ethereal layer was separated and dried over magnesium sulphate. Evaporation of the ether left an almost colourless glass (6.54 g.), $\nu_{\max.}(\text{CHCl}_3)$, 3300-3600 cm^{-1} , $R_t = 1.13$, identical with an authentic sample of mixed C_{20} dammar-24-ene- $\frac{3}{4}$ 20-diol epimers (A8,A9) kindly provided by J. S. Mills.

Acetylation of the dammar-24-ene- $\frac{3}{4}$ 20-diol C_{20} epimeric mixture.

The epimeric mixture of diols (6.54 g., 0.015 mol.), taken up in redistilled pyridine (20 ml.) and acetic anhydride (20 ml.), was allowed to stand at room temperature for 12 hours. Evaporation of the volatile reagents left a residue which was washed through alumina (25 g.) with ether (200 ml.) to remove traces of pyridine and polymeric material.

Evaporation of the ensuing ether solution left a pale yellow gum (6.43 g., 90%), $\nu_{\max}$. (CHCl_3), 3400-3600, 1735, 1250 cm^{-1} , $R_f = 1.36$ (single peak).

Hydrogenation of the C_{20} epimeric mixture of dammar-24-ene-3,20-diol 3-acetates (A10, A11) (9)

The epimeric mixture of acetates (6.43 g., 0.013 mol.) was taken up in (1:1) ethyl acetate/ethanol (50 ml.) and hydrogenated over platinum oxide catalyst (0.29 g.). (380 ml. of hydrogen were taken up at a temperature of 18° and 74.5 cm. pressure). The catalyst was separated by filtration and the solvents were evaporated from the filtrate. The white solid residue of a C_{20} epimeric mixture of dammarane-3,20-diol 3-acetates (A12, A13) weighed 6.17 g., 95%.

Dehydration of the C_{20} epimeric mixture of dammarane-3,20-diol 3-acetates (A12, A13). (9)

The epimeric mixture of dammarane-3,20-diol 3-acetates (6.17 g., 0.013 mol.) in glacial acetic acid (120 ml.) and 2N sulphuric acid (4 ml.) was heated under reflux for 2 hours. The excess of acetic acid was then distilled and the residue was poured into water (200 ml.) and ether (200 ml.). The ethereal layer was separated, washed with 5% aqueous potassium hydroxide solution (3 x 50 ml.), water (100 ml.) and dried with anhydrous magnesium sulphate. Evaporation of the ether left a residue (5.31 g.) which was chromatographed on alumina (250 g.). Elution with light petroleum

(500 ml.) gave a dark coloured gum (0.710 g.) which gas-liquid chromatography showed to be a mixture of compounds with low retention times, $R_t = 0.26, 0.39$.

Further elution with light petroleum (500 ml.) afforded a clear gum (1.87 g.) which crystallised, $R_t = 1.00$, $\nu_{\max.}$ (CHCl_3), 1735, 1250 cm^{-1} . Two recrystallisations from dichloromethane/methanol gave crystals of m.p. $92-4^\circ$. A mixed melting point with tirucall-13-ene-3 β -ol acetate gave m.p. 92° . Tirucall-13-ene-3 β -ol acetate also gave an identical infra-red spectrum to the above compound.

Light petroleum (250 ml.) gave another fraction (0.495 g.) which did not crystallise and then a further (750 ml.) gave another gum (0.690 g.) which slowly crystallised, $R_t = 0.90$, $\nu_{\max.}$ (nujol), 1740, 1245 and 1265 cm^{-1} (doublet), $\nu_{\max.}$ (CS_2), 1740, 1245 cm^{-1} . Recrystallisation once from dichloromethane/methanol and three times from ethanol afforded euph-13-ene-3-ol 3-acetate (isoeuphenyl acetate) (A14), m.p. $110-11^\circ$, $(\alpha)_D^{19} = -12.1^\circ$ (Found: C, 81.4, H, 11.5. Calc. for $\text{C}_{32}\text{H}_{54}\text{O}_2$: C, 81.5; H, 11.6%). Lit.⁽⁹⁾ m.p. $111-13^\circ$.

Elution with ether (1 L.) gave material (1.56 g.). Gas-liquid chromatography showed a mixture $R_t = 1.00, 0.90$ and 1.34 (major product), $\nu_{\max.}$ (nujol), 3550 (sharp), 1735, 1705, 1245 cm^{-1} .

Calc. 10

Further elution with (2:1) light petroleum/benzene (1.5L.) and (1:1) light petroleum/benzene (750ml.) afforded the epimeric mixture of 16-oxotirucall-13-ene-3 β -ol 3-acetate (A15) as a pale yellow glass (1.50 g., 48%), $\nu_{\text{max.}}$ (CHCl₃), 1730, 1690, 1630 1250 cm.⁻¹, λ_{max} (EtOH) = 243 m μ , ϵ = 20,700, R_t = 1.75 (single peak). A portion was bulb distilled b.p. 200-210⁰ (bath temp.)/0.03 mm. (Found: C, 78.9; H, 10.5. Calc. for C₃₂H₅₂O₃: C, 79.1; H, 10.8%).

Oxidation of the combined mixture of tirucall-13-ene-3 β -ol 3-acetate and euph-13-ene-3 β -ol 3-acetate (A6,A14) with t-butyl chromate.

A solution of t-butyl chromate in carbon tetrachloride (35 ml. containing 4.9 g. of chromium trioxide)⁽⁷⁾ was slowly added to a cooled solution of the mixture of acetates (3.00 g., 0.0064 mol.) in dry benzene (40 ml.) and glacial acetic acid (20 ml.). The reaction mixture was allowed to stand at room temperature for 2½ days, then poured into water (300 ml.) and extracted with ether (3 x 100 ml.). The ethereal extract was washed with 10% aqueous sodium bisulphite solution (3 x 100 ml.), 10% aqueous sodium bicarbonate solution (3 x 100 ml.), water (100 ml.) and dried over magnesium sulphate. Evaporation of the ether left a crude residue of 3.14 g. This material was chromatographed on alumina (150 g.).

Elution with (2:1) light petroleum/benzene (750 ml.) gave a yellow gum (0.476 g.), $\nu_{\max}$. (CHCl₃), 1730, 1660, 1250 cm.⁻¹, $\lambda_{\max}$. (EtOH) = 256 mu, ϵ = 10,200. The epimeric mixture of 12-oxotirucall-13-ene-3 β -ol 3-acetate (A16) and 12-oxoeuph-13-ene-3 β -ol 3-acetate (A17) was purified by distillation b.p. 220-230° (bath temp.)/0.03 mm. (Found: C, 78.6; H, 10.5. Calc. for C₃₂H₅₂O₃: C, 79.1; H, 10.8%). *

Elution with ether gave material (0.623 g.) with no characteristic infra-red spectrum and no defined gas

chromatographic peaks.

The ozonolysis of tirucall-13-ene-3 β -ol 3-acetate (A6)

Tirucall-13-ene-3 β -ol 3-acetate (0.539 g., 0.0014 mol.) was taken up in (1:1) methanol/ethyl acetate (100 ml.) and ozonised oxygen (containing 5 mmoles O₃/hour) was passed for 30 minutes into the stirred solution, maintained at -70°. The solvent was evaporated and the residue was taken up in glacial acetic acid (100 ml.) containing 30% hydrogen peroxide (4 ml.) and water (5 ml.) and stirred overnight at room temperature. The excess of peroxide was decomposed by the addition of a trace of palladium charcoal catalyst and 20 minutes further stirring. Filtration through celite and evaporation of solvent left a residue which was dissolved in ether, the ethereal solution washed with water, 10% aqueous potassium hydroxide solution, water and dried with magnesium sulphate. Evaporation of the ether left a residue weighing 0.495 g., which was chromatographed on alumina (50 g.).

Elution with (5:1) light petroleum/benzene (500 ml.) afforded a yellow gum (0.188 g.) of extremely short retention time $R_f = 0.08$.

(1:1) Light petroleum/benzene (1 L.) gave a clear gum (0.260 g.) which slowly crystallised to give, after two recrystallisations from methanol, the ozonide of tirucall-13-ene-3-ol 3-acetate (A18) as a solid of m.p. 139-40°.

$\nu_{\text{max.}}$ (CHCl_3), 1735, 1250, 1060-1090 cm.^{-1} (broad absorption, possible C-O stretching of an ozonide).⁽¹¹⁾ Decomposition occurred at 200°/0.1 mm. also gas-liquid chromatography showed indistinct maxima consistent with decomposition (Found: C, 74.5; H, 10.5. $\text{C}_{32}\text{H}_{54}\text{O}_5$ requires: C, 74.1; H, 10.45%).

The reaction of tirucall-13-ene-3 β -ol 3-acetate (A6) with osmium tetroxide and hydrogen peroxide. (12,13)

A solution of tirucall-13-ene-3 β -ol 3-acetate (0.493 g., 0.0010 mol.) in ether (20 ml.) was treated with a solution of osmium tetroxide (0.039 g., 0.00015 mol.) in ether (2 ml.) and 30% hydrogen peroxide (1 ml.). The resultant mixture was allowed to stand with occasional shaking for 2 days. The excess of peroxide was decomposed with palladised charcoal and filtration and extraction of organic material from the filtrate with ether afforded a product weighing 0.450 g. after evaporation of solvents. This product was chromatographed on alumina (50 g.). Elution with light petroleum (450 ml.) gave a white solid (0.085 g.). $\nu_{\text{max.}}$ (CHCl_3), 1735, 1250 cm.^{-1} , $R_f = 1.00$, identical with the starting material.

Benzene (400 ml.) gave a yellow gum (0.166 g.), $\nu_{\text{max.}}$ (CHCl_3), 1730, 1690, 1630, 1250 cm.^{-1} , $R_f = 1.75$, identical with 16-oxotirucall-13-ene-3 β -ol 3-acetate (A7).

Ether eluted a further 0.035 g. of material, which could not be identified, from the column.

The reaction of osmium tetroxide and euph-13-ene-3 β -ol 3-acetate (A14). (14)

Osmium tetroxide (0.460 g., 0.0018 mol.) dissolved in redistilled dry pyridine (2 ml.) was added to a solution of euph-13-ene-3 β -ol 3-acetate (0.875 g., 0.0019 mol.) in pyridine (5 ml.). After standing for 2 days the excess of solvent was removed by distillation under reduced pressure. The residue was taken up in dry benzene (40 ml.) and added to a suspension of lithium aluminium hydride (1 g.) in (1:1) dry benzene/ether (20 ml.). The mixture was heated under reflux for 2½ hours and then the complex and excess of lithium aluminium hydride were decomposed with wet ether, water and dilute hydrochloric acid. Separation of the ether soluble material and evaporation of the ether left a residue weighing 0.981 g. A portion (0.362 g.) was chromatographed on alumina (25 g.).

Benzene (275 ml.) eluted 0.069 g. of a yellow gum which showed no absorption in the infra-red at 3500 cm.⁻¹ (hydroxyl) and could therefore not be reduced starting material or a desired product. (1:1) Benzene/ether (150 ml.), however, eluted 0.208 g. of material which slowly crystallised. Two recrystallisations from methanol gave euph-3 β , 13,17-triol with one methanol of crystallisation as

leaflets m.p. 189-90°, $\nu_{\max.}$ (CHCl₃), 3500 cm.⁻¹ (Found: C, 74.9; H, 11.4. C₃₀H₅₄O₃, CH₃OH requires: C, 75.0; H, 11.8%). Lit.⁽¹⁵⁾ Jeger et al. record a m.p. of 185° for the triol (A19) recrystallised from hexane/chloroform.

The cleavage of euph-3 β ,13,17-triol (A19) with lead tetra-acetate. (14,15)

A solution of lead tetra-acetate (2.5 g.) in glacial acetic acid (30 ml.) was added to a solution of euph-3 β ,13,17-triol (0.610 g., 0.0013 mol.) in glacial acetic acid (10 ml.). After standing at room temperature for 2 days the excess of acetic acid was distilled, water and ether were added to the residue and the ether layer was separated. Evaporation of the ether left material which was acetylated with acetic anhydride and pyridine in the usual manner. The acetylated products were chromatographed on alumina (50 g.)

Elution with (1:1) light petroleum/benzene (1 L.) gave the expected diketone (A20) as a white solid (0.385 g.) which after two recrystallisations from methanol gave m.p. 137°, $\nu_{\max.}$ (CHCl₃), 1730, 1700, 1250 cm.⁻¹, (Found: C, 76.1; H, 11.1. Calc. for C₃₂H₅₄O₄: C, 76.2; H, 10.8%) Lit.⁽¹⁵⁾ m.p. 137-8°.

The reaction of tirucall-13-ene-3 β -ol 3-acetate (A6) with osmium tetroxide and cleavage of the resultant glycol with lead tetra-acetate. (5)

Tirucall-13-ene-3 β -ol 3-acetate (0.918 g., 0.00195 mol.)

was similarly converted in the manner described earlier, p.55, with the aid of osmium tetroxide (0.500 g., 0.0020 mol.) and lead tetra-acetate (3.0 g.) followed by acetylation to the acetoxy-diketone (A21) (0.334 g., 34%). Recrystallisation from methanol gave crystals of m.p. 119-121°, (Found: C, 76.5; H, 10.8. Calc. for $C_{32}H_{54}O_4$; C, 76.2; H, 10.8%). Lit.⁽⁵⁾ m.p. 116-7°.

Attempted Baeyer-Villiger oxidation of the acetoxy-diketone (A21)^(16,17,18)

Peroxytrifluoroacetic acid⁽¹⁹⁾ (0.20 ml.) containing 0.0022 mol. of active oxygen/ml. was slowly added to a vigorously stirred ice-cold solution of the acetoxy-diketone (0.194 g., 0.0038 mol.) dissolved in dichloromethane (2 ml.) containing a slurry of anhydrous disodium hydrogen phosphate (0.142 g.). The resulting mixture was heated under reflux for 3 hours, diluted with water and extracted with ether. The ethereal extract was washed with dilute aqueous sodium bicarbonate solution, water and then dried with magnesium sulphate. Evaporation of the ether left a residue weighing 0.191 g. which was chromatographed on alumina (30 g.) to yield, upon elution with (1:1) light petroleum/benzene (720 ml.), 0.045 g. of a yellow gum, $\nu_{\max.}$ ($CHCl_3$), 1735, 1250 cm^{-1} . Elution with benzene (300 ml.) gave a further 0.108 g. of solid

material, $\nu_{\max}$. (CHCl_3), 1730, 1700, 1250 cm^{-1} identical with the starting material.

The experiment was repeated using acetoxo-diketone (0.236 g., 0.00047 mol.), peroxytrifluoroacetic acid (0.30 ml.) containing 0.0023 mol. of active oxygen/ml. and heating under reflux for 4 hours, but the same percentage of starting material was recovered.

The attempted ring closure of the acetoxo-diketone (A2B)

- a) The use of sodium amalgam⁽²¹⁾ in (1:1) n-propanol/
glacial acetic acid.⁽²⁰⁾

2% Sodium amalgam (30 g.) was added over a period of 30 minutes to a stirred solution of the acetoxo-diketone (0.143 g., 0.00028 mol.) in (1:1) n-propanol/glacial acetic acid (15 ml.). After stirring for a further 30 minutes the products were poured into water (100 ml.) and the aqueous phase was extracted with ether. The ethereal extract was washed in 10% aqueous potassium hydroxide, water and dried. Evaporation of the ether left starting material (0.138 g.), $\nu_{\max}$. (CHCl_3), 1730, 1700, 1250 cm^{-1} .

- b) The use of aluminium powder/mercuric chloride in
dry benzene.^(24,25)

The acetoxo-diketone (0.293 g., 0.00058 mol.), aluminium powder (0.085 g.), mercuric chloride (0.047 g.) and dry benzene (0.5 ml.) were stirred together under reflux

for 20 hours. Benzene (0.5 ml.) and water (0.5 ml.) were added, stirring and heating being continued for a further 3 hours. The reaction mixture was then poured into water and extracted with ether. The ethereal extract yielded starting material (0.261 g.), $\nu_{\text{max.}}$ (CHCl_3), 1730, 1700, 1250 cm.^{-1} .

c) The use of molten sodium in dry xylene. (22,23)

The acetoxy-diketone (0.300 g., 0.0006 mol.), in dry xylene (2.5 ml.), was stirred under oxygen free dry nitrogen. Sodium (0.082 g.) was added and the temperature was raised until the xylene refluxed. Heating was continued for 48 hours. After cooling, a little ethanol (2 ml.) was added to decompose any sodium residue and then the products were poured into dilute hydrochloric acid (50 ml.) and extracted with ether. The ethereal extract was washed with dilute aqueous potassium hydroxide, dilute hydrochloric acid, water and dried. Evaporation of the ether left a residue weighing 0.195 g. which was chromatographed on alumina (10 g.).

Elution with (2:1) benzene/ether (100 ml.) gave a clear gum which quickly solidified (0.034 g.) m.p. 205-7°, $\nu_{\text{max.}}$ (CHCl_3), 3600 (sharp), 3600-3300 cm.^{-1} (broad), suggesting the formation of a tetracyclic triol. (Found: C, 77.1; H, 11.4. $\text{C}_{30}\text{H}_{54}\text{O}_3$ requires: C, 77.8, H, 11.75%).

Attempts to prepare the tricyclic relay (A22)

a) Ozonolysis of 16-oxotirucall-13-ene-3 β -ol 3-acetate (A7)⁽⁵⁾

A solution of 16-oxotirucall-13-ene-3 β -ol 3-acetate (1.29 g., 0.0027 mol.) in (1:1) ethyl acetate/glacial acetic acid (80 ml.) was vigorously stirred at -10°. A stream of dry ozonised oxygen, containing 8.4 mmoles ozone/hour, was passed into the solution for a period of 2.5 hours, after which the products were allowed to come to room temperature in a stream of nitrogen. Distilled water (5 ml.) and 30% hydrogen peroxide were added and the resultant mixture was vigorously stirred for 24 hours. The excess of peroxide was decomposed by the addition of a little platinum oxide and the products were filtered through celite. The solvent was removed from the filtrate by distillation under reduced pressure and the residue was taken up in ether. The ethereal solution was extracted with 10% aqueous potassium hydroxide. The alkaline extract was reacidified with dilute hydrochloric acid and the liberated organic acids (0.402 g.) were isolated with ether and esterified with diazomethane.^(27,28) An infra-red spectrum showed absorption at 3500 cm.⁻¹ (hydroxyl). Acetylation with acetic anhydride/pyridine gave material showing no absorption at 3500 cm.⁻¹. This material (0.387 g.) was chromatographed on alumina (50 g.).

Elution with (1:1) light petroleum/benzene (500 ml.) gave methyl 2,6-dimethylheptanoate (A23) (0.124 g.), a clear sweet smelling liquid, which was bulb-distilled, b.p. 85-90° (bath temp.)/20 mm., (Found: C, 70.3; H, 11.8. Calc. for $C_{10}H_{20}O_2$: C, 69.9; H, 11.7%). Lit.⁽⁵⁾ b.p. 75-80° (bath temp.)/12 mm.

(7:1) Benzene/ether eluted a clear gum (0.208 g.) which solidified and was recrystallised twice from methanol/dichloromethane to give crystals of the acetoxy-keto ester (A22) m.p. 199-201° (Kofler), (Found: C, 70.75; H, 9.50. Calc. for $C_{24}H_{38}O_5$: C, 70.9; H, 9.44%). Lit.⁽⁵⁾ m.p. 195-6°.

The initial ethereal extract, after removal of the acidic portion, was washed with water, dried with magnesium sulphate and the ether evaporated to leave a residue (1.71 g. from three runs). This was chromatographed on alumina (100 g.)

Elution with (2:1) light petroleum/benzene (1.4 L.) and (1:1) light petroleum/benzene (600 ml.) gave 0.663 g. of a yellow viscous liquid, ν_{max} . ($CHCl_3$), 1730, 1690, 1630, 1250 cm^{-1} , λ_{max} . (EtOH) = 243 m μ , ϵ = 11,600, identical with 16-oxotirucall-13-ene-3-ol 3-acetate (A7).

Further elution with benzene (500 ml.) gave a clear gum (0.056 g.), ν_{max} . ($CHCl_3$), 1780, 1740, 1730, 1690 (w), 1630 (w), 1250 cm^{-1} . The complexity of the carbonyl region was attributed to a mixture of oxygenated compounds being present, γ -lactone, saturated C=O of a 5-membered ring ketone, acetate and also a trace of the $\alpha\beta$ -unsaturated

ketone (A7).

Ether (1 L.) eluted a mixture of hydrolysed products (0.445 g.) $\nu_{\text{max.}}$ (CHCl_3), 3500 cm.^{-1} (broad and strong). Gas-liquid chromatography gave broad indistinct peaks.

In a further experiment the reaction conditions were essentially as above, using 16-oxotirucall-13-ene-3 β -ol 3-acetate (1.19 g., 0.0025 mol.) in "Analar" ethyl acetate (50 ml.). However, tetracyanoethylene (0.320 g., 0.0025 mol.) was added prior to the passage of ozonised oxygen.⁽²⁹⁾ Tetracyanoethylene showed $\lambda_{\text{max.}}$ (EtOAc) = 257 m μ , this peak was no longer present after ozonolysis. The yield of acidic material was not improved, being only 0.170 g.

The results of eight ozonolysis experiments are condensed in the table below. The experiments already described are 3 and 8 respectively.

wt. of 16-oxotirucall-13-ene-3 β -ol 3-acetate (g.)	Solvent	Temperature.	Time O_3 passed ³ (hr.)	Acid products (g.)
1. 0.810	Ethylacetate ⁽⁵⁾	-70°	3.5	0.470
2. 0.569	"	"	5	0.269
3. 1.290	Et.Ac./Acetic Acid ⁽²⁶⁾	-10°	2.5	0.402
4. 1.290	"	"	5.25	0.500
5. 0.165	"	"	6	0.059
6. 0.939	"	"	6	0.355
7. 0.227	Methanol ^(30,31,32)	-70°	3.5	0.026
8. 1.190	EtAc.(TCNE present) ⁽²⁹⁾	-70°	0.33	0.170

In experiment (3) the ozonised oxygen stream contained 14.4 m.moles ozone/hour, in the other seven experiments a stream containing 8.4 m.moles/hour was passed.

- b) The action of alkaline 30% hydrogen peroxide on an epimeric mixture of 16-oxotirucall-13-ene-3 β -ol 3-acetate and 16-oxoeuph-13-ene-3 β -ol 3-acetate (A7.A15)⁽³⁾

30% Hydrogen peroxide (6 ml.) and aqueous 4N potassium hydroxide (6 ml.) were simultaneously added to a stirred solution of an epimeric mixture of 16-oxotirucall-13-ene-3 β -ol 3-acetate and 16-oxoeuph-13-ene-3 β -ol 3-acetate (1.41 g., 0.0029 mol.) in methanol (100 ml.). The reaction vessel was kept at 0° for 7 days. The excess of methanol was distilled and the remainder was poured into an excess of water and ether. The ethereal extract was washed with dilute hydrochloric acid, water, and dried. Evaporation of the ether left a residue (1.025 g.) $\nu_{\text{max.}}$ (CHCl₃), 3500, 1690, 1630 cm.⁻¹. Acetylation with acetic anhydride and pyridine gave starting material (1.00 g.), $\nu_{\text{max.}}$ (CHCl₃) 1730, 1690, 1630, 1250 cm.⁻¹, R_f = 1.75 (single peak despite being an epimeric mixture).

- c) The reaction of osmium tetroxide and 16-oxotirucall-13-ene-3 β -ol 3-acetate (A7)

A solution of 16-oxotirucall-13-ene-3 β -ol 3-acetate (0.350 g., 0.0018 mol.) in dry pyridine (10 ml.) was treated with osmium tetroxide (0.500 g., 0.0020 mol.) and kept at

room temperature for 5 days. The solvent was removed by distillation under reduced pressure. To the residue was added dry benzene (100 ml.), dry ether (30 ml.) and lithium aluminium hydride (1 g.). The resultant mixture was heated under reflux for 4 hours and worked up as usual to give a product weighing 0.760 g. Reaction with lead tetra-acetate (3 g.) in the manner described on p. 56, gave a compound identified as tirucall-13-ene-3 β ,16-diol (A31) (0.663 g.) m.p. 106-7°, $\nu_{\text{max.}}$ (CHCl₃), 3500 cm.⁻¹ identical with a sample of tirucall-13-ene-3 β ,16-diol from direct reduction of 16-oxotirucall-13-ene-3 β -ol 3-acetate. (Found: C, 81.75; H, 11.6. C₃₀H₅₂O₂ requires: C, 81.0; H, 11.8%.)

- d) The action of potassium permanganate/sodium periodate on 16-oxotirucall-13-ene-3 β -ol 3-acetate (A7). (34,35,36).

Potassium carbonate (1 g.) in water (12 ml.) was added to a vigorously stirred solution of 16-oxotirucall-13-ene-3 β -ol 3-acetate (0.835 g., 0.0017 mol.) in *t*-butanol/water azeotrope (21.7% water) (25 ml.) followed by 7.5 ml. of a solution made up from sodium periodate (3 g.) and water (30 ml.) A 0.8% aqueous solution of potassium permanganate (1 ml.) was added and the remaining periodate solution was slowly added over a period of 30 minutes. The pH of the solution was between 8.5 and 9. The reaction mixture which remained pink showing an excess of permanganate throughout the

experiment, was stirred for a total period of 2 hours. Sodium bisulphite (0.5 g.) was added to stop the reaction and the mixture was concentrated under reduced pressure. After cooling to 5° the products were acidified with cold aqueous 50% sulphuric acid and the mixture was extracted with ether. The ethereal extract was washed with dilute aqueous sodium bisulphite, water and dilute aqueous potassium hydroxide. Reacidification of the alkaline extract afforded 0.026 g. of organic acid material. The neutral material remaining in the ethereal solution was found to be starting material (0.711 g.), $\nu_{\text{max.}}$ (CHCl_3), 1730, 1690, 1630, 1250 cm.^{-1} $R_t = 1.75$.

Kolbe Electrolyses

a) The coupling of myristic acid (A24) (37)

Recrystallised myristic acid, m.p. 56-7°, (0.231 g., 0.0010 mol.) was dissolved in methanol (2 ml.) containing sodium (0.216 g., 0.0094 mol./l.). The solution was placed in an electrolytic cell containing platinum electrodes 0.75 sq.cm. in area. The cell was surrounded by an ice/brine bath. A current of 0.16 amps was passed for $\frac{1}{2}$ hour, during which time the methanol was refluxing. The pH at this stage was 8. The products were poured into water and ether. The ethereal extract was washed with dilute aqueous potassium hydroxide, water, then dried. Evaporation of

the ether left a white solid (0.176 g., 96%).

Recrystallisation from light petroleum gave crystals of *n*-hexacosane, m.p. 56° . An infra-red spectrum showed CH absorptions only. A gas-liquid chromatogram showed the product to be a single compound. The chromatographic column in this instance contained 30% apiezon 'L' and 2.7% sodium caproate on 90-100 mesh embacel as the stationary phase. The column was run at a temperature of 165° and a gas flow pressure of 10 lb./sq.in. Lit.⁽³⁷⁾ m.p. $57-8^{\circ}$.

- b) The attempted coupling of the hydroxy-keto acid (A25) and 2,5,5-trimethyl-2-carboxymethylcyclohexanone (A26) ^(8,394)

The acetoxy-keto ester (A22) (0.059 g., 0.00015 mol.) was hydrolysed with a solution of 5% methanolic potassium hydroxide (15 ml.) by heating under reflux for $2\frac{1}{2}$ hours. The resultant sparingly soluble hydroxy-keto acid (0.051 g., 0.00015 mol.) was dissolved in methanol (3 ml.) to which 2,5,5-trimethyl-2-carboxymethylcyclohexanone (0.104 g., 0.00053 mol.) and sodium (0.165 g., 0.0072 mol./L.) had been added. The electrolytic cell was immersed in an ice/brine bath and a current averaging 0.20 amps (current density of 0.27 amps/sq.cm.) was passed for 1 hour, during which time the methanol was refluxing. The excess of methanol was evaporated and the residue taken up in ether. The ethereal extract was washed with dilute aqueous potassium hydroxide solution, water and dried. Evaporation

of the ether left a residue weighing 0.099 g. A gas-liquid chromatogram run at 165° and 10 lb./sq.in. gas inlet pressure, showed mainly one compound to be present.

Chromatography on alumina (10 g.) gave a white solid (0.030 g.) as the light petroleum/benzene (1:1) extract, $\nu_{\text{max.}}$ (CHCl_3), 1705 cm^{-1} (v.s.) Sublimation at 100-10° (bath temp.)/0.03 mm. gave 1,2-bis (2'-oxo-1'.4'.4'-trimethylcyclohexyl) ethane (A27) (Found: C, 77.8; H, 11.0. $\text{C}_{20}\text{H}_{34}\text{O}_2$ requires: C, 78.2; H, 11.2%).

The potassium hydroxide extract was reacidified to give, after ether extraction, acidic material 0.030 g.

$\nu_{\text{max.}}$ (CHCl_3), 3500 (very broad absorption to 2400), 1705 cm^{-1} (broad).

The experiment was repeated but in this case the 2,5,5-trimethyl-2-carboxymethylcyclohexanone was slowly added over the first 15 minutes of the electrolysis. The results, however, were as in the above experiment.

Experiments on the fission of the 13,18-double bond in δ -amyrin (A28).

β -Amyrin acetate (A29)

β -Amyrin benzoate was isolated from Manila elemi resin using the procedure described by Vesterberg and Westerlind.⁽⁴¹⁾ It had m.p. 230-4°, after three recrystallisations from light petroleum (b.p. 60-80°). Lit.⁽⁴¹⁾ m.p. 230°.

Hydrolysis of the benzoate with methanolic potassium hydroxide (5%) gave β -amyrin (A30) m.p. 194° . Lit. (42) m.p. 193° . Acetylation with acetic anhydride/pyridine in the usual manner gave the acetate m.p. $237-9^{\circ}$, after recrystallisation from light petroleum (b.p. $60-65^{\circ}$) (3.0 g. from 14.1 g. of benzoate). Lit. (43) m.p. $240-41^{\circ}$.

δ -Amyrin (A28).

β -Amyrin acetate (7.5 g., 0.016 mol.) was oxidised with selenium dioxide using conditions analogous to those described by Spring and co-workers (43) to give β -amyradienyl acetate (5.14 g., 69%), as plates m.p. $226-8^{\circ}$ from methanol/chloroform $\lambda_{\text{max.}}$ (EtOH) = 243, 251, 260 m μ and ϵ = 22,200, 32,700, 16,100 respectively. Lit. (43) m.p. $225.5-227^{\circ}$, $\lambda_{\text{max.}}$ (EtOH) = 243, 251, 260 m μ , ϵ = 27,300, 29,100, 19,500. Hydrogenation with Adams catalyst in glacial acetic acid (44) gave δ -amyrin acetate (3.39 g., 64%) m.p. $209-10^{\circ}$. Lit. (45) m.p. $208.5-209.5^{\circ}$. The characteristic ultra-violet absorption was no longer present. Hydrolysis with methanolic potassium hydroxide (5%) gave δ -amyrin as fine crystals (3.00 g., 97%) m.p. $210-11^{\circ}$. Lit. (46) m.p. $210-12^{\circ}$.

The ozonolysis of δ -amyrin acetate (A32)

Ozonised oxygen (containing 8 m.moles of ozone/hour) was passed for 3 hours into a stirred solution of δ -amyrin acetate (0.500 g., 0.0011 mol.) in 'Analar' ethyl acetate (100m.

maintained at -70° . The reaction mixture was worked up as in the experiment described on p. 60, to give a neutral solid product (0.404 g.), $\nu_{\max.}$ (CHCl_3) 1730, 1250 cm^{-1} , identical with the starting material, m.p. 209° .

The reaction of osmium tetroxide and δ -amyrin acetate (A32)⁴⁶

δ -Amyrin acetate (0.949 g., 0.0020 mol.) was dissolved in redistilled dry pyridine (50 ml.) containing osmium tetroxide (0.500 g., 0.0020 mol.) and the solution was heated under reflux for $2\frac{1}{2}$ weeks. After distilling the excess of pyridine a solution of sodium sulphite (3 g.) in (1:1) ethanol/water (150 ml.) was added and the mixture was heated under reflux for 12 hours then filtered. The ethanol was distilled from the filtrate and the residue was extracted with ether. The ethereal solution was dried and evaporated to give unchanged starting material (0.776 g.), m.p. and mixed m.p. 208° , $\nu_{\max.}$ (CHCl_3) 1730, 1250 cm^{-1} .

The preparation of monocyclic precursors for ring E of the pentacyclic amyirin class of triterpenes.

3-Chloro-5,5-dimethylcyclohex-2-en-1-one (A32a).

Recrystallised dione (62.4 g., 0.45 mol.), prepared by the method of Shriner and Todd,⁽⁴⁷⁾ dissolved in dry chloroform (2.5 L.) was treated with phosphorus trichloride (45 ml., 70.3 g., 0.51 mol.) in the manner described by Halseall and Thomas,⁽⁴³⁾ to give 3-chloro-5,5-dimethylcyclohex-2-en-1-one (49.7 g. 70.5%) as a colourless liquid

b.p. 90-95°/20 mm., $n_D^{20} = 1.4950$, (Found: C, 60.4; H, 6.91; Cl, 22.6. Calc. for $C_8H_{11}ClO$: C, 60.5; H, 6.99; Cl, 22.3%).
 Lit.⁽⁵¹⁾ b.p. 87-90°/20 mm., $n_D^{20} = 1.4944$.

3,3-Dimethylcyclohexanone (A33).

3-Chloro-3,5-dimethylcyclohex-2-en-1-one (49.7 g., 0.31 mol.) in dry ethanol (700 ml.) was shaken with palladium on charcoal catalyst (20 g., 10%) in an atmosphere of hydrogen.⁽⁴⁹⁾ The initial rate of hydrogenation was very rapid, but slowed considerably after 7 L. had been taken up, however the rate increased with more catalyst (10 g.) until after a period of 22 hours, 10 L. of hydrogen had been taken up. Ammonia solution (15 ml., d, 0.880) was added and the reaction continued until no further hydrogen was taken up (15 L. in all). The ethanol was evaporated, the product was isolated with ether and distilled, the fraction of b.p. 59-69°/13 mm. being collected. Redistillation afforded 3,3-dimethylcyclohexanone (17.5 g., 44%) as the fraction b.p. (63-69°)/13 mm. Lit.⁽⁵⁰⁾ b.p. (66-68°)/14 mm.

2-Ethoxycarbonyl-3,3-dimethylcyclohexanone (A34).

3,3-Dimethylcyclohexanone (7.92 g., 0.063 mol.) was carbethoxylated by the method of Adams et al.⁽⁵²⁾ to give 2-ethoxycarbonyl-3,3-dimethylcyclohexanone (6.44 g., 0.033 mol. 61%), b.p. 115-120°/10 mm., $n_D^{17} = 1.4714$, $\lambda_{max.} (EtOH) = 256 \text{ m}\mu$, $\epsilon = 1620$, (Found: C, 66.2; H, 9.23. Calc. for

$C_{11}H_{18}O_3$: C, 66.6; H, 5.10%. Lit. (52) b.p. 125-128°/
14 mm., $n_D^{20} = 1.4716$.

2,5,5-Trimethylcyclohexan-1,3-dione (A35) (48)

Methyl iodide (25 ml., 57 g., 0.40 mol.) was slowly added (15 minutes) to a solution of dimedone (40 g., 0.29 mol.) in dry ethanol (150 ml.) containing sodium (6.6 g., 0.29 mol.) maintained at less than 5°. The mixture was allowed to come to room temperature and heated under reflux for 3.5 hours, then the ethanol was evaporated, the residue taken up with ether (500 ml.) and the ethereal solution washed with 10% aqueous sodium bicarbonate solution. The aqueous phase was separated and acidified with dilute hydrochloric acid to give 2,5,5-trimethylcyclohexan-1,3-dione (12.2 g., 27%) m.p. 159-161°, after recrystallisation from acetone, λ_{max} (EtOH) = 251 mμ, $\epsilon = 13,620$. Lit. (48) m.p. 158-9°.

The experiment was carried out three times on a similar scale to give an average yield of 26%.

The ethereal solution remaining after washing with sodium bicarbonate was washed with dilute hydrochloric acid, water, and dried and evaporated. The residue, when hydrolysed by boiling for 4 hours with a solution of potassium hydroxide (20 g.) in methanol (140 ml.)/water (40 ml.) gave dimedone (10 g.), m.p. and mixed m.p. 149°.

2,5,5-Trimethyl-2-ethoxycarbonylmethylcyclohexan-1,3-dione (A36)

~~CHCl₃~~ 2,5,5-Trimethylcyclohexan-1,3-dione (9.01 g., 0.056 mol.) in dry benzene (300 ml.) was added under dry oxygen-free nitrogen to solid sodium ethoxide, prepared from sodium (1.55 g., 0.058 mol.) and dry ethanol (20 ml.). The resulting mixture was heated under reflux as ethyl bromoacetate (10 ml., 15 g., 0.09 mol.) was added. After 14 hours refluxing the benzene was distilled and the residue poured into water (300 ml.), the aqueous mixture was extracted with ether and the ethereal extract was washed with 10% aqueous sodium bicarbonate solution, water and dried. Evaporation of the ether left a residue (6.44 g.) which was chromatographed on alumina (300 g.).

Elution with (3:1) light petroleum/benzene (900 ml.) and (1:1) light petroleum/benzene (2.1 L.) gave 2,5,5-trimethyl-2-ethoxycarbonylmethylcyclohexan-1,3-dione (3.66 g., 29%) as a colourless liquid b.p. 160-170° (bath temp.)/0.1 mm., m.p. 41-43°, $\nu_{\max.}$ (CHCl₃), 1735, 1703 cm.⁻¹, (Found: C, 65.3; H, 8.41. Calc. for C₁₃H₂₀O₄: C, 65.0; H, 8.41%). Lit.⁽²⁾ m.p. 42.5-43°.

Elution with benzene (1.2 L.) and ether (0.9 L.) gave a gum (0.799 g.) containing a mixture of O-alkylated material and unchanged starting material $\nu_{\max.}$ (CHCl₃), 3500, 1720 (broad), 1610 cm.⁻¹ (H-bonded ketone C=O).

The reaction was repeated using 2,5,5-trimethylcyclohexan-1,3-dione (2.5 g., 0.016 mol.), a yield of 41% being obtained.

The action of ethanedithiol on 2,5,5-trimethyl-2-ethoxycarbonylmethylcyclohexan-1,3-dione (A36). (2,53)

A mixture of 2,5,5-trimethyl-2-ethoxycarbonylmethylcyclohexan-1,3-dione (3.45 g., 0.014 mol.), ethane dithiol (1.55 g., 0.014 mol.) and boron trifluoride etherate (1.5 ml., 48% w/w) was allowed to stand at room temperature for 12 hours. The reaction products were poured into water and extracted with ether. The ethereal extract was dried and the solvent evaporated to leave an oil (3.23 g.) which was chromatographed on alumina (150 g.).

Elution with (3:1) light petroleum/benzene (600 ml.) gave 2,5,5-trimethyl-2-ethoxycarbonylmethylcyclohexan-1,3-dione bis-ethanedithioketal (A37) as a solid (0.946 g.) which after two recrystallisations from light petroleum (b.p. 60-80°) gave colourless needles of m.p. 124-5°. $\nu_{\max}$. (CHCl₃), 1730 cm.⁻¹. (Found: C, 52.4; H, 7.29; S, 32.15. Calc. for C₁₇H₂₈O₂S₄: C, 52.0; H, 7.13; S, 32.6%). Lit.⁽²⁾ m.p. 118-9°.

Further elution with (3:1) light petroleum/benzene (600 ml.) and benzene (450 ml.) gave 2,5,5-trimethyl-2-ethoxycarbonylmethylcyclohexan-1,3-dione mono-ethanedithioketal (A38) as a solid (2.6 g., 59%) which after recrystallisation from light petroleum (b.p. 60-80°) gave needles of m.p. 88.5-89°.

$\nu_{\max}$. (CHCl₃), 1735, 1705 cm.⁻¹. (Found: C, 57.0; H, 7.64; S, 20.0. Calc. for C₁₅H₂₄O₃S₂: C, 56.9; H, 7.65; S, 20.3%). Lit.⁽²⁾ m.p. 88-89°.

2,5,5-Trimethyl-2-ethoxycarbonylmethylcyclohexanone (A39)

2,5,5-Trimethyl-2-ethoxycarbonylmethylcyclohexan-1,3-dione mono-ethanedithioketal (0.36 g., 0.0011 mol.) was taken up in dry ethanol (2 ml.) and added to a stirred suspension of Raney nickel (~ 3 g.)⁽⁵⁴⁾ in absolute ethanol (40 ml.). The reaction mixture was heated under reflux for 14 hours. The products were filtered through celite to remove the catalyst and the filtrate was concentrated to a volume of 20 ml. The last traces of nickel were removed by centrifuging. Complete evaporation of the solvent left a liquid residue (0.152 g., 58.5%). This was bulb distilled to give 2,5,5-trimethyl-2-ethoxycarbonylmethylcyclohexanone as a fraction of b.p. $100-110^\circ$ (bath temp.)/0.05 mm. $V_{\max}$. (CHCl_3) 1735, 1705, 1190, 1030 cm^{-1} (Found: C, 69.3; H, 9.73; S, nil. $\text{C}_{13}\text{H}_{22}\text{O}_3$ requires: C, 69.0; H, 9.84%).

The reaction was repeated using 2,5,5-trimethyl-2-ethoxycarbonylmethylcyclohexan-1,3-dione mono-ethanedithioketal (0.907 g., 0.0029 mol.) giving a yield of 83%.

2,5,5-Trimethyl-2-carboxymethylcyclohexanone (A26).

2,5,5-Trimethyl-2-ethoxycarbonylmethylcyclohexanone (0.546 g., 0.0024 mol.) was boiled under reflux for 4 hours with a 3% aqueous methanolic solution of potassium hydroxide (10 ml. (4:1) methanol/water). The excess of methanol was distilled and the remainder was poured into dilute hydrochloric acid (50m

and the resultant mixture was extracted with ether to give in the usual way 2,5,5-trimethyl-2-carboxymethylcyclohexanone as a viscous liquid (0.466 g., 98%). b.p. 100-125° (bath temp.) /0.05 mm., which slowly set to give crystals m.p. 50-52°,

$\nu_{\text{max.}}$ (CHCl₃), 1780, 1720, 1705 cm.⁻¹ (Found: C, 66.2; H, 8.92. C₁₁H₁₈O₃ requires, 66.6; H, 9.15%).

A comparison table of gas-liquid chromatographic retention times (R_t) for compounds described in this section is illustrated below.

<u>Name of Compound</u>	<u>Retention time (R_t).</u>
1. Tirucall-13-ene-3 β -ol 3-acetate (A6)	1.00
2. Tirucall-8-ene-3 β -ol 3-acetate (A4)	1.06
3. Tirucall-8-ene-3 β ,21-diol 3-acetate-21-methanesulphonate (A3)	1.29
4. Tirucall-8-ene-3 β -ol (A5)	1.03
5. 16-Oxotirucall-13-ene-3 β -ol 3-acetate (A7)	1.75
6. Epimeric C ₂₀ mixture of dammar-24-ene-3 β , 20-diols ²⁰ (A8 + A9)	1.13
7. Epimeric C ₂₀ mixture of dammar-24-ene-3 β , 20-diol ²⁰ 3-acetates (A10 + A11)	1.36
8. Euph-13-ene-3 β -ol 3-acetate (A14)	0.90
9. Epimeric C ₂₀ mixture of 16-oxotirucall-13-ene-3 β -ol 3-acetate and 16-oxoeuph-13-ene-3 β -ol 3-acetate (A7 + A15)	1.75
10. The tricyclic acetoxy-keto ester (A22)	0.48

Section B.

THE ATTEMPTED PREPARATION OF A HYDROXYLATED 'AB' INTERMEDIATE WHICH COULD BE INCORPORATED INTO AN 'AB + DE' SYNTHESIS OF A PENTACYCLIC MEMBER OF THE OLEANANE CLASS OF TRITERPENES.

Although the researches into the preparation and utilisation of the tricyclic intermediate (A22) were making definite headway, the success of Littlehailes' route to the pentacyclic mixture of oleanenes (B40, B41) possessing the correct natural configuration⁽¹¹³⁾ provided a tremendous impetus to the desire to obtain a hydroxylated bicyclic AB moiety which after coupling with the octalone (B34) and acid cyclisation would lead to a pentacyclic triterpene possessing both the natural configuration and a 3β -hydroxyl group.

In addition later work has shown that the alkyl halide (B35) can be used to alkylate the octalone (B42)⁽¹¹⁴⁾ the latter possessing an angular methoxycarbonyl group in contrast to the methyl group present in (B34).

The immediate solution to the problem of synthesising a hydroxylated bicyclic intermediate appeared to lie in the preparation of a cyclohexanone derivative such as (B12) which could then be condensed with a molecule of methyl vinyl ketone in the presence of a catalytic amount of base to give the octalone (B34).

A preliminary investigation into this route has already been carried out by Littlehailes.⁽⁴⁹⁾ A Michael addition

of ethyl 2-oxo-3-ethoxycarbonylbutyrate (B8) and ethyl vinyl ketone in the presence of triton B, gave the adduct (B10). This was cyclised under acidic conditions by a process involving the simultaneous decarboxylation of the vinylogous intermediate β -keto acid (B9). The product (B11) was then esterified with diazomethane to give the cyclohexenone derivative (B12). The procedure has the beauty of cheap, easily accessible, starting materials, simplicity, and a very high overall yield.

The projected ring extension with methyl vinyl ketone, however, did not occur in the expected way, the substitution appearing to favour the thermodynamically more stable C₍₆₎ position and an impure product was isolated which was tentatively identified as (B44) from its ultra-violet spectrum. Moreover in the present investigation, the base-catalysed addition of acrylonitrile to the monocyclic intermediate (B12) led to indiscriminate substitution and a disubstituted product which could only be (B25) was isolated. It was at this stage that the work contained in this section really began.

To prevent substitution at the 6 position in (B12) it would be possible to insert a blocking group so that any reversible substitution reaction of (B12) with methyl vinyl ketone or acrylonitrile would now go in the desired 2 position. Many blocking groups devised for this purpose are described

in the literature. Littlehales⁽⁴⁹⁾ in fact prepared the 6-benzylidene derivative by a method devised by Johnson.⁽¹¹⁵⁾ The elimination of the benzylidene group after the desired substitution has taken place, however, presents many difficulties. The principal ones are that a chlorination stage and later the breakdown of a β -diketone with dilute alkali are involved, the latter giving two alternative modes of decomposition leading to grave losses of material (of B45 $\rightarrow$ B46).

The hydroxymethylene group^(117,118) has formed the basis of many blocking groups, notable examples are the isopropoxy derivative⁽¹¹⁹⁾ and the related enamines. These groups can also be easily removed by hydrolytic methods.

However a serious consequence of the presence of these blocking groups is a deactivation of the ketone, no doubt caused by the nitrogen or oxygen atom providing a source of electrons for conjugation. To overcome this feature use was made of the known low conjugative power of the sulphur atom and hence by various procedures the hydroxymethylene function has been converted into groups such as the n-butylthiomethylene⁽¹²¹⁾ or the propylenedithioacetal⁽⁷¹⁾ by different workers.

It is apparent from this discussion that several stages are necessary for the utilisation of a blocking group and until the development of the n-butylthiomethylene group by Ireland and Marshall⁽¹²¹⁾ none gave an overall yield for

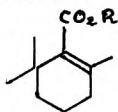
directed alkylation of greater than 50%. Because of the losses that are inevitably associated with a many stage synthesis it is desirable to keep each major stage to a minimum number of operations therefore an alternative route was sought after for the alkylation of the α -unsaturated ketone (B12).

It is known that the direct alkylation of an α -unsaturated ketone invariably leads to substitution of the α -position on that side of the ketone which holds the double bond. Dialkylation occurs geminally with double bond migration rather than substitution at the other α -position. Examples of this reaction sequence are to be found in the work of Littlehales,⁽¹¹³⁾ and also in the classical Woodward⁽⁷¹⁾ dimethylations of the α -unsaturated ring A ketone contained in cholest-4-en-3-one (A47).

In order to determine whether or not the substitution of the cyclohexenone derivative (B12) would follow a similar course to that occurring in the reactions cited above it was decided to apply the methylation technique of Woodward et al.⁽⁷¹⁾ to the alkylation of (B12). This compound (B12), when boiled together with a three-fold excess of potassium t-butoxide and a six-fold excess of methyl iodide gave a mixture of starting material and a second component. The mixture could be resolved only by preparative gas-liquid chromatography. Analysis, infra-red and ultra-violet

spectra confirmed that substitution had occurred and the loss of the absorption maximum at 243 mμ in the ultra-violet characteristic of (B12) showed that the conjugated ketone carbonyl, olefin, ester carbonyl system must have been broken. This could only have happened if substitution had occurred at the desired 2-position to give the gem-dimethyl compound (B26).

It is interesting to note that in this methylated product (B26), although the olefinic bond has shifted apparently into conjugation with the ester grouping no more than end absorption could be observed in the ultra-violet absorption spectrum. However, Nielsen (122) in his summary of ultra-violet data remarks on this feature which is apparently typical of a cyclohexene derivative having the arrangement of substituents shown. (123,124,125)



It appears that the substituents prevent coplanarity of the ester carbonyl and the olefin and hence they lose their conjugation. In fact the particular example above where (R=H) has $\lambda_{\text{max.}} = 206 \text{ m}\mu$ and $\epsilon = 3,400$ which is comparable with 1,2-dimethylcyclohexene having $\lambda_{\text{max.}} = 208 \text{ m}\mu$ and $\epsilon = 2,500$.

The yield obtained in the methylation of the cyclohexenone derivative (B12) was only 10-15% possibly because of

the steric effect of the adjacent ester grouping. This effect would be lost in the homologue (B22) and an attempt was made to prepare this substance.

The ketal derivative (B23) was prepared by azeotropic distillation of (B12) and ethylene glycol in the presence of a trace of *p*-toluenesulphonic acid. Reduction with lithium aluminium hydride and decomposition of the products with only one equivalent of water followed by continuous ether extraction gave the alcohol (B24) in almost quantitative yield. It was found important to strictly adhere to these conditions for if the lithium aluminium reduction complex were decomposed with an excess of water and the normal ether isolation procedure followed, only the α -unsaturated ketone (B12) could be recovered.

It was now intended to tosylate or mesylate the alcohol by standard procedures then to replace the sulphonic ester group by cyanide. This was to be followed by an alkaline hydrolysis and esterification of the resultant carboxylic acid with diazomethane prior to removal of the ketal grouping. It was necessary to preserve the ketal group as the acid involved was the vinyllogue of a β -keto-acid. However, it was found that both mesylate and tosylate were unstable and only black oils resulted.

The obstacle was surmounted by using the Arndt-Eistert procedure. (69,70) The acid chloride (B20) was prepared and

characterised as its amide (B21). It was, however, somewhat unstable and was only distilled with difficulty, never more than a 50% yield being obtained. A steady reaction occurred with diazomethane and measurement of the volume of nitrogen evolved indicated considerable conversion to the diazoketone. The acid chloride (B20) could not be allowed to react with diazomethane indefinitely for fear of attack on the $\alpha\beta$ -unsaturated ketone group and therefore the reaction time was never more than 5 hours.

Prior to the addition of the silver catalyst in the form of a solution of silver benzoate in triethyl amine the excess diazomethane and ether was carefully evaporated. However ether was not removed completely until methanol had been added as it was found that the diazoketone was unstable in concentrated solution. Addition of the catalyst caused immediate nitrogen evolution and distillation of the products gave a poor yield of the desired ester (B22).

Clearly, however, a tricky reaction sequence such as this was not adaptable to large-scale operation. It was therefore decided to prepare the next higher homologous ester (B19) by a cyclisation route similar to that used for the preparation of (B12).

Ethyl 2-ethoxycarbonyl-3-oxoadipate (B13) was prepared in the manner of Riegel and Lilienfeld⁽⁶⁴⁾ and decarboxylated to give (B15).⁽⁶⁶⁾ Base-catalysed methylation gave (B16)

and condensation with methyl vinyl ketone in the presence of triton B gave (B17). Methyl vinyl ketone was used because the product from the condensation of (B16) with ethyl vinyl ketone, (B47), would have two alternative modes of ring closure. As at this stage the compound being synthesised was of interest for comparative alkylation studies only and although there were reasons for believing the cyclisation would go preferentially in the required direction it was decided to eliminate the danger of two alternative modes of cyclisation.

Acid cyclisation in fact gave high yields of (B13) which was esterified with diazomethane to give (B19).

The disadvantages associated with the use of the reversible Michael addition procedure for introducing an alkyl substituent into a cyclohexanone derivative such as (B12) or (B19) have already been outlined and the merits of direct alkylation indicate that this is the course to be followed. Previous methods of ring extension have often involved the intermediate formation of a 1,5-diketone which is then cyclised under acidic or basic conditions to give an $\alpha\beta$ -unsaturated ketone. (76,127) With this in mind the β -haloketones spring to mind as possible direct alkylating agents for the keto esters (B12) and (B19). Further consideration, however, reveals that the reagents necessary to induce the formation of a carbanion in molecules such as (B12) and

(B19); strong bases such as potassium t-butoxide, sodium t-amlyoxide, sodium triphenylmethide or sodamide, are all reagents which rapidly induce the elimination of hydrogen halide from the β -haloketones and then induce polymerisation of the resultant vinyl ketone.

In compounds such as (B49) where the inducement required to form a carbanion is mild the above difficulties are surmounted by using a weaker base such as methoxide and the reaction takes on the Michael character, equilibria being set up between olefin and halide, olefin and base, olefin and carbanion etc. ⁽¹²⁶⁾ Another and better known example of this is the classical Robinson ring extension ⁽¹²⁷⁾ in which the vinyl ketone is protected as the methiodide of the β -dialkylaminoketone e.g. (B51). This is discussed later, p. 91.

These problems would be eliminated if the carbonyl function of the β -haloketone was masked as a ketal. It was thought that the ketal would be an excellent protecting group being stable to alkali during the alkylation reaction and easily removed on subsequent treatment with acid. Very little data was found, however, for the preparation of β -haloketals or for their use in base catalysed alkylations. Nevertheless it was decided to prepare the β -haloketals (B6 and B7) related to but-1-en-3-one.

It was decided to introduce the ketal group by the

alcoholysis of an acetylene. Hennion and co-workers^(56,57) had shown that the mercuric chloride/boron trifluoride etherate catalyst induced the addition of alcohols to acetylenic systems giving enol ethers or ketals.

But-1-yne-4-ol was an available starting material which could be easily converted by the method of Eglington and Whiting⁽⁵⁵⁾ to the p-toluenesulphonate (B1) and then by reaction with sodium iodide in acetone to the iodide (B2). Hennion's methods applied to (B1) or (B2) should then give a desired ketal derivative such as (B6) or (B7).

Application of this reaction to the addition of methanol to (B2), however, resulted in the recovery of starting material, and similar results were encountered when the reaction was applied to the p-toluenesulphonate (B1). As the catalyst worked perfectly in the case of pent-1-yne it appeared that in some way the *p*-toluenesulphonyloxy or iodo-groups were directly affecting the normal function of the catalyst.

An interesting observation arose when the reaction was applied to but-1-yne-4-ol itself. Hennion and Murray⁽⁵⁷⁾ claimed that this reaction gave rise to an unstable 2,2-dimethoxybutan-4-ol which rapidly decomposed when distilled from a trace of p-toluenesulphonic acid to give the enol-ether (B50). A compound having the same physical characteristics as those quoted by Hennion and Murray was

isolated in good yield when the reaction was repeated during the course of these investigations. However, the compound isolated in this case was undoubtedly 1-methoxybutan-3-one (B3) as was evidenced by a strong ketone carbonyl absorption band in the infra-red, the nuclear magnetic resonance spectrum showing single O-Me and C-Me absorptions of equal intensity and a 2,4-dinitrophenylhydrazone which had the same m.p. as that recorded in the literature for authentic 1-methoxybutan-3-one 2,4-dinitrophenylhydrazone.

It was decided to suspend this route to the ketals and follow up the work of Salmi⁽⁶⁰⁾ who had prepared the ethylene ketal of ethyl acetoacetate (B4) by a more conventional procedure. A mixture of ethylene glycol, ethyl acetoacetate and a trace of p-toluenesulphonic acid was azeotropically distilled to give (B4) in good yield. Salmi had then used the Beauvauld-Blanc reduction procedure to convert the ester to an alcohol. It was found that lithium aluminium hydride performed this function much more efficiently and gave quantitative yield of (B5), provided that the lithium aluminium hydride complex was decomposed with only one equivalent of water and continuous ether extraction was employed. In fact the same conditions used in the case of the cyclohexene derivative (B24).

The alcohol (B5) was then tosylated quantitatively at room temperature by p-toluenesulphonyl chloride in pyridine.

In order to protect the ketal grouping in the working up procedure it was found necessary to pour the products into aqueous potassium hydroxide and then to wash well with water and finally to remove the last traces of pyridine by filtering through Woelm neutral alumina. Any attempt at distillation or the use of acid-deactivated alumina resulted in instant decomposition.

The tosylate was then converted under the mild conditions of sodium iodide in acetone to the iodide (B7) which with care could be distilled to give a clear mobile liquid, stable for an indefinite period when in the dark at 0°.

Attempts were now made to determine the optimum conditions required for the alkylation of the α -unsaturated keto-ester (B12). As it was known that a tosyl-group in many respects resembles a halide in its reactions it was decided to first attempt alkylations of (B12) with the molecule (B6). The successful methylation of (B12) described earlier on p. 49 suggested that potassium t-butoxide might be the best base to use and accordingly alkylation was carried out in a similar manner to the above case using an excess of base and tosylate (B6). It was expected that any slight instability the tosylate might have when in neutral moist air at room temperature would be eliminated by the strong basic conditions employed in alkylation. However only the unchanged cyclohexanone derivative (B12) was isolated from the reaction mixture.

To discover if the reaction were influenced by base strength, the stronger base sodium triphenylmethide in dry ether was used but the results were not changed. It was also known that diglyme (diethyleneglycol dimethyl ether) could considerably speed up the course of a reaction by virtue of an ability to chelate the metallic cations present in the reaction,⁽⁷³⁾ Yet the replacement of ether by diglyme did not affect the course of the reaction in any way. The use of sodium triphenylmethide also considerably complicated the working up procedure as it was necessary to remove the resulting triphenylmethane by adsorption chromatography prior to investigating the reaction products.

It was considered that an alternative reaction course might result from the occurrence of O-alkylation rather than the desired C-alkylation. The possible enol-ether so formed would then most probably be lost in the working up procedure. However it is known that the use of a non-polar solvent such as toluene or xylene can minimise such effects⁽¹²⁸⁾ and therefore the reaction was repeated using sodium t-amyloxide in dry xylene. That O-alkylation was not the cause of a poor reaction was evidenced by again recovering the unchanged monocyclic keto-ester (B12).

To determine whether or not structural modification in the reactants would improve the course of alkylation in any way the same sequence of reactions was repeated with the

second monocyclic keto-ester (B19) but again essentially similar results were achieved. Also replacement of the tosylate (B6) by the iodide (B7) made no significant difference to the course of the alkylation reaction.

In every case, however, the presence of the carbanion was evident by either the speedy removal of the characteristic deep red colour of the triphenylmethide ion or by the presence of the typical deep orange colour associated with an alkoxide induced carbanion mixture. More substantial evidence lay of course in the already described methylation of (B12) utilising potassium *t*-butoxide, and also in the demonstration that ethylbromoacetate would alkylate (B19) in the presence of sodium triphenylmethide to give the diester (B21).

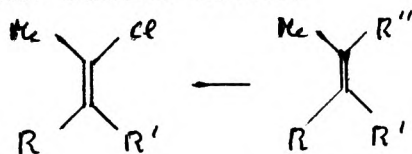
It was therefore reluctantly concluded that the β -ketal tosylate and iodide (B6 and B7) were neither sufficiently stable nor active enough to be utilised in alkylation procedures of the kind required.

Attention was now turned to the Wichterle procedure for ring extension, (76,77,78) an example of which is the alkylation of the keto-ester (B49) with 1,3-dichlorobut-2-ene and the subsequent hydrolysis and ring closure of the intermediate chloro-ketone with concentrated sulphuric acid.

Application of this reaction to both (B12) and (B19) using sodium *t*-amylxide as the base and dry xylene as solvent resulted in ready alkylation and between 30 and 40% of the

chlorocrotyl derivatives (B28 and B29) were isolated as clear oils. Each analysed correctly and other physical data indicated they were the desired compounds. Again it was noted that the ultra-violet spectrum of (B29) showed only end absorption, as might be expected from a double bond in such an environment.

Although Dauben⁽⁷⁸⁾ had shown that an angular methoxycarbonyl substituent had a determining influence on the direction of ring closure it was not expected that the comparable methyl substituent in (B29) would affect the closure in like manner. In fact profoundly different results were obtained. Strong acid treatment of (B29) gave almost quantitative recovery of the starting monocyclic keto-ester (B19) and the reaction with (B29) led to the isolation in high yield of a sharp melting crystalline solid, showing a single peak on gas-liquid chromatography which analysed accurately for an isomer of the starting material (B29). Nuclear magnetic resonance spectra of (B29) and the product showed only one major difference, namely that a methyl group had altered its environment in the manner shown.



The ultra-violet spectrum showed only end absorption and the infra-red showed a single but very strong peak in the carbonyl region in chloroform. The marked change in

physical properties coupled with the lengthy retention time from gas-liquid chromatography suggested that some form of ring closure coupled with methyl group migrations must have occurred. However, without further investigation no completely convincing structure could be assigned to the isomer.

The problem of devising a route to a useful bicyclic intermediate was finally solved in rather a different manner. It was decided that there were too many alternative courses of reaction to be considered when substituting a complex molecule such as (B12) and therefore it was decided to remove some of these undesirable alternatives by reducing the olefinic band. This was done very efficiently with lithium in liquid ammonia.⁽⁸⁰⁾ Application of the classical Robinson ring extension was now proposed it being known that substitution occurred ' α ' to the ketone and preferred a position that was already monosubstituted.

The Robinson ring-extension proceeds via the generation of an $\alpha\beta$ -unsaturated ketone in situ by base-induced decomposition of a β -keto-alkyl quaternary ammonium salt and has found wide application for Michael addition alkylations.⁽¹²⁹⁾ In the earliest examples the yields were generally poor⁽¹²⁷⁾ but with improved experimental conditions^(130,82) very acceptable yields have been recorded.⁽¹³¹⁾ The monocyclic keto-ester (B30) was therefore alkylated with the methiodide of

1-N,diethylaminobutan-3-one (B31), prepared as described by Wilds and Shunk,⁽⁸²⁾ in the presence of sodamide using pyridine/ether as solvent. The bicyclic keto-ester (B32) was isolated in low yield from the reaction mixture as a clear fairly mobile liquid. It gave a single peak on gas-liquid chromatography, analysed correctly and gave the characteristic ultra-violet absorption of an $\alpha\beta$ -unsaturated ketone.

Introduction of the characteristic gem-dimethyl grouping with a twelve molar excess of methyl iodide and three-fold excess of potassium t-butoxide gave almost quantitative conversion to the octalone (B33).

The isolation of the octalone (B33) represents a big step towards the preparation of an AB intermediate which could be incorporated into an AB plus DE type synthesis of a pentacyclic triterpene. The monocyclic keto-ester (B12) can be cheaply and efficiently prepared in quantity by a reaction sequence involving only two major steps, namely the alkaline and acid condensation stages. Reduction in high yield gives (B30) which by a one stage process gives the bicyclic compound (B32). It is also probable that the yield of this latter stage will be considerably improved when carried out on a larger scale, as it was observed that traces of moisture lowered the yields in the small scale experiments which were carried out. The introduction of the gem-dimethyl group is yet another high yield reaction.

Many routes are now open to convert (B33) to a molecule such as (B53) which in turn by standard homologation procedures could be converted to the alcohol (B54) with suitable protection of the ring ketone group. Tosylation of the alcohol followed by a halide replacement reaction will then give a molecule (B55) suitable for the alkylation of (B34). It is also expected that the octalone (B53) will have a preferentially trans-structure, as a study of models indicates the presence of far more interaction between substituents in the cis- than the trans-isomer.

The investigation of routes from (B33) to (B53) are being carried out. Direct double bond isomerisation using both strongly acidic and strongly basic conditions is being attempted. Other possibilities include the Woodward⁽⁷¹⁾ bromination/dehydrobromination technique used with such effect to introduce the $\Delta^{7(3)}$ bond in cholest- $\Delta^{5(6)}$ -en-3-one (B64) to be followed by acid induced isomerisation of the double bonds to the required position, and also the Hell, Volhard and Zelineky α -bromination of the free acid followed by dehydrobromination. Again the ring ketone group would have to be suitably protected.

Work is also progressing on another slight variant. The diketone (B56) has been prepared by the condensation of ethyl β -oxoadipate and methyl vinyl ketone and ring closure has been effected in the presence of sodium ethoxide to

yield the diester (B57). Difficulty was found in determining the optimum conditions necessary to obtain good yields of (B56). The non existence in ethyl β -oxoadipate of the methyl group present in ethyl 2-methyl-3-oxoadipate (B16) enhanced the lability of the α -protons under basic conditions to such an extent that side reactions occurred and the high yields previously experienced in the condensation of (B16) and methyl vinyl ketone were not realised. However, suitable adjustments of the reactant concentrations and reaction time led to a 50% realisation of the desired product.

It is proposed to repeat the condensation with ethyl vinyl ketone effecting ring closure to give (B58) and then to extend the ring in the manner already described. Manipulation of the two ester groups would then be necessary to derive a useful intermediate for triterpene synthesis.

It is probable that the two ester groups will be in different environments such that their rates of reaction will be different, say on hydrolysis thus leading to the formation of two isomers (B59, B60) each now containing a carboxylic acid and an ester group. The same result could be achieved by the initial formation of the anhydride and esterifying this with one equivalent of ethanol. Reduction with sodium borohydride would then give two hydroxy ^{acids} ~~esters~~ which ^{after esterification} could be separated by chromatography. Hydrogenation

of the $\Delta^{5(6)}$ double bond which would be present from the ring closure reaction and dehydration of the alcohol would give (B61). Hydrolysis to the acid and replacement of the carbonyl by bromine would give a molecule essentially the same as (B55).

A further possibility would be the conversion of the diester function into a tricyclic intermediate via the acyloin reaction. Again two isomers would probably form (B62,B63) and separation would be necessary. The dehydration of (B62) would give an unsaturated ketone that might then be used in further synthetic work. The tricyclic derivative will, however, be racemic and at some stage resolution must be effected.

SECTION B

Note: (a) Gas-liquid chromatograms in this section were taken on a Pye Argon machine. Because a gas-liquid chromatographic column has a limited useful life and also because it is virtually impossible to make up two columns of identical response even if the same batch of stationary phase and support material is used in each, the gas-liquid chromatographic data obtained in this section is necessarily related to two columns. The columns each contained 30% apiezon 'L' and 2.7% sodium caproate on 90-100 mesh embacel as the stationary phase. One series of experiments used a column 'a' at a temperature of 150° and a gas inlet pressure of 10 lb./sq.in., the retention times in this case are denoted relative to 2,4-dimethyl-3-methoxycarbonylcyclohex-2-enone by R_{ta} . In all other experiments a second column 'b' was used at a temperature of 200° and a gas inlet pressure of 12 lb./sq.in., and the retention times are denoted relative to 6,10-dimethyl-5-methoxycarbonyl- Δ^1 -octal-2-one by R_{tb} .

(b) Nomenclature: the accepted numbering of the cyclohexanone and decalin carbon skeletons is used in this section.

But-1-yne-4-toluene-p-sulphonate (B1)

Recrystallised toluene-p-sulphonyl chloride (57 g., 0.30 mol.) in redistilled pyridine (27 g.) was reacted with redistilled but-1-yne-4-ol (19.4 g., 0.28 mol.) in the manner described by Eglington and Whiting⁽⁵⁵⁾ to give but-1-yne-4-toluene-p-sulphonate (57 g., 92%) as a liquid $n_D^{20} = 1.5254$, $\nu_{\max.}$ (l.f.), 3300, 1600, 1350, 1175 cm^{-1} , Lit.⁽⁵⁵⁾ $n_D^{19} = 1.5262$.

4-Iodobut-1-yne (B2)

A solution of sodium iodide (38.2 g., 0.25 mol.) in acetone (200 ml.) was added to but-1-yne-4-tosylate (57 g., 0.25 mol.) and the resulting mixture was stirred at 20° for 17 hours then poured into a large excess of ether (2 L.) The precipitate of sodium toluene-p-sulphonate was removed by filtration and the filtrate was dried and distilled. 4-Iodobut-1-yne (18.3 g., 45%) was collected as the fraction b.p. 72°/90 mm., $n_D^{22} = 1.5502$. Lit.⁽⁵⁵⁾ b.p. 61°/80 mm., $n_D^{19} = 1.5504$.

The reaction of $\text{HC}\equiv\text{C}\cdot\text{CH}_2\text{CH}_2\cdot\text{X}$ and anhydrous methanol in the presence of mercuric oxide/boron trifluoride catalyst.

a) $\text{X} = \text{CH}_3$

Red mercuric oxide (0.300 g.), boron trifluoride etherate (0.6 ml.), trichloroacetic acid (0.025 g.) and anhydrous methanol (0.15 ml.) were gently warmed and

immediately cooled. (56) Anhydrous methanol (3 ml.) was added to this catalyst and the resultant stirred suspension was treated with pent-1-yne (2.00 g., 0.029 mol.). An immediate rise in temperature was observed with the formation of a white precipitate which slowly dissolved. After $1\frac{1}{2}$ hours at 35° anhydrous potassium carbonate (1 g.) was added to the cooled products, the mixture was filtered and the ensuing filtrate was distilled to give 2,2-dimethoxypentane (1.98 g., 52%) as the fraction of b.p. $50-54^{\circ}/80$ mm., $n_D^{19} = 1.3980$. Lit. (56) b.p. $30-31^{\circ}/15$ mm., $n_D^{23} = 1.3986$.

b) X = I

The preparation of the catalyst and the general procedure adopted was as previously described. In this instance 4-iodobut-1-yne (5.00 g., 0.028 mol.) and anhydrous methanol (3 ml.) were used. The reaction time was $2\frac{1}{2}$ hours and the products were worked up as before to give unchanged starting material (3.50 g.) b.p. $72-74^{\circ}/90$ mm. $V_{\max.}(1.f.)$ 3300, 2100, 1240, 1160 cm.^{-1} .

c) X = O_2SO OH_2

Anhydrous methanol (2.5 ml.) was added to the catalyst prepared as in (a) and but-1-yne-4-toluene-p-sulphonate (5.00 g., 0.022 mol.) was slowly dropped (10 minutes) into the stirred suspension. An exothermic reaction occurred after 3 minutes and the solution turned dark brown. After 2 hours at 50° anhydrous potassium carbonate (1 g.) was added

to the products and the mixture was filtered the precipitate being washed with acetone (5 ml.). The combined washings and filtrate were stirred with a solution of sodium iodide (3.5 g., 0.023 mol.) in acetone (20 ml.) for 17 hours at 20°. Isolation of the products in the usual manner gave 4-iodobut-1-yne (3.0 g.) $\nu_{\max}$. (l.f.) 3300, 2100, 1240, 1160 cm^{-1} .

d) $\underline{X = OH}$ (57)

Dry methanol (14 ml.) was added to the mercuric oxide/boron trifluoride catalyst prepared as in (a) and the mixture, cooled to 0°, was stirred as but-1-yne-4-ol (5.0 g., 0.71 mol.) was slowly added (15 minutes). There was an immediate white precipitate followed by a darkening of the reaction mixture as the temperature was raised to 50°. After 2 hours the products were worked up in the usual manner to give 1-methoxybutan-3-one (B3) (3.40 g., 47%) as a clear liquid b.p. 36-38°/12 mm., 139-40°/760 mm., $n_D^{20} = 1.4061$, $\nu_{\max}$. (l.f.) 1705, 1110 cm^{-1} , τ (CCl_4) = 7.83, 6.85 (equal intensity), (Found: C, 58.5; H, 9.96. Calc. for $\text{C}_5\text{H}_{10}\text{O}_2$: C, 58.8; H, 9.80%). The 2,4-dinitrophenylhydrazone had m.p. 86°. Lit. (58,59) b.p. 139-40°/760 mm., 2,4-dinitrophenylhydrazone m.p. 86°.

The reaction was repeated three times, in each case the same product was obtained in approximately the same yield.

Calc. for $\text{C}_5\text{H}_{10}\text{O}_2$: C, 58.5;
b.p. 35.7°/12 mm., $n_D^{20} = 1.4061$

Ethyl 3-oxobutyrate ethyleneketal (B4) ⁽⁶⁰⁾

Ethyl acetoacetate (60.0 g., 0.46 mol.), ethane 1,2-diol (32.0 g., 0.52 mol.), benzene (50 ml.) and a few crystals of toluene-p-sulphonic acid were heated in an apparatus having a Dean and Stark head and azeotropic distillation was carried out for 18 hours. The benzene was then distilled and the residue purified by fractional distillation. After two fractionations ethyl 3-oxobutyrate ethyleneketal (25.6 g., 32%) was obtained as a clear liquid b.p. 98-101°/17 mm., $n_D^{21} = 1.4315$, $v_{\max}$ (l.f.) 1735, 1040 cm^{-1} . Lit. ⁽⁶⁰⁾ b.p. 99.5-101-0°/17-18 mm., $n_D^{20} = 1.4326$.

1-Hydroxy-3-oxobutane ethyleneketal (B5)

Ethyl 3-oxobutyrate ethyleneketal (36.2 g., 0.21 mol.) was added slowly (30 minutes) to a vigorously stirred suspension of lithium aluminium hydride (4.5 g.) in dry ether (100 ml.) and the mixture was heated under reflux for 6 hours. After cooling, wet ether (400 ml.) and water (9 ml.) were added and the resultant suspension was continuously ether extracted for 48 hours. The lithium and aluminium hydroxides were removed by filtration and the excess ether was evaporated. The residual liquid was distilled and 1-hydroxy-3-oxobutane ethyleneketal (23.8 g., 94%) was collected as a fraction b.p. 83°/11 mm. $n_D^{19.5} = 1.444$, (Found: C, 54.1; H, 8.97. Calc. for $\text{C}_6\text{H}_{12}\text{O}_3$: C, 54.5; H, 9.15%). Lit. ⁽⁶¹⁾ b.p. 85.7°/11 mm., $n_D^{20} = 1.4448$.

1-p-Toluenesulphonyloxy-3-oxobutane ethyleneketal (B6)

1-Hydroxy-3-oxobutane ethyleneketal (7.37 g., 0.56 mol.) was slowly added to a stirred mixture of recrystallised toluene-p-sulphonyl chloride (11.0 g., 0.58 mol.) in pyridine (6.5 ml.),⁽⁵⁵⁾ the temperature not being allowed to rise above 25°. After 18 hours the reaction products were basified, poured into water (1 L.) and extracted with ether. The ethereal extract was washed fifteen times with water (100 ml. portions), then dried and evaporated. The residue was taken up in a further small quantity of ether (10 ml.) and chromatographed on a column of Woelm neutral alumina (20 g., activity II-III) to remove traces of pyridine. Elution with ether (200 ml.) afforded 1-p-toluenesulphonyloxy ethylene ketal as a clear viscous oil (14.8 g., 89.5%),

$\nu_{\text{max.}}$ (l.f.), 1590, 1350, 1160, 1050 (broad), 950 cm^{-1} ,
 $n_D^{20} = 1.5296$.

The material could not be distilled as decomposition occurred.

1-Iodo-3-oxobutane ethyleneketal (B7)

Sodium iodide (1.82 g., 0.012 mol.) in dry acetone (12 ml.) was stirred with 1-p-toluenesulphonyloxy-3-oxobutane ethyleneketal (3.26 g., 0.012 mol.) at 27° for 48 hours. Dilution with dry ether precipitated sodium toluene-p-sulphonate which was collected and washed with further quantities of dry ether. The combined filtrate and washings were evaporated

to leave 1-iodo-3-oxobutane ethylene ketal as a colourless mobile liquid (1.88 g., 68%), $n_D^{20} = 1.4290$, $V_{\text{max.}}$ (l.f.), 1050, 950, 850 cm.^{-1} . A portion was bulb distilled 70-75° (bath temp.)/0.1mm. great care being exercised to prevent the bath temperature rising above 80° at which temperature decomposition occurred. (Found: C, 29.9; H, 4.71; I, 53.4. $\text{C}_6\text{H}_{11}\text{O}_2\text{I}$ requires: C, 29.8; H, 4.59; I, 52.7%).

Ethyl 2-oxo-3-ethoxycarbonylbutyrate (B8) (49)

Sodium (69 g., 3 mol.) was stirred vigorously in dry boiling xylene (750 ml.) for 15 minutes, allowed to cool and treated continuously with absolute ethyl alcohol (138 g., 3 mol.) until all the sodium had dissolved. Ethyl oxalate (438 g., 3 mol.) was added with cooling to the viscous solution of sodium etoxide then the solution was warmed slightly as ethyl propionate (330 g., 3 mol.) was added. After 4½ hours between 50° and 60° the mixture was cooled and an excess of dilute sulphuric acid was added to the semi-solid mass with stirring and further cooling. The xylene layer was separated and washed with 10% aqueous sodium bicarbonate solution, then with water. After drying the solvent was evaporated to leave a residue which was distilled to give ethyl 2-oxo-3-ethoxycarbonylbutyrate (250 g., 41%) as a mobile liquid b.p. 123-128°/16 mm. Lit. (49) b.p. 127°/19 mm.

Ethyl vinyl ketone (B9)

1-Chloropentane-2-one, prepared by the method of McMahon et al.,⁽⁶²⁾ as modified by Woodward et al.,⁽⁶³⁾ was converted into ethyl vinyl ketone b.p. 44-7°/100 mm. in 55% yield, using the procedure of the latter workers.

Lit.⁽⁶³⁾ b.p. 45-47°/100 mm.

Ethyl 2,6-dioxo-3-methyl-3-ethoxycarbonyloctanoate (B10)

A mixture of ethyl 2-oxo-3-ethoxycarbonylbutyrate (20 g., 0.099 mol.) and triton B (prepared as described on p. 127) was stirred under nitrogen at 0° as ethyl vinyl ketone (9.5 g., 0.11 mol.) was slowly added. The reaction vessel was allowed to come to room temperature and stirring was continued for 12 hours. The products were poured into water and extracted with ether, the ethereal extract being washed with dilute hydrochloric acid, with aqueous 10% sodium bicarbonate solution (5 x 100 ml.), water and then dried. Evaporation of the ether left a liquid residue which was distilled to give 2,6-dioxo-3-methyl-3-ethoxycarbonyloctanoate (23.5 g., 80%) b.p. 137-40°/0.1 mm., $n_D^{17.5} = 1.4490$.
Lit.⁽⁴⁹⁾ b.p. 139-40°/0.1 mm., $n_D^{24} = 1.4470$.

2,4-Dimethyl-3-carboxycyclohex-2-enone (B11)

A suspension of ethyl 2,6-diketo-3-methyl-3-ethoxycarbonyloctanoate (23.5 g., 0.082 mol.) in sulphuric acid/water (40 ml./140 ml.) was heated under reflux for 6 hours then

poured into water (250 ml.) and extracted with ether.

The ethereal extract was washed with dilute aqueous sodium hydroxide, the alkaline extract was reacidified with dilute hydrochloric acid and the liberated 2,4-dimethyl-3-carboxycyclohex-2-enone was isolated with ether as a solid (10.5 g., 71%), m.p. 130° after two recrystallisations from acetone. Lit.⁽⁴⁹⁾ m.p. $131-131.5^{\circ}$.

2,4-Dimethyl-3-methoxycarbonylcyclohex-2-enone (B12)

2,4-Dimethyl-3-carboxycyclohex-2-enone (10.5 g., 0.063 mol.) was esterified by adding an ethereal solution of diazomethane (300 ml. containing diazomethane 1 g., 0.024 mol./100 ml.)^(27,28) After standing for 10 minutes the excess of diazomethane and ether was evaporated under reduced pressure and the residue was distilled to give 2,4-dimethyl-3-methoxycarbonylcyclohex-2-enone (10.8 g., 39%) as a pale yellow liquid b.p. $85-7^{\circ}/0.2$ mm., $n_D^{19} = 1.4900$, $\lambda_{\max.}$ (EtOH) = 240 mμ, $\epsilon = 12,000$, $\nu_{\max.}$ (l.f.), 1725, 1670, 1245, 1050 cm^{-1} , $R_{\text{ta}} = 1.00$. (Found: C, 66.3; H, 7.95. Calc. for $\text{C}_{10}\text{H}_{14}\text{O}_3$: C, 66.0; H, 7.74%). The 2,4-dinitrophenylhydrazone recrystallised from ethanol had m.p. $198-9^{\circ}$. Lit.⁽⁴⁹⁾ b.p. $100^{\circ}/0.05$ mm., 2,4-dinitrophenylhydrazone m.p. $201-201.5^{\circ}$.

Ethyl 2-ethoxycarbonyl-3-oxoadipate (B13)⁽⁶⁴⁾a) Magnesium derivative of diethyl malonate.⁽⁶⁵⁾

A solution of redistilled diethyl malonate (151 ml., 160 g., 1.0 mol.) in absolute ethanol (80 ml.) was slowly added to a mixture of magnesium (25 g., 1.0 mol.), absolute ethanol (25 ml.) containing a catalytic quantity of carbon tetrachloride (1 ml.) and dry ether (300 ml.). The mixture was heated under reflux for 18 hours. The ether and ethanol were distilled and the syrupy residue was taken up in dry benzene (300 ml.) which was then distilled. The residue was taken up in a further quantity of dry ether (300 ml.).

b) 3-Ethoxycarbonylpropionyl chloride (B14)

A mixture of succinic anhydride (130 g., 1.30 mol.) and absolute ethanol (150 ml., 2.3 mol.) was heated on a water bath until the ethanol ceased to reflux (about 1 hour). The excess ethanol was removed under reduced pressure and after cooling thionyl chloride (150 ml., 240 g., 2.02 mol.) was added and the reactants were boiled under reflux for 1 hour, then distilled. 3-Ethoxycarbonylpropionyl chloride (215 g., quant.) was obtained as a colourless liquid b.p. 106-12°/20 mm. Lit.⁽⁶⁴⁾ b.p. 110-115°/30 mm.

c) 3-Ethoxycarbonylpropionyl chloride (215 g., 1.30 mol.) in dry ether (150 ml.) was added to the ethereal solution of magnesium malonic ester at such a rate as to ensure that the

heat of reaction caused the ether to reflux. After the addition was completed the reactants were heated under reflux for a further 3 hours. The solution was cooled and the products were hydrolysed by carefully adding a 10% solution of sulphuric acid. The ether layer was separated and the aqueous phase further extracted with ether. The combined ethereal extracts were washed with water, dried, and distilled to give ethyl 2-ethoxycarbonyl-3-oxoadipate (200 g., 69.5%) b.p. 152-162°/0.5 mm., $n_D^{21} = 1.4480$. Lit.⁽⁷⁹⁾ b.p. 144°/0.2 mm., $n_D^{20} = 1.4506$.

Ethyl 3-oxoadipate (B15) (66)

Water (300 ml.) was added to ethyl 2-ethoxycarbonyl-3-ketoadipate (100 g., 0.35 mol.) and the vigorously stirred mixture was boiled at such a rate that over a period of 4 hours 220 ml. of a mixture of ethanol and water distilled through an 18 inch fractionating column. The residue was extracted with ether and the ethereal solution was washed with dilute aqueous potassium bicarbonate solution, dilute hydrochloric acid, water and dried. Evaporation of the ether left a liquid which was distilled to give ethyl 3-oxoadipate (44.1 g., 59%), b.p. 119-21°/0.7 mm., $n_D^{21} = 1.4384$. Lit.⁽⁶⁴⁾ b.p. 122-6°/0.5 mm.

Ethyl 2-methyl-3-oxoadipate (B16) (67)

A solution of ethyl 3-oxoadipate (35.1 g., 0.16 mol.) in dry benzene (120 ml.) was added with cooling to a cold stirred

suspension of sodium powder (4.03 g., 0.175 mol.) in dry benzene (50 ml.) under dry oxygen-free nitrogen. After 30 minutes the mixture was heated under reflux for 3 hours then cooled as a solution of methyl iodide (30.3 ml., 69.7 g., 0.49 mol.) in dry benzene (30 ml.) was added. The mixture was kept at room temperature for 45 minutes, boiled under reflux for 30 minutes and then allowed to stand at room temperature for 12 hours and poured into water. Ethyl 2-methyl-3-oxoadipate (20.8 g., 55%) was isolated with ether as a clear liquid b.p. 120-122°/0.4 mm., $n_D^{22} = 1.4377$. Lit. (67) b.p. 113-115°/0.1 mm.

Ethyl 4,8-dioxo-5-methyl-5-ethoxycarbonylnonanoate (B17)
dry

Methyl vinyl ketone (3.75 ml., 3.22 g., 0.046 mol.) was added to a mixture of ethyl 2-methyl-3-oxoadipate (9.98 g., 0.043 mol.) and triton B (prepared as described on p.127) under dry oxygen-free nitrogen at 0°. The stirred solution was allowed to come to room temperature and after 18 hours was poured into water and extracted with ether. The ethereal extract was washed with dilute hydrochloric acid, aqueous 10% sodium bicarbonate solution, water and dried. Evaporation of the ether left a clear liquid which was distilled to give ethyl 4,8-dioxo-5-methyl-5-ethoxycarbonylnonanoate (9.03 g., 69.5%) b.p. 164-8°/0.3 mm., $n_D^{22.5} = 1.4625$, $\nu_{\text{max.}}$ (l.f.), 1735 (strong), 1705 (strong),

1180 cm^{-1} (Found: C, 60.1; H, 8.24. $\text{C}_{15}\text{H}_{24}\text{O}_6$ requires: C, 60.1; H, 8.09%).

3,2'-Carboxyethyl-4-methylcyclohex-2-enone (B18)

Ethyl 4,8-dioxo-5-methyl-5-ethoxycarbonylnonanoate (3.00 g., 0.010 mol.) was boiled for 6 hours with a solution of 50% sulphuric acid (30 ml.) poured into water and extracted with ether. The ethereal solution was extracted with aqueous 10% potassium hydroxide and the alkaline solution was acidified with dilute hydrochloric acid to liberate 3,2'-carboxyethyl-6-methylcyclohex-2-enone, isolated with ether as a viscous yellow liquid (1.25 g., 69%) which slowly crystallised. Three recrystallisations from light petroleum/benzene gave crystals m.p. $89.5-90^\circ$, $\nu_{\text{max.}}$ (CHCl_3), 1700, 1660, 990, 955 cm^{-1} (Found: C, 66.2; H, 7.66. $\text{C}_{10}\text{H}_{14}\text{O}_3$ requires: C, 66.0; H, 7.75%).

3,2'-methoxycarbonylethyl-4-methylcyclohex-2-enone (B19)

3,2'-Carboxyethyl-4-methylcyclohex-2-enone (2.16 g., 0.012 mol.) was esterified by treating with an ethereal solution of diazomethane (75 ml. containing diazomethane 1g., 0.024 mol./100 ml.)^(27,28) at room temperature for 10 minutes. The excess of diazomethane and ether was evaporated and the pale yellow mobile liquid residue purified by distillation. 3,2'-Methoxycarbonylethyl-4-methylcyclohex-2-enone (1.72 g., 74%), was collected as the

fraction, b.p. $100-3^{\circ}/0.05$ mm., $n_D^{18} = 1.4924$, $\nu_{\max.}$ (l.f.) 1750, 1665, 1650, 1175 cm^{-1} (Found: C, 67.7; H, 8.39. $\text{C}_{11}\text{H}_{16}\text{O}_3$ requires: C, 67.4; H, 8.22%).

2,4-Dimethylcyclohex-2-enone-3-carboxylic acid chloride (B20)⁽⁶⁸⁾

Thionyl chloride (9.2 ml., 14.8 g., 0.12 mol.) was added slowly with cooling to 2,4-dimethyl-3-carboxycyclohex-2-enone (10 g., 0.055 mol.). After 1 hour the temperature was raised to 60° for a further 30 minutes then the excess of thionyl chloride was distilled and the residue was purified by fractional distillation. 2,4-Dimethylcyclohex-2-enone-3-carboxylic acid chloride (5.1 g., 51%) was collected as the fraction of b.p. $88-92^{\circ}/0.1$ mm., $\nu_{\max.}$ (l.f.) 1780, 1660, 1070, 860, 740 cm^{-1} .

The acid chloride was characterised as its amide (B21) m.p. 129° (Kofler) after two recrystallisations from water and drying to constant weight over phosphoric oxide at 100° ,

$\nu_{\max.}$ (nujol) 3600, 3300, 3230, 1650 (broad). (Found: C, 64.6; H, 7.96; N, 8.49. $\text{C}_9\text{H}_{13}\text{O}_2\text{N}$ requires C, 64.6; H, 7.86; N, 8.39%). From aqueous solution the amide is obtained as its monohydrate. (Found: C, 58.3; H, 7.95; N, 7.80. $\text{C}_9\text{H}_{13}\text{O}_2\text{N} \cdot \text{H}_2\text{O}$ requires: C, 58.5; H, 8.16 N, 7.57%).

The reaction of 2,4-dimethylcyclohex-2-enone-3-carboxylic acid chloride and diazomethane. (Arndt, Eistert and Wolff rearrangements). (69,70)

2.4 2,4-Dimethylcyclohex-2-enone-3-carboxylic acid chloride (2.00 g., 0.012 mol.) was slowly added (10 minutes) to a stirred solution of diazomethane in ether (150 ml. containing diazomethane 1 g., 0.024 mol./100 ml.) (27,28) 170 ml. of nitrogen were evolved in 1 hour at $17^{\circ}/755$ mm. The excess of diazomethane evaporated as the ether volume was reduced to 20 ml., dry methanol (25 ml.) was added and the solution was vigorously stirred as silver benzoate (2 g.) in triethylamine (25 ml.) was slowly added. After the addition of 6 ml. a white precipitate formed and a slow evolution of nitrogen occurred, which rapidly increased after the addition of 12 ml., the reaction mixture darkened considerably. Further additions of the silver benzoate solution (up to 20 ml. in all) were made as the nitrogen evolution slackened. After 30 minutes 150 ml. of nitrogen had been evolved, and the reaction mixture was filtered. The products were isolated from the filtrate as before and distilled to give 2,4-dimethyl-3-methoxycarbonylcyclohex-2-enone (B12) (0.523 g.) b.p. $125-135^{\circ}$ (bath temp.)/0.1 mm., $n_D^{19} = 1.4903$, $R_{ta} = 1.00$. $\nu_{max.}$ (l.f.) 1725, 1670, 1245, 1050 cm.^{-1} , and 2,4-dimethyl-3-methoxycarbonylmethylcyclohex-2-enone (B22) (0.547 g., 23%), b.p. $135-140^{\circ}$ (bath temp.)/0.1 mm., $n_D^{18} = 1.5000$, $R_{ta} = 2.27$, $\nu_{max.}$ (l.f.), 1745,

1670, 1640 cm^{-1} (Found: C, 66.7; H, 8.12. $\text{C}_{11}\text{H}_{16}\text{O}_3$ requires: C, 67.3; H, 8.21%).

2,4-Dimethyl-3-methoxycarbonylcyclohex-2-enone ethyleneketal (B23).

2,4-Dimethyl-3-methoxycarbonylcyclohex-2-enone (3.49 g., 0.019 mol.), benzene (50 ml.), ethylene glycol (1.43 g., 0.023 mol.) and a few crystals of p-toluene sulphonic acid were heated in an apparatus having a Dean and Stark head attachment. Azeotropic distillation was carried out for 36 hours. Distillation then gave 2,4-dimethyl-3-methoxycarbonylcyclohex-2-enone ethyleneketal (1.81 g., 42%) as the fraction b.p. $98-99^\circ/0.1 \text{ mm.}$, $n_D^{23} = 1.4915$, $d_{\text{max.}}^{20} (1.6)$ 1710, 1630, 1240, 1060 cm^{-1} (Found: C, 63.65; H, 8.16. $\text{C}_{12}\text{H}_{18}\text{O}_4$ requires: C, 63.6; H, 8.05%).

2,4-Dimethyl-3-hydroxymethylcyclohex-2-enone ethyleneketal (B24)

2,4-Dimethyl-3-methoxycarbonylcyclohex-2-enone ethyleneketal (1.81 g., 0.0080 mol.) in dry ether (10 ml.) was slowly added to a stirred suspension of lithium aluminium hydride (1.2 g., 0.036 mol.) in dry ether (150 ml.). After heating under reflux for 12 hours, water (5 ml.) was carefully added to the cold mixture and the resultant suspension was continuously extracted with ether for 48 hours. Filtration and evaporation of the filtrate gave a clear liquid residue which was distilled to give 2,4-dimethyl-3-hydroxymethylcyclohex-2-enone ethylene ketal (1.07 g., 68%). b.p. $145-50^\circ/0.2 \text{ mm.}$,

$n_D^{23} = 1.5040$. $\nu_{\max.}$ (l.f.) 3500, 1080, 990, 905 cm^{-1}
 (Found: C, 66.0; H, 9.34. $\text{C}_{11}\text{H}_{18}\text{O}_3$ requires: C, 66.6;
 H, 9.20%).
 etha.

The condensation of 2,4-dimethyl-3-methoxycarbonylcyclohex-2-enone (B12) and acrylonitrile.

Acrylonitrile (0.300 g., 0.0057 mol.) was added under oxygen-free dry nitrogen to a stirred mixture of 2,4-dimethyl-3-methoxycarbonylcyclohex-2-enone (1.00 g., 0.0055 mol.) and triton B (prepared as described on p.127) at 0° . The reactants were allowed to come to room temperature and after 20 hours were poured into water (200 ml.) and the resulting mixture extracted with ether. The ethereal extract was washed with dilute hydrochloric acid, water and dried and the ether evaporated to leave a liquid residue (0.894 g.) from which unchanged keto-ester (0.602 g.) was distilled b.p. $120-125^\circ$ (bath temp.)/0.1 mm., $n_D^{19} = 1.4905$, $\nu_{\max.}$ (l.f.) 1725, 1670, 1245, 1050 cm^{-1} . The non-distilled material (0.290g.), which showed a strong infra-red nitrile absorption band at 2260 cm^{-1} (nitrile) was chromatographed on alumina (30 g.).

(1:1) Light petroleum/benzene (210 ml.) and benzene (180 ml.) eluted a further 0.114 g. of keto-ester, characterised as above. (9:1) Benzene/ether (150 ml.) and (8:1) benzene/ether (150 ml.) eluted 2,4-dimethyl-2,6-di(2'-cyanoethyl)-3-methoxycarbonylcyclohex-3-enone (B25) (0.130 g.), which did not distil but decomposed at a bath temperature

of $220^{\circ}/0.1$ mm., $\nu_{\text{max.}}$ (CHCl_3), 2260, 1710 (single broad peak), 1230, 1050 cm.^{-1} . The characteristic α,β -unsaturated ketoester ultra-violet absorption maximum at 240 m μ in ethanol was no longer present and was replaced by end absorption. After drying over phosphoric oxide at $68^{\circ}/0.1$ mm. a sample was analysed. (Found: C, 67.1; H, 7.14; N, 9.19. $\text{C}_{16}\text{H}_{20}\text{O}_3\text{N}_2$ requires: C, 66.7; H, 7.02; N, 9.71%)

The alkylation of 2,4-dimethyl-3-methoxycarbonylcyclohex-2-enone (B12) with methyl iodide.

a) In the presence of potassium t-butoxide. (71)

Potassium (0.640 g., 0.016 mol.) in dry t-butanol (12 ml.) was added to a stirred solution of 2,4-dimethyl-3-methoxycarbonylcyclohex-2-enone (0.931 g., 0.0051 mol.) in dry t-butanol (25 ml.) at 40° under dry oxygen-free nitrogen followed immediately by a solution of methyl iodide (2.03 ml., 4.68 g., 0.033 mol.) in t-butanol (2 ml.). The mixture was boiled under reflux for 1 hour poured into water and extracted with ether. The ethereal extract was washed with dilute hydrochloric acid, dilute potassium hydroxide, water, then dried and distilled to give unchanged keto-ester (0.500 g.), b.p. $90-100^{\circ}$ (bath temp.)/0.03 mm., $\nu_{\text{max.}}$ (l.f.) 1725, 1670, 1245, 1050 cm.^{-1} as a first fraction and a second fraction (0.205 g.) containing a mixture of unchanged keto-ester and 2,2,4-trimethyl-3-methoxycarbonylcyclohex-3-enone (B26),

$R_{ta} = 1.00$ and $R_{tb} = 1.19$. This material was incorporated into the next experiment.

b) In the presence of sodium triphenylmethide. (72)

Sodium triphenylmethide in dry ether (60 ml. of a solution made up and standardised as described on p. 127, 0.0066 mol.) was passed under oxygen-free dry nitrogen into stirred 2,4-dimethyl-3-methoxycarbonylcyclohex-2-enone (1.00 g., 0.0055 mol.) ^{+ MeI (3 equivs.)} at 0°. After the mixture had been heated under reflux for 20 hours the products were poured into water (200 ml.) and a viscous liquid was isolated with ether. Distillation separated the mixture of unchanged keto-ester and 2,2,4-trimethyl-3-methoxycarbonylcyclohex-3-enone (B26) from triphenylmethane as a fraction of b.p. 100-110° (bath temp.)/0.04 mm., 0.756 g. $R_{ta} = 1.00$ and 1.19. This material combined with the mixture from experiment (a) (0.961 g.) was separated by preparative gas-liquid chromatography, using a 3½ metre coiled copper tube of ⅜ inch internal diameter containing 30% apiezon 'L' and 2.7% sodium caproate on 90-100 mesh embacel as the stationary phase, a temperature of 160° and a gas inlet pressure of 10 lb./sq.in. 2,2,4-Trimethyl-3-methoxycarbonylcyclohex-3-enone (B26) was obtained as a clear liquid (0.147 g.), b.p. 100-105° (bath temp.)/0.04 mm., $n_D^{18} = 1.4763$, $R_{ta} = 1.19$, no absorption maximum in the ultra-violet at 240 mμ in ether but showed end absorption. (Found C, 67.5; H, 8.56. $C_{11}H_{16}O_3$ requires C, 67.4; H, 8.19%).

The attempted condensation of 2,4-dimethyl-3-methoxycarbonyl-cyclohex-2-enone (B12) and 1-p-toluenesulphonyloxy-3-oxobutane ethyleneketal (B6).

1570 cm., ratio

a) In the presence of potassium t-butoxide.

(21) Potassium (0.650 g., 0.017 mol.) in dry t-butanol (12 ml.) was added to a vigorously stirred solution of 2,4-dimethyl-3-methoxycarbonylcyclohex-2-enone (0.998 g., 0.0055 mol.) in dry t-butanol (20 ml.) under nitrogen at 30° followed immediately by a solution of 1-p-toluenesulphonyloxy-3-oxobutane ethyleneketal (9.50 g., 0.033 mol.) in dry t-butanol (10 ml.). The solution was boiled under reflux for 7 hours. A precipitate of potassium p-toluenesulphonate was present in the products which were poured into water and the mixture extracted with ether. The ethereal extract was washed with water only, then dried and the solvent evaporated to leave a residue which contained unchanged keto-ester (0.790 g.) (characterised on p.104) as the only identifiable product.

b) In the presence of sodium triphenylmethide (72)

Sodium triphenylmethide in dry ether (60 ml., containing 0.066 mol. of sodium standardised as on p.127) was added under nitrogen to a stirred solution of the keto-ester (1.00 g., 0.055 mol.) at room temperature and 1-p-toluenesulphonyloxy-3-oxobutane ethyleneketal was added to the resulting red mixture. After 2½ hours under reflux a sample (10 ml.) was removed and thrown into water. The

products isolated with ether showed a diminution in intensity of the α,β -unsaturated ketone band in the infra-red at 1670 cm.^{-1} , but no alteration in intensity of the *p*-toluene-sulphonyloxy absorptions at 1350 and 1160 cm.^{-1} , $R_{\text{ta}} = 1.00$ (single peak).

The solvent was replaced by dry diglyme⁽⁷³⁾ (50 ml., diethylene glycol dimethyl ether) and the temperature raised to 50° for 12 hours. After a further 4 hours at 100° the products were cooled, thrown into water and isolated with ether. The ketals present were decomposed by heating under reflux for 45 minutes⁽⁷⁴⁾ with 8% (1:10) aqueous/methanolic sulphuric acid (50 ml.). Dilution with water (300 ml.) and ether extraction gave a viscous residue (3.54 g.) possibly containing some of the desired 1,5-diketone condensation product, $\nu_{\text{max.}}$ (l.f.) 1710 cm.^{-1} (broad and strong).

This residue (3.54 g.) was taken up in dry methanol (50 ml.) containing sodium (0.75 g.) and refluxed under nitrogen for 2 hours.⁽⁷⁵⁾ Isolation of the products in the usual way with ether left a residue (3.01 g.) which was chromatographed on alumina (250 g.). (1:1) Light petroleum/benzene (2.5 L.) eluted triphenyl methane and other compounds having strong aromatic absorptions (2.15 g.) $\nu_{\text{max.}}$ (nujol) $1590, 755, 725, 695\text{ cm.}^{-1}$. Further elution with (1:1) light petroleum/benzene (1.0 L.) gave unchanged starting keto-ester (0.500 g.) (characterised as on p.104).

The alkylation of 3,2'-methoxycarbonylethyl-4-methylcyclohex-2-enone (B19) with ethyl bromoacetate.

Ethyl bromoacetate (0.68 ml., 1.03 g., 0.0078 mol.) was slowly added to a stirred mixture of 3,2'-methoxycarbonyl-4-methylcyclohex-2-enone (1.00 g., 0.0051 mol.) and sodium triphenylmethide in dry ether (50 ml., containing sodium 0.0061 mol. standardised as on p.124) under nitrogen.

A precipitate of sodium bromide formed as the reactants were heated under reflux for 20 hours. The products were poured into water (300 ml.) and isolated with ether to give a viscous liquid (2.80 g.) which was chromatographed on alumina (100 g.).

Elution with (1:1) light petroleum/benzene (300 ml.) removed triphenylmethane (1.74 g.) $\nu_{\text{max.}}$ (nujol) 1590, 755, 725, 695 cm^{-1} . Further elution with (1:1) light petroleum/benzene gave unchanged keto-ester (0.542 g.) $\nu_{\text{max.}}$ (l.f.) 1750, 1665, 1650, 1175 cm^{-1} .

Elution with ether gave a clear liquid (0.297 g.) which distilled at b.p. 200-210° (bath temp.)/0.3mm. to give 2-ethoxycarbonylmethyl-3,2'-methoxycarbonylethyl-4-methylcyclohex-2-enone (B27), $\nu_{\text{max.}}$ 1745, (v.strong), 1665, 1650, 1175 (v. broad and strong), 1030 cm^{-1} (Found: C, 63.6; H, 7.63. $\text{C}_{15}\text{H}_{22}\text{O}_5$ requires: C, 63.9; H, 7.81%).

The attempted condensation of 3,2'-methoxycarbonylethyl-4-methylcyclohex-2-enone (B19) and 1-p-toluenesulphonyloxy-3-oxobutane ethyleneketal (B6)

a) In the presence of sodium t-amyloxide.

1-p-toluenesulphonyloxy-3-oxobutane ethyleneketal (2.19 g. 0.0076 mol.) was added to a stirred solution of 3,2'-methoxycarbonylethyl-4-methylcyclohex-2-enone (1.00 g., 0.0051 mol.) and sodium t-amyloxide (0.890 g., 0.0077 mol.) in dry xylene (10 ml.) under dry oxygen-free nitrogen. The mixture, having been heated under reflux for 24 hours, was poured into water and the products were isolated with ether as an oil (1.07 g.). This, when washed through a column of alumina (20 g.) with ether (200 ml.) gave a pale yellow oil (0.375 g.) identified as unchanged keto-ester, $\nu_{\max.}$ (l.f.) 1750, 1665, 1650, 1175 cm^{-1}

b) In the presence of sodium triphenylmethide.

1-p-toluenesulphonyloxy-3-oxobutane ethyleneketal (3.00 g., 0.0105 mol.), 3,2'-methoxycarbonylethyl-4-methylcyclohex-2-enone (1.00 g., 0.0051 mol.) and sodium triphenylmethide in dry ether (60 ml., containing sodium (0.0051 mol.) standardised as on p. 127) were reacted together as is described in the experiment on p. 115. Again the only identifiable product was unchanged starting keto-ester (B19) (0.650 g.) $\nu_{\max.}$ (l.f.) 1750, 1665, 1650, 1175 cm^{-1}

The condensation of 1-iodo-3-oxobutane ethyleneketal (B7) and 3,2'-methoxycarbonylethyl-4-methylcyclohex-2-enone (B19)

a) In the presence of sodium triphenylmethide.

3,2'-Methoxycarbonylethyl-4-methylcyclohex-2-enone (0.720 g., 0.0037 mol.), 1-iodo-3-oxobutane ethyleneketal (1.88 g., 0.0078 mol.) and sodium triphenylmethide in dry ether (40 ml. of a solution containing sodium (0.0045 mol.) standardised as described on p. 127) were reacted together in the manner described for the tosylate on p. 115, by heating under reflux for 48 hours. The products were poured into water and isolated with ether. The viscous oil (2.86 g.) so obtained was chromatographed on alumina (150 g., Woelm neutral, activity II, III). Elution with (5:1) light petroleum/benzene (450 ml.) gave triphenylmethane (1.34 g.) $\nu_{\text{max.}}$ (nujol) 1590, 755, 725, 695 cm^{-1} (3:1) light petroleum/benzene (800 ml.) gave 1-iodo-3-oxobutane ethyleneketal (0.807 g.) $\nu_{\text{max.}}$ (l.f.) 1050, 950, 850 cm^{-1} and (1:1) light petroleum/benzene (800 ml.) gave unchanged keto-ester (0.450 g.) $\nu_{\text{max.}}$ (l.f.) 1750, 1665, 1650, 1175 cm^{-1}

b) In the presence of sodium t-amylloxide.

Sodium t-amylloxide (2.02 g., 0.018 mol.) in dry benzene (8 ml.), 3,2'-methoxycarbonylethyl-4-methylcyclohex-2-enone (1.26 g., 0.0064 mol.) and 1-iodo-3-oxobutane ethyleneketal (9.01 g., 0.037 mol.) were reacted together in the manner described for the tosylate on p. 118. Again the only

identifiable product was the keto-ester (0.754 g.) $\nu_{\max.}$ (1.f.) 1750, 1665, 1650, 1175 cm^{-1}

The reaction of 1,3-dichlorobut-2-ene and 3,2'-methoxycarbonyl-ethyl-4-methylcyclohex-2-enone (B19) (76,77,78)

3,2'-Methoxycarbonylethyl-4-methylcyclohex-2-enone (2.01 g., 0.010 mol.) was slowly added to a stirred suspension of sodium *t*-amyloxide (1.35 g., 0.012 mol.) in dry toluene (20 ml.) at 0° under dry oxygen-free nitrogen. The mixture was treated with 1,3-dichlorobut-2-ene (3.82 g., 0.030 mol.), heated under reflux for 24 hours then poured into water (200 ml.). The products, isolated with ether and distilled gave unchanged keto-ester (0.956 g.), b.p. $100-103^\circ/0.05 \text{ mm.}$, $n_D^{19} = 1.4944$, and 2,3'-chlorocrotyl-3,2'-methoxycarbonylethyl-4-methylcyclohex-2-enone (B28) (0.872 g., 30%), b.p. $146-152^\circ/0.05 \text{ mm.}$, $n_D^{19} = 1.5110$, $\nu_{\max.}$ (1.f.), 1725, 1655, 1640, 1155 cm^{-1} , (Found: C, 63.0; H, 7.69; Cl. 12.3. $\text{C}_{15}\text{H}_{21}\text{O}_3\text{Cl}$ requires: C, 63.2; H, 7.45; Cl. 12.5%)

The attempted ring closure of 2,3'-chlorocrotyl-3,2'-methoxycarbonylethyl-4-methylcyclohex-2-enone (B28) (76,77,78)

Cold 95% sulphuric acid (1 ml.) was slowly added to 2,3'-chlorocrotyl-3,2'-methoxycarbonyl-4-methylcyclohex-2-enone (0.872 g., 0.0030 mol.) at 0° . After 30 minutes the reactants were allowed to come to room temperature and then after 48 hours were poured into a saturated potassium bicarbonate solution (100 ml.) and extracted with ether.

The ethereal solution afforded a clear liquid (0.105 g.)
 b.p. 120-130° (bath temp.)/0.01 mm. identical with 3,2'-methoxy-
 carbonylethyl-4-methylcyclohex-2-enone, $n_D^{20} = 1.4930$,
 $\nu_{\max.}$ (l.f.) 1750, 1665, 1650, 1175 cm^{-1}

The potassium bicarbonate solution was acidified and
 extracted with ether giving (0.393 g.) of 3,2'-carboxyethyl-
 4-methylcyclohex-2-enone which after two recrystallisations
 from light petroleum/chloroform, had m.p. and mixed m.p. 86°.

The alkylation of 2,4-dimethyl-3-methoxycarbonylcyclohex-2-
 enone (B12) with 1,3-dichlorobut-2-ene. (76,77,78)

2,4-Dimethyl-3-methoxycarbonylcyclohex-2-enone (3.01 g.,
 0.018 mol.) was added to a solution of sodium t-amyloxide
 (2.32 g., 0.020 mol.) in dry toluene (15 ml.) at room
 temperature under dry oxygen-free nitrogen. 1,3-Dichlorobut-
 2-ene (6.73 g., 0.055 mol.) was added to the resulting deep
 red solution and the mixture was heated under reflux. The
 solution turned pale yellow and a thick precipitate of sodium
 chloride was formed. After 3 hours, the products were
 poured into water and isolated with ether to give a clear
 liquid residue (3.10 g.), which was distilled. Unchanged
 keto-ester (1.02 g.) was collected as a fraction b.p. 80-90°/
 0.05 mm., $n_D^{20} = 1.4905$. 2,4-dimethyl-2,3'-chloroacetyl-3-
 methoxycarbonylcyclohex-3-enone (B29) (1.67 g., 36%)
 b.p. 134-138°/0.05 mm. was also collected, $n_D^{19} = 1.5077$,
 $\nu_{\max.}$ (l.f.) 1730, 1700, 1250, 1050 cm^{-1} , end absorption

only in the ultra-violet. (Found: C, 61.8; H, 7.24;

Cl. 13.1. $C_{14}H_{19}O_3Cl$ requires: C, 62.0; H, 7.05; Cl.13.1%).

The attempted ring closure of 2,4-dimethyl-2,3'-chlorocrotyl-3-methoxycarbonylcyclohex-3-enone (B29).

Employing the conditions of the previous experiment cold 95% sulphuric acid (2.ml.) was reacted with 2,4-dimethyl-2,3'-chlorocrotyl-3-methoxycarbonylcyclohex-3-enone (1.69 g., 0.0063 mol.) to give 0.675 g. of neutral products and 0.305 g. of acid products. The latter were esterified with diazomethane and the combined esters (0.969 g.) were chromatographed on alumina (50 g.).

(3:1) Light petroleum/benzene (150 ml.) eluted (0.189 g.) of material which gas-liquid chromatography showed to be a mixture and was not identified. Further elution with (3:1) light petroleum/benzene (1 L.) and (2:1) light petroleum/benzene (150 ml.) gave a crystalline solid (0.639 g.) m.p.114° after two recrystallisations from light petroleum (b.p.60-80°),

$\nu_{\max}$. (nujol) 1728, 1720, 1400-1000 (much fine structure) 789 cm^{-1} , $\nu_{\max}$. (CHCl_3) 3030, 2990, 2960, 2950, 1730 (broad), 1293, 1275, 1250 (v.broad). An ultra-violet spectrum in ethanol showed weak end absorption at 210 m μ ; $R_{\text{tb}} = 1.4$,

τ (CDCl_3) = 8.87, 8.25, 8.23, 6.24. (Found: C, 62.1; H, 7.23;

Cl.13.1. $C_{14}H_{19}O_3Cl$. requires: C, 62.0; H, 7.05;

Cl.13.1%).

2,4-Dimethyl-3-methoxycarbonylcyclohexanone. (B30)

2,4-Dimethyl-3-methoxycarbonylcyclohex-2-enone (4.01 g., 0.022 mol.) in dry ether (20 ml.) was added to a stirred solution of lithium (0.750 g.) in liquid ammonia (150 ml.)⁽⁸⁰⁾ After 25 minutes ammonium chloride (2.5 g.) was added to the blue solution and the ammonia was evaporated. Water and ether were added to the residue, the ethereal layer was separated, washed with dilute hydrochloric acid, water, dried and evaporated to give a liquid residue which was distilled.

2,4-Dimethyl-3-methoxycarbonylcyclohexanone (2.18 g., 54%) was obtained b.p. $80^{\circ}/0.03$ mm., $n_D^{18} = 1.4666$. (Found: C, 65.0; H, 8.87. $C_{10}H_{16}O_3$ requires: C, 65.2; H, 8.75%).

The condensation of 2,4-dimethyl-3-methoxycarbonylcyclohexanone (B30) and 1-diethylaminobutan-3-one methiodide (B31)^{81,82}

2,4-Dimethyl-3-methoxycarbonylcyclohexanone (3.39 g., 0.021 mol.) and 1-diethylaminobutan-3-one methiodide (from methyl iodide (1.6 g.) and 1-diethylaminobutan-3-one (1.6 g.), 0.011 mol.) in dry pyridine (15 ml.) were added to a stirred solution of freshly prepared sodamide (from sodium 0.532 g., 0.023 mol.)⁽⁴⁸⁾ in dry ether (20 ml.). After 12 hours at room temperature and one hour under reflux the products were slowly poured into excess ice cold dilute hydrochloric acid and the mixture was extracted with ether. The ethereal extract was washed ten times with dilute hydrochloric acid, water, then dried and evaporated to leave a dark viscous residue

which was eluted through alumina (20 g.) with more ether (200 ml.). Evaporation of the solvent left a clear liquid residue (1.82 g.) which was distilled to give unchanged keto-ester (0.768 g.), b.p. 100-130°(bath temp.)/0.01 mm., $n_D^{20} = 1.4685$ and a fraction b.p. 145-150°(bath temp.)/0.01 mm. (0.417 g., 10.5%) from which 6,10-dimethyl-5-methoxycarbonyl- Δ^1 -octal-2-one (B32) was isolated as a clear viscous liquid $\nu_{\text{max.}}(\text{CHCl}_3)$ 1745, 1670, 1630, 1170, 1020, 870 cm^{-1} , $\lambda_{\text{max.}}(\text{EtOH})$ 237 μ , $\epsilon = 13,900$, $R_{\text{tb}} = 1.00$, (Found: C, 71.1; H, 8.69. $\text{C}_{14}\text{H}_{20}\text{O}_3$ requires: C, 71.2; H, 8.56%).

The dimethylation of 6,10-dimethyl-5-methoxycarbonyl- Δ^1 -octal-2-one (B32)

6,10-Dimethyl-5-methoxycarbonyl- Δ^1 -octal-2-one (0.174 g., 0.00074 mol.) in dry *t*-butanol (5 ml.) was added to a solution of potassium *t*-butoxide (from potassium 0.099 g., 0.0025 mol.) in dry *t*-butanol (2 ml.) under oxygen-free dry nitrogen, and was immediately followed by a solution of methyl iodide, (1.0 ml., 2.3 g., 0.017 mol.) in dry *t*-butanol (2 ml.). The mixture was heated under reflux for 2 hours. The products were poured into water and 1,1,6,10-tetramethyl-5-methoxycarbonyl- $\Delta^{8(9)}$ -octal-2-one (B53) was isolated by ether in the usual way as a clear liquid (0.165 g., 85%), b.p. 130-145°(bath temp.)/0.01 mm., $\nu_{\text{max.}}$ 1740, 1710, 1380, 1360, 1160 cm^{-1} , no absorption in the ultra-violet, $R_{\text{tb}} = 0.85$. (Found: C, 72.5; H, 9.09. $\text{C}_{16}\text{H}_{24}\text{O}_3$ requires: C, 72.3; H, 9.17%).

Ethyl 4,8-dioxo-5-ethoxycarbonylnonanoate (B56)

Ethyl β -oxoadipate (10 g., 0.046 mol.), tritan B (prepared as described on p. 127) and methyl vinyl ketone (5.19 g., 0.075 mol.) were stirred together at 0° in an atmosphere of dry oxygen-free nitrogen. The temperature was raised to 18° and after 12 hours the products were poured into water and isolated with ether to give ethyl 4,8-dioxo-5-ethoxycarbonylnonanoate (5.19 g., 40%), b.p. 160-4°/0.1 mm., $n_D^{20} = 1.4524$, $\nu_{\max.}$ (l.f.) 1735, 1710 cm^{-1} (Found: C, 58.7; H, 7.75. $\text{C}_{16}\text{H}_{22}\text{O}_6$ requires: C, 58.7; H, 7.40%).

3,2'-Ethoxycarbonylethyl-4-ethoxycarbonylcyclohex-2-enone (B57)

Ethyl 4,8-dioxo-5-ethoxycarbonylnonanoate (5.19 g., 0.018 mol.) was added under oxygen-free dry nitrogen to a stirred solution of sodium (0.460 g., 0.020 mol.) in dry ethanol at room temperature. After one hour the products were poured into water and isolated with ether. Distillation gave 3,2'-ethoxycarbonylethyl-4-ethoxycarbonylcyclohex-2-enone (2.09 g., 48%), b.p. 145-150° (bath temp.)/0.05 mm., $\nu_{\max.}$ (l.f.) 1730, 1660, 1630, 1180 cm^{-1} , $n_D^{17} = 1.4792$ (Found: C, 59.5, H, 7.09. $\text{C}_{12}\text{H}_{16}\text{O}_5$ requires C, 59.9, H, 6.72%).

APPENDIX

Details are given below of the methods employed for the preparation and purification of reagents and solvents used in the previous sections.

- a) Ethanol was dried over magnesium by the method of Lund and Bjerrum, ⁽⁸³⁾ and distilled (b.p. 78-9°).
- b) Methanol was dried as in (a) and distilled (b.p. 64-65°).
- c) t-Butanol and t-Amyl alcohol were dried by refluxing over sodium for 1 hour then distilling b.p. 82-83° and 101-102° respectively.
- d) Ether, Benzene, Toluene and Xylene were dried by being allowed to stand over calcium chloride for 24 hours, filtering, and standing over sodium wire for 24 hours then distilling prior to use. b.p. 34-36°, 79-80°, 110°, and 139-142° respectively.
- e) Pyridine was refluxed with potassium hydroxide for 1 hour under anhydrous conditions, then distilled, the fraction of b.p. 115-116°/760 mm. being collected and stored over potassium hydroxide.
- f) Liquid ammonia was dried by distilling from sodium and trapping with a dry ice condenser.
- g) Sodamide was prepared by adding sodium to dry liquid ammonia containing a trace of ferric nitrate and evaporating the excess ammonia when the immediate blue colour had turned to grey. ⁽⁴⁸⁾ The last traces of ammonia were removed by a

stream of oxygen-free dry nitrogen.

h) Triton B was prepared by concentrating a mixture of (1:1) ethanol/benzene (100 ml.) and an aqueous solution of benzyltrimethylammonium hydroxide (2 ml. 40% w/w) to a volume of 30 ml. by slow azeotropic distillation. In each of the experiments described previously 15 ml. of this solution was used.

i) Sodium triphenylmethide was prepared in dry ether solution by shaking a mixture of 2% sodium amalgam (134 g.), triphenyl chloromethane (9 g., m.p. 111-113° recrystallised from 1:5 acetylchloride/light petroleum (b.p. 100-120°) (13 ml.)) and dry ether (200 ml.) under nitrogen for 12 hours. (72) Titration of the sodium hydroxide liberated on pouring a fixed volume of sodium triphenylmethide into water with standard N/10 hydrochloric acid using methyl red as indicator showed 71% conversion of triphenylchloromethane to the sodio derivative.

j) Diglyme b.p. 160-162° was dried by distilling from lithium aluminium hydride.

REFERENCES

1. Menard, Wyler, Hiestand, Arigoni, Jeger and Ruzicka, Helv. Chim. Acta, 1955, 38, 1517.
2. Ryback, D.Phil.Thesis, Oxford, 1963.
3. Haines and Warren, J., 1949, 2554.
4. Barton and Seone, J., 1956, 4150.
5. Arigoni, Jeger and Ruzicka, Helv.Chim.Acta, 1955, 38, 222.
6. Matthieu and Ourisson, Selected Constants. Optical Rotatory Power II. Triterpenoids., Pergamon Press, 1958.
7. Heusler and Wettstein, Helv.Chim.Acta, 1952, 35, 284.
8. Mills and Werner, J., 1955, 3132.
9. Mills, J., 1956, 2196.
10. Dunstan, Fazakerley, Halsall and Jones, Croatica Chemica Acta, 1957, 29, 177.
11. Bellamy, The Infra-red Spectra of Complex Molecules, 1959, 122.
12. Eastham, Miles and Krauth, J.Amer.Chem.Soc., 1959, 81, 3114.
13. Butenandt and Wolz, Ber., 1938, 71, 1483.
14. Arigoni, Viterbo, Dunnenberger, Jeger and Ruzicka, Helv.Chim.Acta, 1954, 37, 2306-2322.
15. Christen, Dunnenberger, Roth, Heusser and Jeger, Helv.Chim.Acta, 1952, 35, 1756-74.
16. Emmons and Lucas, J.Amer.Chem.Soc., 1955, 77, 2287.
17. Hawthorne, Emmons and McCallum, J.Amer.Chem.Soc., 1958, 80, 6393.
18. Baeyer and Villiger, Ber., 1899, 32, 3625.
19. Emmons, J.Amer.Chem.Soc., 1954, 76, 3468.

20. Squire, J.Amer.Chem.Soc., 1951, 73, 2586.
21. Organic Syntheses, Collective Volume II, 1946, 609.
22. McElvain, Organic Reactions, 1948, IV, 262.
23. Prelog, Frenkiel, Kobelt, and Barman, Helv. Chim. Acta, 1947, 30, 1741.
24. Barnett and Lawrence, J., 1935, 1104.
25. Gruber and Adams, J.Amer.Chem.Soc., 1935, 57, 2555.
26. Turner, J.Amer.Chem.Soc., 1950, 72, 582.
27. Arndt, Organic Syntheses, Collective Volume II, 1946, 165.
28. Vogel, Practical Organic Chemistry, 1956, 971.
29. Criegee and Gunther, Ber., 1963, 96, 1565.
30. Pryde, Anders, Teeter and Cowan, J.Org.Chem., 1960, 25, 618.
31. Bailey, J.Org.Chem., 1957, 22, 1548.
32. Bailey and Shashikant, J.Org.Chem., 1958, 23, 1089.
33. Plattner, Heusser and Kulkarni, Helv.Chim.Acta, 1948, 31, 1822.
34. Edward, Holder, Lunn, and Puskas, Canad. J. Chem., 1961, 39, 599.
35. Lemieux and von Rudloff, Canad. J. Chem., 1955, 33, 1701, 1710, 1714.
36. Lemieux and von Rudloff, Canad.J.Chem., 1956, 34, 1413.
37. Linstead, Elvidge and Whalley, A Course in Modern Techniques of Organic Chemistry, Butterworths Press, London, 1955.
38. Corey, Sauers and Swann, J.Amer.Chem.Soc., 1957, 79, 5826.
39. Greaves, Linstead, Shephard, Thomas and Weedon, J., 1950, 3326.

40. Glasstone and Hickling, Trans. Electrochem. Soc., 1939, 75, 333.
41. Vesterberg and Westerlind, Ann., 1922, 428, 247.
42. Matsumoto, Wainae and Miyake, Nippon Kwagaku Kwaishi, 1955, 75, 1057.
43. Budziarck, Manson and Spring, J., 1951, 3336.
44. Brownlie, Payez, Spring, Stevenson and Strachan, J., 1956, 1377.
45. David, Bull. Soc. Chim. France, 1949, 155-60.
46. Halsall, Jones and Swayne, J., 1954, 1902.
47. Shriner and Todd, Org. Syntheses, Coll. Vol. II. 200.
48. Halsall and Thomas, J., 1956, 2431.
49. Littlehailes, D. Phil. Thesis, Oxford, 1962.
50. Leggate, D. Phil. Thesis, Oxford, 1960.
51. Rushton, D. Phil. Thesis, Oxford, 1960.
52. Adams, Loewe, Theobald and Smith, J. Amer. Chem. Soc., 1942, 64, 2653.
53. Fieser, J. Amer. Chem. Soc., 1954, 76, 1945.
54. Mozingo, Org. Syntheses, Coll. Vol. III, 131.
55. Eglinton and Whiting, J., 1950, 3650.
56. Killian, Hennion and Nieuwland, J. Amer. Chem. Soc., 1934, 56, 1384.
57. Hennion and Murray, J. Amer. Chem. Soc., 1942, 64, 1220.
58. Nazarov, Vartanyan, Matsuyan and Zhamagortsyan, Zhur. Obshchei Khim, 1953, 23, 1986-90.
59. Oroschnik, Karmas and Mebane, J. Amer. Chem. Soc., 1952, 74, 3807-13.
60. Salmi, Ber., 1938, 71, 1803.

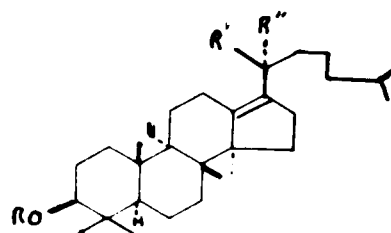
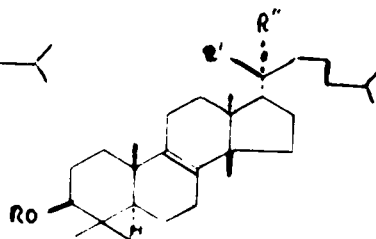
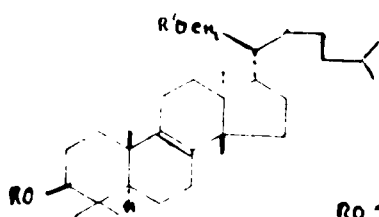
61. Williman and Shinz, Helv.Chim.Acta, 1949, 32, 2151.
62. McMahon, Roper, Untermohlen, Hasek, Harris and Brant,
J.Amer.Chem.Soc., 1948, 70, 2971.
63. Woodward, Sondheimer, Taub, Heusler, McLamore,
J.Amer.Chem.Soc., 1952, 74, 4239.
64. Riegel and Lilienfeld, J.Amer.Chem.Soc., 1945, 67, 1274.
65. Lund and Voigt, Org.Syntheses, Coll.Vol.II, 594.
66. MacDonald and Stedman, J.Canad.Chem.Soc., 1955, 33, 458-67.
67. Bachmann and Holmen, J.Amer.Chem.Soc., 1951, 73, 3660.
68. Vogel, Elementary Practical Org.Chem., 1957, pp.193,307.
69. Bachmann and Struve, Organic Reactions, Vol.I., 38.
70. Newmann and Beal, J.Amer.Chem.Soc., 1950, 72, 5163.
71. Woodward, Patchett: Barton, Ives and Kelly, J., 1957, 1131.
72. Renfrow and Hauser, Org.Syntheses, Coll.Vol.II, 667.
73. Russo and Zook, J.Amer.Chem.Soc., 1960, 82, 1258.
74. Allen, Bernstein and Littell, J.Amer.Chem.Soc.,
1954, 76, 6116.
75. Wilds and Shunk, J.Amer.Chem.Soc., 1943, 65, 476.
76. Wichterle, Prochazka and Hofmann, Coll.Czech.Chem.Comm.,
1948, 13, 300 and Chem.Abstracts, 1948, 42, 81621.
77. Prelog, Barman and Zimmermann, Helv.Chim.Acta, 1949, 32, 1284.
78. Dauben and McFarland, J.Amer.Chem.Soc., 1960, 82, 4245.
79. Eisner, Elvidge and Linstead, J., 1950, 2226.
80. Gregory and Long, J., 1961, 3059.
81. du Fen, McQuillan and Robinson, J., 1937, 53.
82. Wilds and Shunk, J.Amer.Chem.Soc., 1943, 65, 469.
83. Lund and Bjerrum, Ber., 1931, 64, 210.

84. Halsall, Meakins and Swayne, J., 1953, 4139.
85. Ruzicka, Hosking and Wick, Helv.Chim.Acta, 1931, 14, 811.
86. Ruzicka and Hauserman, Helv.Chim.Acta, 1942, 25, 439.
87. Bilham and Kon, J., 1942, 25, 439.
88. Curtis, Heilbron, Jones and Woods, J., 1953, 457.
89. Birch, Collins, Muhammad and Turnbull, J., 1963, 2762.
90. Kamernitzky and Akhrem, Tetrahedron, 1962, 18, 705.
91. Warren and Watling, J., 1958, 179.
92. Criegee, Blust and Zuiko, Ber., 1954, 87, 766.
93. Bailey, Chem.Rev., 1958, 58, 925.
94. Bailey, Ber., 1955, 88, 795.
95. Wallenberger, Tetrahedron Letters, 1959, No.9, 5.
96. Moriconi, O'Connor, Wallenberger, J.Amer.Chem.Soc., 1959, 81, 6466.
97. Pryde, Andrews, Teeter and Cowan, J.Org.Chem., 1960, 25, 618.
98. Corey and Sauers, J.Amer.Chem.Soc., 1957, 79, 3925;
ibid., 1959, 81, 1757.
99. Stork, Davies and Meisels, J.Amer.Chem.Soc., 1959, 81, 5516
100. Salauze, Bull.soc.chim.France, Mem., 1925, 37, 522.
101. Weedon, Quart.Revs.. (London), 1952, 6, 380.
102. Weedon, Advances in Org.Chem., 1960, Vol.1, 1.
103. Kunuzi. J.Amer.Chem.Soc., 1953, 75, 1597.
104. Stallberg, Arkiv Kemi, 1958, 12, 153.
105. Perkin, Ray, Robinson, J., 1928, 1511.
106. Mehr, Becker, and Spaerri, J.Amer.Chem.Soc., 1955, 77, 984.

107. Stoll and Rouve, Helv.Chim.Acta, 1947, 30, 1822.
108. Hassal, Organic Reactions, 1957, Vol.IX, 73.
109. Friess and Farnham, J.Amer.Chem.Soc., 1950, 72, 5518.
110. Doering and Dorfman, J.Amer.Chem.Soc., 1953, 75, 5595.
111. Ireland and Marshall, J.Org.Chem., 1962, 27, 1620.
112. Braude and Coles, J., 1950, 2014.
113. Barltrop, Rogers and Littlehailles, Tetrahedron Letters, 1962, No.10, 429.
114. Locke, Private communication.
115. Johnson, J.Amer.Chem.Soc., 1943, 65, 1317.
116. Birch, Jaeger and Robinson, J., 1945, 582.
117. Johnson and Posvic, J.Amer.Chem.Soc., 1947, 69, 1620.
118. Burr, Holton and Webb, J.Amer.Chem.Soc., 1950, 72, 4903.
119. Published by v. Auwers, Ber., 1938, 7113, 2082.
120. Birch and Robinson, J., 1944, 501.
121. Ireland and Marshall, J.Amer.Chem.Soc., 1959, 81, 6336.
122. Nielsen, J.Org.Chem., 1957, 22, 1539.
123. Caliezi and Schinz, Helv.Chim.Acta, 1952, 35, 1637.
124. Dauben and Hance, J.Amer.Chem.Soc., 1953, 75, 3352.
125. Braude and Evans, J., 1955, 3331.
126. Ferry and McQuillin, J., 1962, 103.
127. Robinson, J., 1936, 1087.
128. Graham and McQuillin, J., 1963, 4634 and 4726.
129. Brewster and Eliel, "Organic Reactions", Wiley, New York 1953, Vol.VII, 99.

130. Cornforth and Robinson, J., 1947, 1855.
131. McQuillin, J., 1955, 578.
132. Ruzicka, Stoll, Scherrer, Schinz, and Seidel,
Helv.Chim.Acta, 1932, 15, 1459.
133. Rodd, Chemistry of Carbon Compounds, Elsevier Press,
1956, Vol. IIIB, 834.

PLATE I (A1 - A19a)



A1: $R = R' = Ac$

A1a: $R = R' = H$

A2: $R = Ac, R' = H$

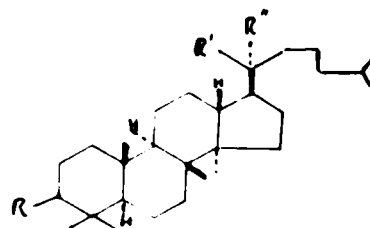
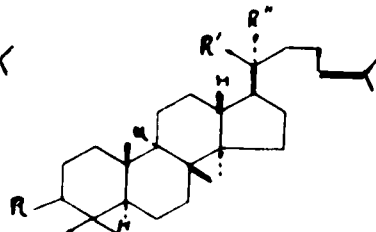
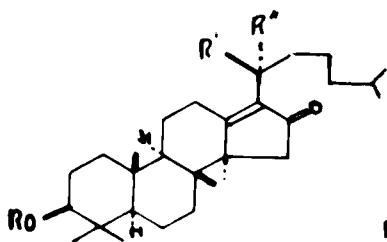
A3: $R = Ac, R' = SO_2CH_3$

A4: $R = Ac, R' = Me, R'' = H$

A5: $R = H, R' = Me, R'' = H$

A6: $R = Ac, R' = Me, R'' = H$

A1b: $R = Ac, R' = H, R'' = Me$



A7: $R = Ac, R' = Me, R'' = H$

A15: $R = Ac, R' = H, R'' = Me$

A8: $R = \beta OH, R' = Me, R'' = OH$

A8a: $R = \beta OH, R' = Me, R'' = OH$

A9: $R = \beta OH, R' = OH, R'' = Me$

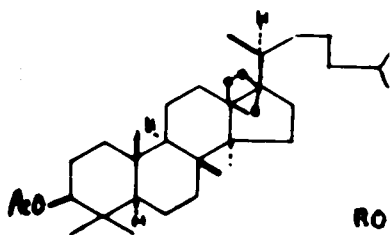
A9a: $R = \beta OH, R' = OH, R'' = Me$

A10: $R = \beta OAc, R' = Me, R'' = OH$

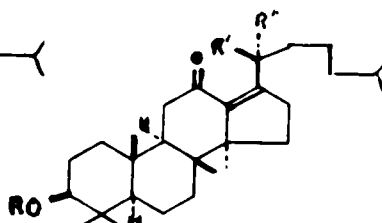
A11: $R = \beta OAc, R' = OH, R'' = Me$

A12: $R = \beta OAc, R' = Me, R'' = OH$

A13: $R = \beta OAc, R' = OH, R'' = Me$

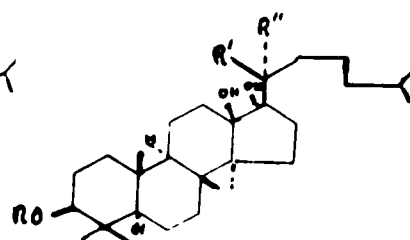


A14



A16: $R = Ac, R' = Me, R'' = H$

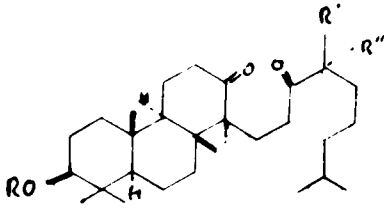
A17: $R = Ac, R' = H, R'' = Me$



A18: $R = H, R' = H, R'' = Me$

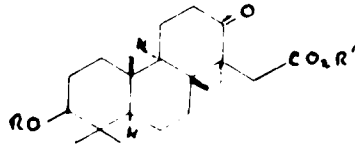
A19a: $R = H, R' = Me, R'' = H$

PLATE II (A20 - A36)



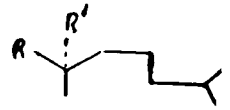
A20: $R: Ac, R': H, R'': Me$

A21: $R: Ac, R': Me, R'': H$



A22: $R: Ac, R': Me$

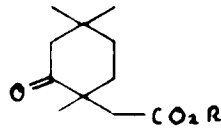
A25: $R: H, R': H$



A23: $R: Me, R': H$

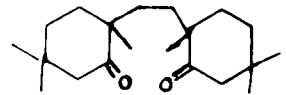
$CH_3 (CH_2)_{12} CO_2H$

A24

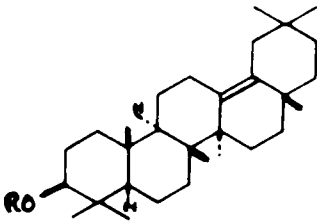


A26: $R: H$

A26a: $R: C_2H_5$

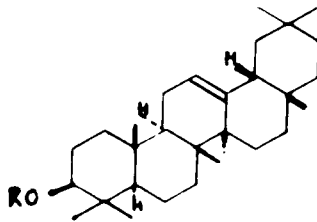


A27



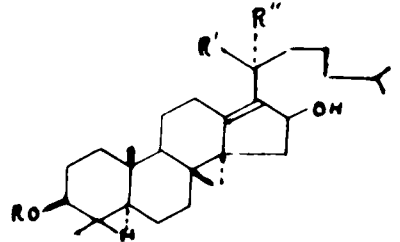
A28: $R: H$

A32: $R: Ac$

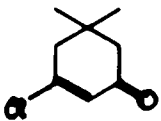


A29: $R: Ac$

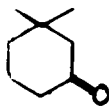
A30: $R: H$



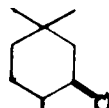
A31: $R: H, R': Me, R'': H$



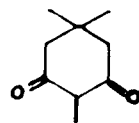
A32a



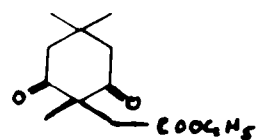
A33



A34



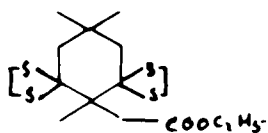
A35



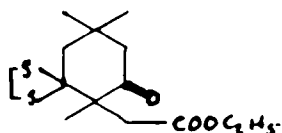
A36

PLATE III (A34 - A51)

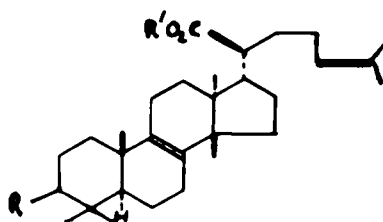




A37

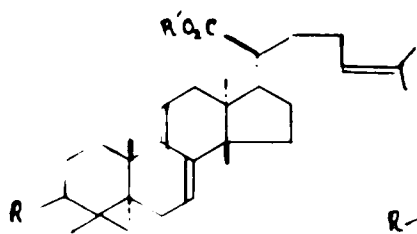


A38



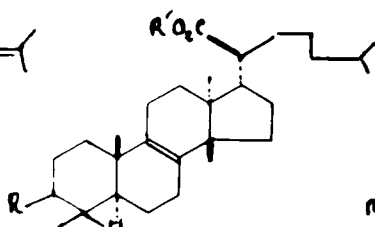
A39: R = α OH, R' = H

A40: R = ketone, R' = H



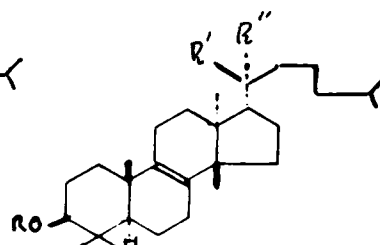
A41: R = α OH, R' = H

A42: R = ketone, R' = H

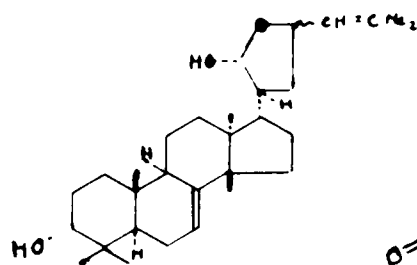


A43: R = α OH, R' = H

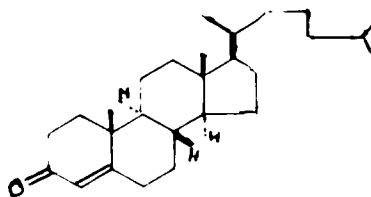
A44: R = ketone, R' = H



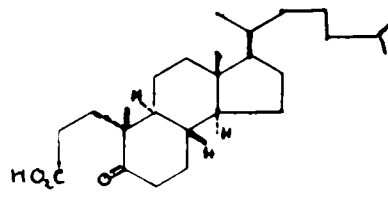
A45: R = H, R' = H, R'' = Me



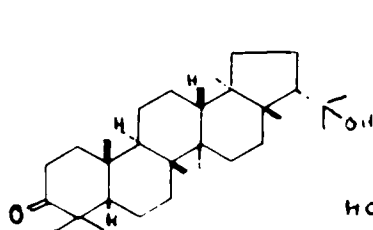
A46



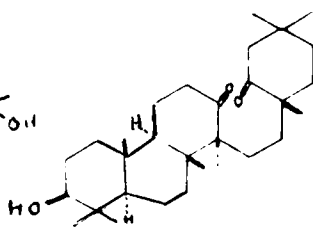
A47



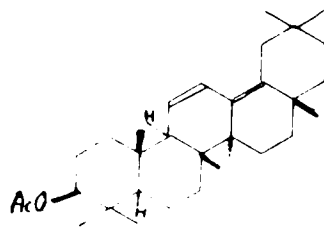
A48



A49



A50



A51

PLATE IV (A52 - A54)

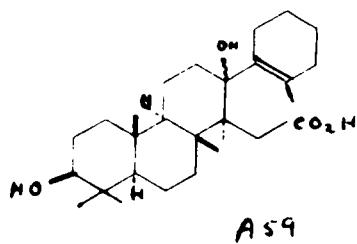
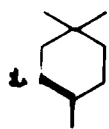
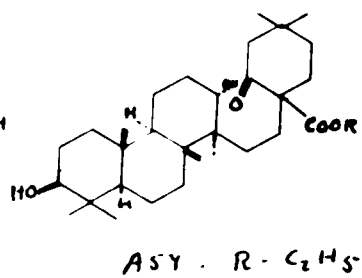
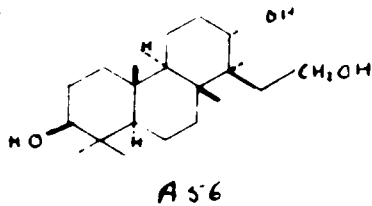
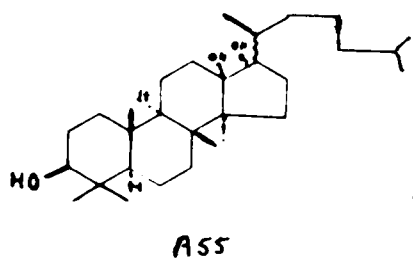
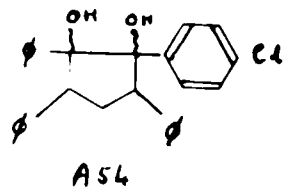
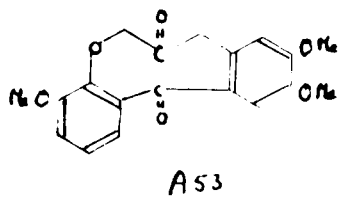
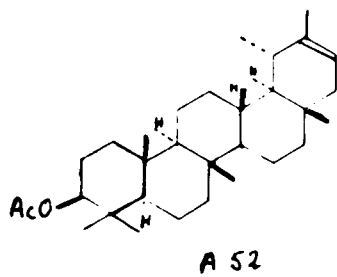
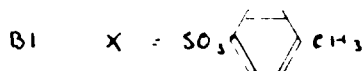
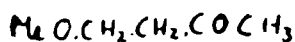
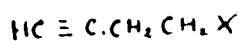
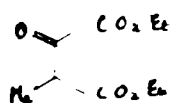
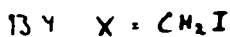
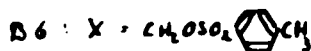


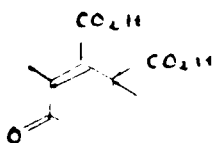
PLATE V (B1 - B26)



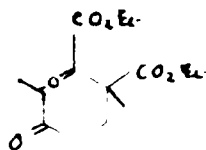
B3



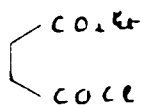
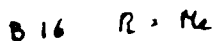
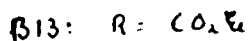
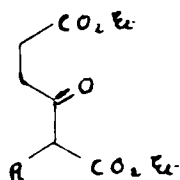
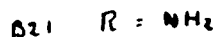
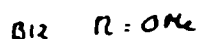
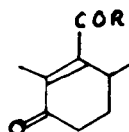
B8



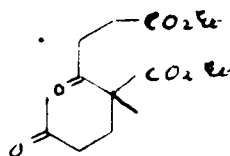
B9



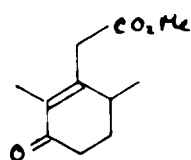
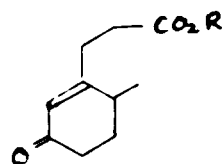
B10



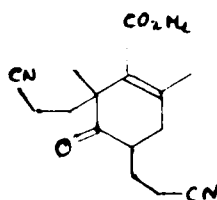
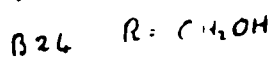
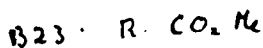
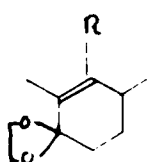
B18



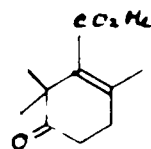
B19



B22

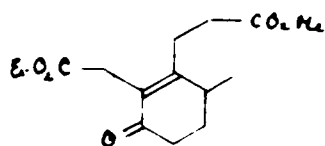


B25

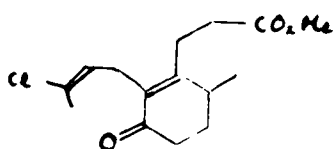


B26

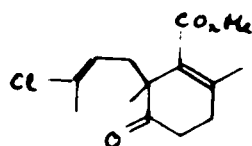
PLATE VI (B27 - B42)



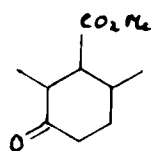
B27



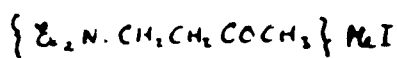
B28



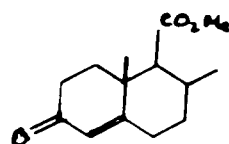
B29



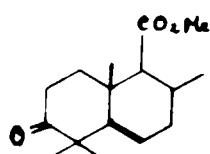
B30



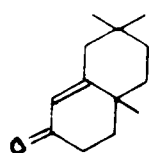
B31



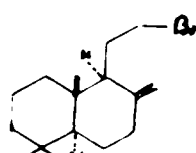
B32



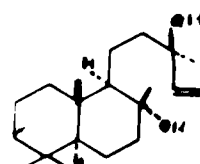
B33



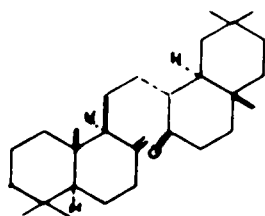
B34



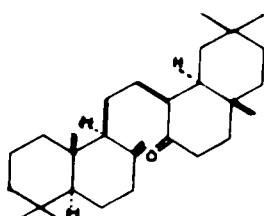
B35



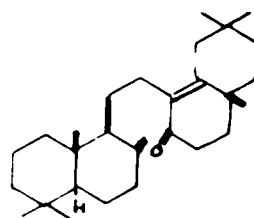
B36



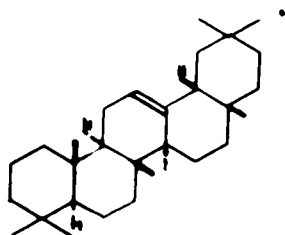
B37



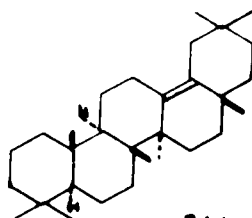
B38



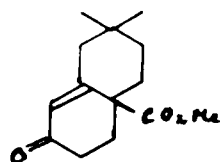
B39



B40



B41



B42

PLATE VII (B43 - B58)

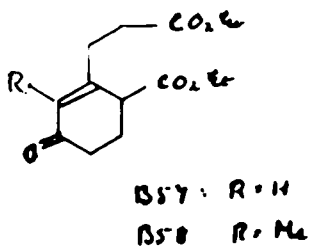
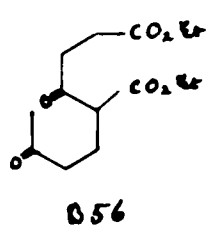
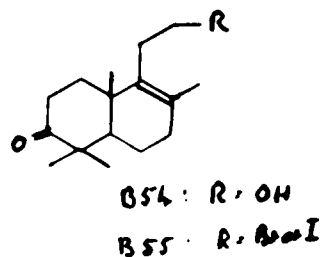
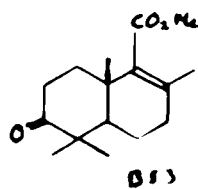
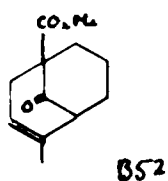
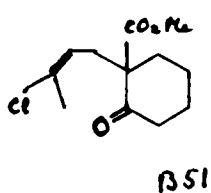
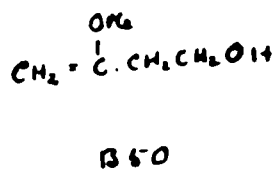
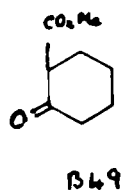
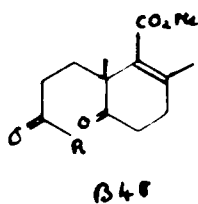
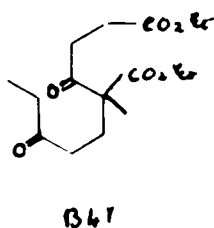
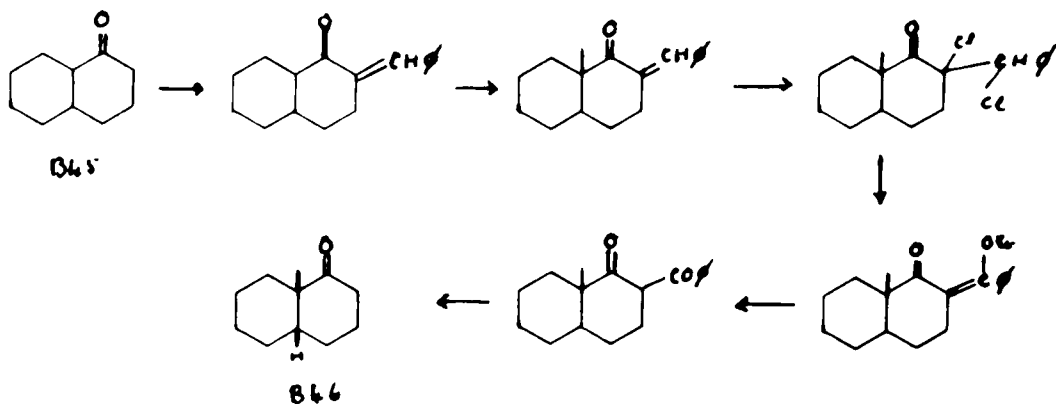
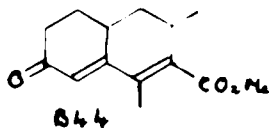
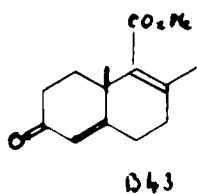
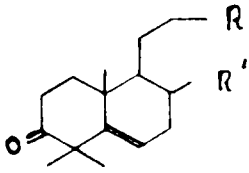
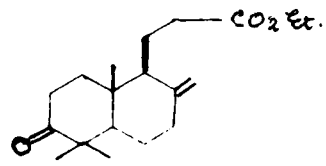


PLATE VIII (B59 - B64)

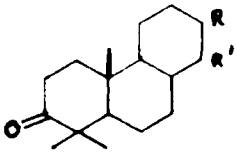


B59: $R = CO_2Et$, $R' = CO_2H$

B60: $R = CO_2H$, $R' = CO_2Et$

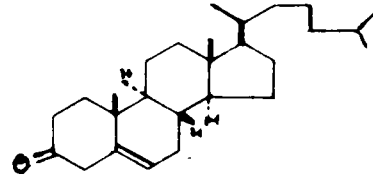


B61



B62: $R = OH$, $R' = \text{heptane}$

B63: $R' = OH$, $R = \text{heptane}$



B64

ABSTRACT

In the Introduction to this Thesis recent progress in the biogenesis of triterpenes is discussed with particular reference to the dammarene diols (XI a and b). This example is also taken to illustrate the techniques now used in the elucidation and determination of such complex structures. There follows a survey of the methods used in the total synthesis of pentacyclic triterpenes. Because of difficulties presented by both the structure and the stereochemistry of such molecules the approaches have necessarily been limited to three main courses of attack, the acid-catalysed cyclisation of squalene (XII), the combination of two decalin derivatives to provide rings AB and DE of the pentacyclic system, and the combination of a of a tricyclic ABC moiety with a monocyclic unit to provide ring E.

The main body of this Thesis is divided into two sections (A and B). In the first a detailed investigation is made into a previously reported route from elemadienolic acid (I) to a possible ABC tricyclic intermediate ($I \rightarrow IX$)⁽¹⁾ with particular emphasis being placed on yields and reproducibility. It is shown that the route has several undesirable features and a superior alternative is offered ($X \rightarrow XI \rightarrow IX$). In connection with this work two potential

monocyclic ring E precursors have been synthesised (XIIIa and XIVa) and an attempted electrolytic coupling of (XIIIa) and (IX) has been carried out.

The second section represents a continuation of the work of Littlehalles⁽²⁾ and is devoted to the synthesis of a hydroxylated bicyclic AB unit (XV) which could be utilised in alkylating the decalone (XVI) with the aim of constructing a pentacyclic triterpene of the amyrin series.

Section A.

The tricyclic intermediate (IX) was first isolated by the route illustrated (I → IX) in quantities sufficient for little more than characterisation purposes.⁽³⁾ More recently Ryback⁽¹⁾ has made a preliminary investigation into the practical utilisation of such a route with special regard to the isolation of (IX) in large enough quantities for use in further synthetic operations. However his results were not conclusive and it was decided to reinvestigate some of the operations involved.

As supplies of tirucallenediol (II) were at hand it was decided to look first at its conversion into isotirucall-enyl acetate (VIIa). It was found that although deacetylation went in high yield, the yield from the semi-hydrolysis of the diacetate (III) was not reproducible and was often poor necessitating a laborious fractional recrystallisation and recycling procedure in order to obtain quantities of the

monoacetate (IV). The formation of the methanesulphonyl derivative (V), its reduction with lithium aluminium hydride to give tirucalleny acetate (VI) and the subsequent acid isomerisation to isotirucalleny acetate (VIIa) all went in high yield. Oxidation of (VIIa) with *t*-butyl chromate gave a reproducible 50% conversion to the $\alpha\beta$ -unsaturated ketone (VIIIa).

The cleavage of the $\Delta^{13(17)}$ double bond in the unsaturated ketone (VIIIa) was attempted by ozonolysis, osmium tetroxide and lead tetraacetate, alkaline peroxide and the Lemieux periodate/permanganate oxidation. Only ozone caused fission to occur giving the tricyclic keto acid (IX) in poor yield. A summary of the results of these experiments and a discussion of the implications is presented.

The demonstration that at least two stages in this route were unsatisfactory, the difficulty⁽¹⁾ of isolating elemadienonic acid (XVII) in a high degree of purity, and the many stages involved in the conversion of elemadienolic acid (I) to the tricyclic intermediate (IX), instigated the search for an alternative source of (IX). This was afforded by the isolation of the epimeric mixture of dammarene diols (XI a and b) and the related ketones (X a and b) from Dammar resin. Reduction of the ketone content of the mixture to alcohol by lithium aluminium hydride followed by acetylation, hydrogenation and acid-catalysed dehydration

gave a further mixture which contained isotirucallenyl acetate (VIIa) and isoeuphenyl acetate (VIIb). Oxidation of this mixture with t-butyl chromate followed by ozonolysis of the resultant α/β -unsaturated ketones (VIII a and b) gave the tricyclic intermediate (IX), in the manner already described for isotirucallenyl acetate (VIIa) alone. The tricyclic intermediate (IX) could now be effectively and efficiently isolated from a natural source as the end product of a route containing only four major operations.

Two cyclohexane keto-esters (XIIIb) and (XIVb) were synthesised for the purpose of coupling with the tricyclic intermediate (IX). Each was derived from dimedone. In one case, dimedone was converted into the enol-chloride (XVIII) which was hydrogenated to the cyclohexanone (XIX), and carbethoxylated to give the keto-ester (XIVb). In the second case, dimedone was alkylated first with methyl iodide and then ethyl bromoacetate to give (XXI). Eliminating one of the ketone groups via the thioetal and reduction with Raney nickel gave the keto-ester (XIIIb).

It was attempted to electrolytically couple the tricyclic intermediate (IX) with the monocyclic keto-acid (XIIIa) but only the big-cyclohexyl ethane derivative (XXII) could be isolated.

Both isotirucallenyl acetate (VIIa) and isoeuphenyl acetate (VIIb) were converted into the 1,5-diketones (XXIIIa)

and (XXIIIb) in good yields with osmium tetroxide and lead tetraacetate. Attempts to recyclise the 1,5-diketones by a pinacolic reduction succeeded, albeit in poor yield, when the forcing conditions of molten sodium in xylene were employed.

An attempted Baeyer-Villiger oxidation of the 1,5-diketone (XXIIIa), however, was unsuccessful.

In anticipation of the products to be obtained from the coupling of the monocyclic and tricyclic intermediates (XIIIa) and (IX) attempts were made to hydroxylate and fission the $\Delta^{13(18)}$ double bond in σ -amyrin acetate (XXIV), but these proved unsuccessful. The σ -amyrin acetate (XXIV) was obtained from β -amyrin (XXVa) by successive acetylation, selenium dioxide dehydrogenation and partial re-hydrogenation. β -Amyrin (XXVa) was itself isolated as its benzoate from the fractional crystallisation of a mixture of α - and β -amyrin benzoates, (XXVI) and (XXVb).

Also included in this section is a discussion of further methods of converting the tricyclic intermediate (IX) into a pentacyclic triterpene.

Section B.

The base catalysed condensation of ethyl 2-oxo-3-carbethoxybutyrate and ethyl vinyl ketone gave the 1,5-diketone (XXVIII), which after acid-catalysed cyclisation and esterification gave the $\alpha\beta$ -unsaturated keto-ester (XXIX) in high

overall yield. As difficulties were both anticipated and realised in the alkylation of (XXIX), a second monocyclic keto-ester (XXX) was synthesised in order to make comparative studies of their alkylation. The keto-ester (XXX) was synthesised in high yield via the base-catalysed condensation of ethyl α -methyl- β -oxoadipate and methyl vinyl ketone, ring-closure and esterification.

Unsuccessful attempts were made to convert the unsaturated keto-ester (XXIX) into a bicyclic precursor (XL) for rings A and B by a Robinson ring extension and by a Michael addition with acrylonitrile. However, the discovery (see below) that the substance (XXIX) could be alkylated suggested that the same result might be indirectly achieved by alkylating it with a β -halobutan-3-one ketal and then splitting the ketal and cyclising the resultant 1,5-diketone.

With the object of preparing a β -halobutan-3-one ketal several vain attempts were made to add methanol in the presence of mercuric chloride/boron trifluoride etherate catalyst to several related α -substituted but-1-ynes (XXXI a, b and c). Finally the object was realised by converting ethyl acetoacetate into its ketal derivative (XXXIIa), which was reduced with lithium aluminium hydride to the ketal alcohol (XXXIIb), this in turn giving the toluene-p-sulphonate (XXXIIc) and iodide (XXXIIId).

A wide variety of conditions were employed in attempts to alkylate the monocyclic keto-esters (XXIX and XXX) with both the β -ketal toluene-p-sulphonate (XXXIIc) and iodide (XXXIId) but as no alkylated product was ever isolated it appeared that the β -ketal derivatives (XXXIIc) and (XXXIId) were either too unstable or too inactive to accomplish substitution.

However, the monocyclic intermediates (XXIX) and (XXX) were alkylated in several ways. The unsaturated keto-ester (XXIX) was alkylated with methyl iodide and potassium *t*-butoxide, and the homologous keto-ester (XXX) was alkylated by ethyl bromoacetate using sodium triphenylmethide as base. Both (XXIX) and (XXX) were alkylated with 1,3-dichlorobut-2-ene⁽⁴⁾ in the presence of sodium *t*-amylxide but no bicyclic ring closure compounds could be obtained on treatment of the chlorocrotyl derivatives (XXXIII) and (XXXIV) with concentrated sulphuric acid. In fact the latter regressed to the keto-ester (XXX) and the former isomerised to give a solid crystalline product which could not be identified.

Finally, ring extension was achieved by first reducing the olefinic bond in the monocyclic $\alpha\beta$ -unsaturated keto-ester (XXIX) with lithium in liquid ammonia and condensing the resultant saturated keto-ester (XXV) with the methiodide of 1-diethylaminobutan-3-one using sodamide as base.⁽⁵⁾ The

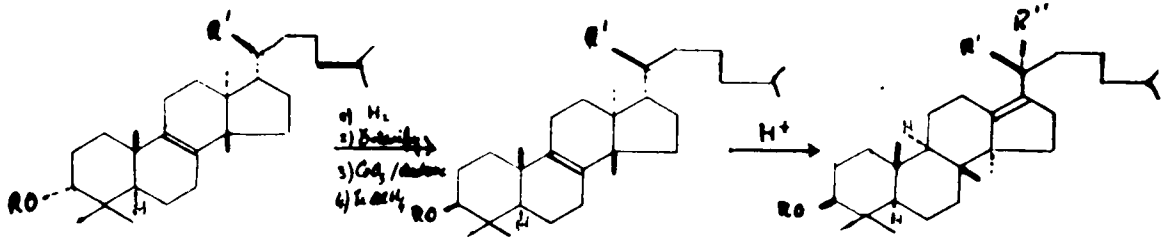
octalone (XXXVI) was isolated and a gem-dimethyl group was introduced to give (XXV VII).

A description of the continuation of this work is given and also included is a variation involving the preparation of the diester (XXXVIII) by a base-catalysed ring closure of the 1,5-diketone (XXXIX), itself derived from the base-catalysed condensation of ethyl β -oxoadipate and methyl vinyl ketone. Ways in which this latter compound can be utilised are also presented.

REFERENCES

1. Ryback, D.Phil.Thesis. Oxford 1962.
2. Barltrop, Rogers and Littlehailes, Tetrahedron Letters, 1962, No.10, 429.
3. Littlehailes, D.Phil.Thesis. Oxford, 1962.
3. Arigoni, Jeger, and Ruzicka, Helv.Chim.Acta, 1955, 38, 222-30.
4. Wichterle, Prochazka and Hofmann, Coll.Czech.Chem.Comm., 1948, 13, 300.
5. Robinson, J., 1936, 1087.

PLATE 1 (I - 816)



I: R = H, R' = CO₂H

II: R = H, R' = CH₂OH

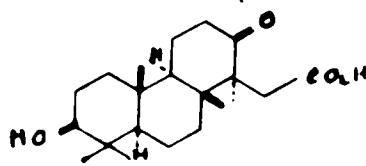
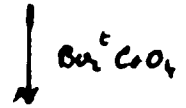
III (a): R = Ac, R' = Me, R'' = H

IV: R = Ac, R' = CH₂OAc

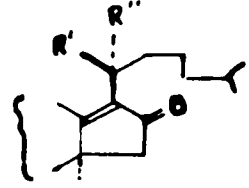
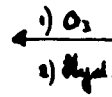
V: R = Ac, R' = CH₂OH

VI: R = Ac, R' = CH₂OSO₂Me

VII: R = Ac, R' = Me

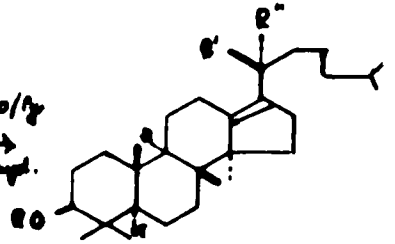
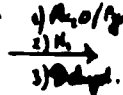
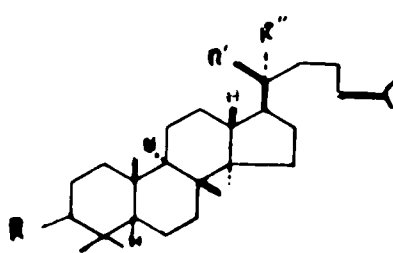


IX



X (a): R' = Me, R'' = H

X (b): R' = H, R'' = Me



XI (a): R = butanoic, R' = Me, R'' = OH

XI (b): R = butanoic, R' = OH, R'' = Me

XII (a): R = pOH, R' = Me, R'' = OH

XII (b): R = pOH, R' = OH, R'' = Me

XIII (a): R = Ac, R' = Me, R'' = H

XIII (b): R = Ac, R' = H, R'' = Me

PLATE 2 (XII - XXIII 4)

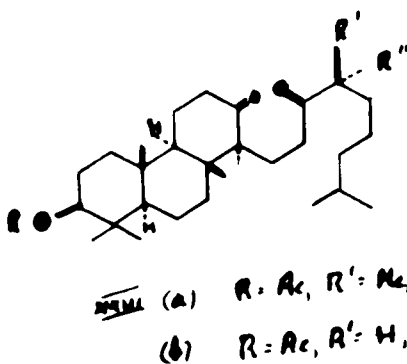
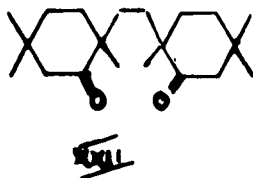
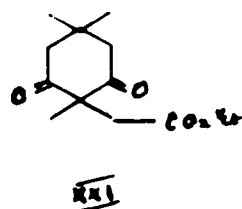
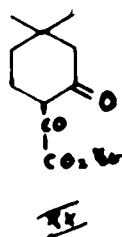
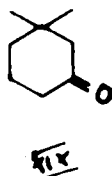
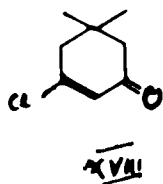
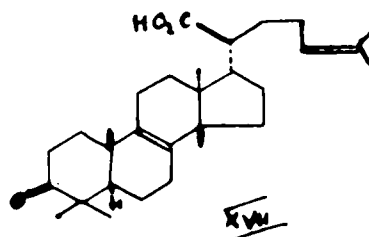
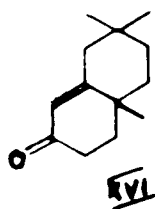
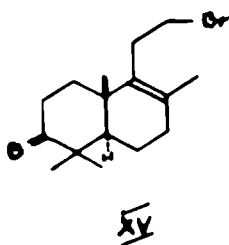
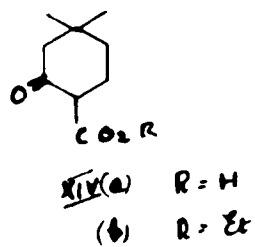
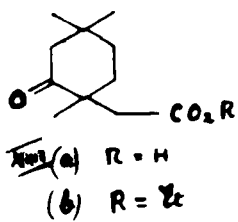
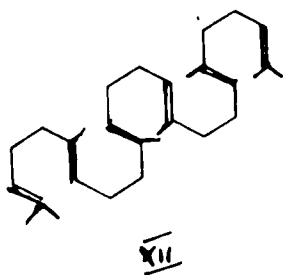
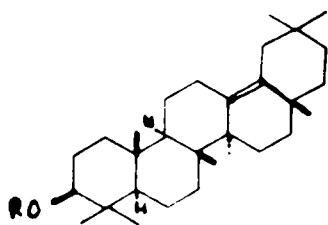
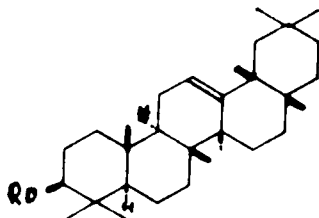


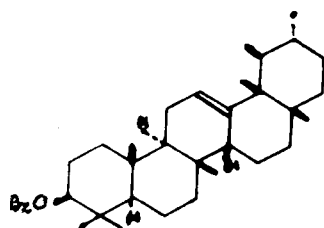
PLATE 3 (xxiv - xl)



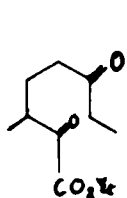
XXXIV R = Ac



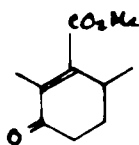
XXXV (a) R = H
XXXV (b) R = Bz



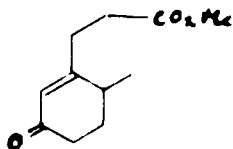
XXXVI



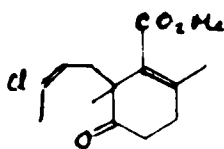
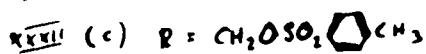
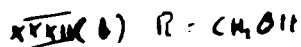
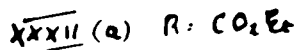
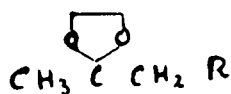
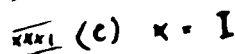
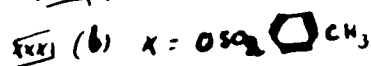
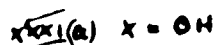
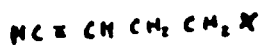
XXXVII



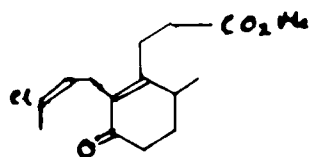
XXXVIII



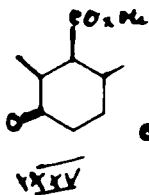
XXXIX



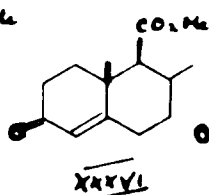
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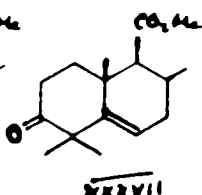
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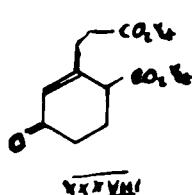
XXXV



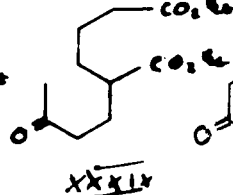
XXXVI



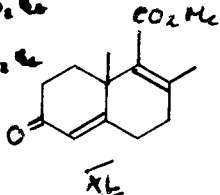
XXXVII



XXXVIII



XXXIX



XL