SYNTHETIC APPROACHES TO PROSTAGLANDINS.

A thesis presented by

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in partial fulfillment of the requirements
for the degree of

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ABSTRACT.

In the first part of this work, the published syntheses of several prostaglandins are reviewed, with special emphasis being placed on the stereochemical control achieved using the different synthetic approaches.

The second section describes some investigations into the preparation and chemistry of a 3-alkyl-1,2,4,- cyclopentane triketone , and its subsequent conversion by another group into several prostaglandins.

The third section deals with some chemistry of norbornanes which arose during attempts to find some useful precursors for a general synthesis. Three independent investigations are reported;

(i) Skeletal rearrangement which was found to occur on reacting certain substituted norbornenes with an electrophile (Br^+) has been shown to be a highly regioselective process, and evidence is presented to support the structures assigned to the products.

(ii) Results of some attempts to prepare 7-alkyl norbornadienes by reaction of a Grignard reagent with 7-^{t}butoxy norbornadiene are discussed.

(iii) The reactions of some olefins and dienes with various aldehydes in an acidic medium are discussed.

ACKNOWLEDGEMENTS.

The author expresses his sincere thanks to Professor J. K. Sutherland for constant guidance and encouragement throughout the course of this work.

Thanks are also given to the technical staff of Imperial College and Manchester University, especially to Messrs. R. V. Carter and H. Paton.

Thanks are also due to Professor D. H. R. Barton, for the opportunity provided to work in his department.

CONTENTS.

Abbreviations used in the text.

T,THP	tetrahydropyran
NBS	N- bromosuccinimide.
LAH	lithium aluminium hydride.
TLC	thin layer chromatography
GLC	gas liquid chromatography.
p.m.r.	proton magnetic resonance.

To my parents and Judith.

REVIEW : SYNTHESES OF SOME PROSTAGLANDINS.

SYNTHETIC APPROACHES TO PROSTAGLANDINS.

Introduction

Since the first isolation of a pharmacologically-active lipid from sheep seminal fluid in 1933, there has been an almost exponential annual increase in the number of publications dealing with the prostaglandins. So great has been the progress in the understanding of the biochemistry of the prostaglandins that the early work on their isolation and structure elucidation is now largely of historical interest. This elegant work [1], linked with such names as Samuelsson and Bergström, coupled with the discovery of profound and diverse biological effects has opened up a new chapter of hormone research.

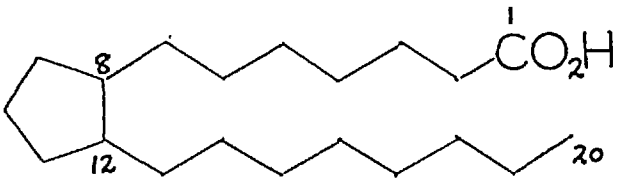
Even at nanomolar concentrations the prostaglandins produce physiological responses in the cardiovascular, nervous, renal, gastric and reproductive systems. Further, the individual prostaglandins show vastly different effects despite the commonality of the C_{20} skeleton.

Chemical syntheses of these compounds has recently assumed some importance due to the discovery that the stereoisomers of naturally occurring prostaglandins show potent biological activity.

Biosyntheses, though successful, will not be reviewed since they lead only to naturally occurring prostaglandins.

To date, sixteen prostaglandins have been characterised; all containing the C_{20} carboxylic acid skeleton (1) which has the

trivial name prostanoic acid.

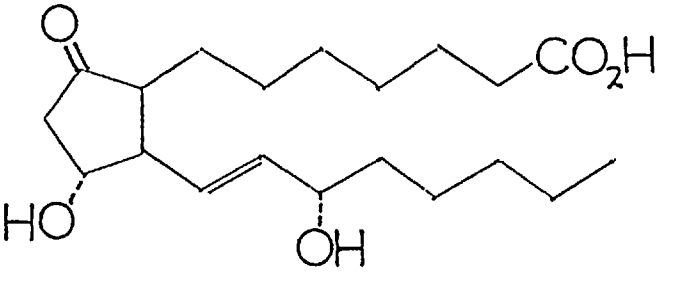


(1)

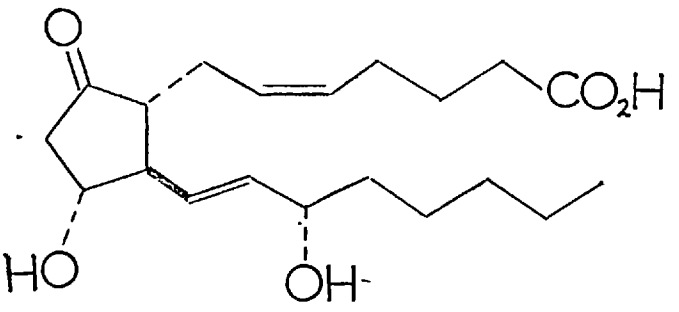
Prostanoic acid is not itself a prostaglandin, as it does not occur in mammalian tissues, nor has it any pharmacological activity.

The prostaglandins are classified in four groups, written as PGA, PGB, PGE and PGF, with an additional suffix to indicate the individual member of a series under consideration.[2]

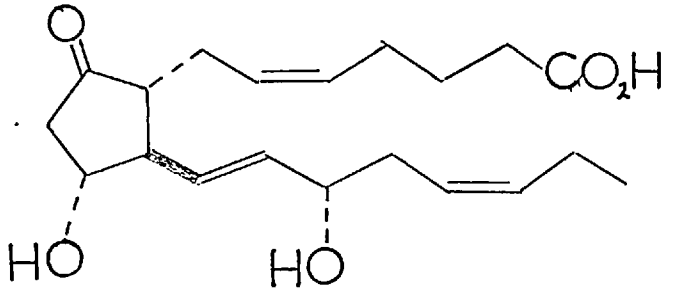
The sixteen known prostaglandins are :-



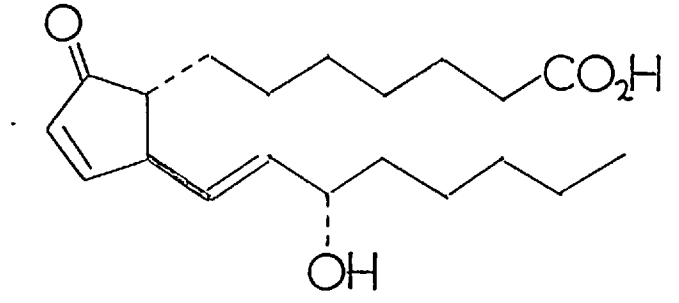
PGE_1



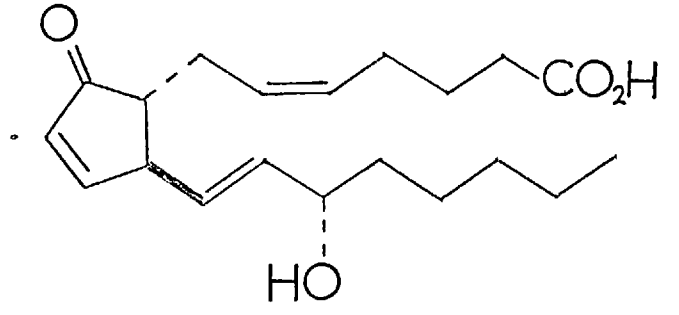
PGE_2



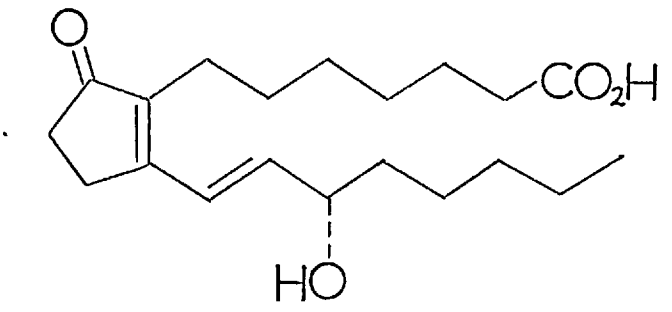
PGE_3



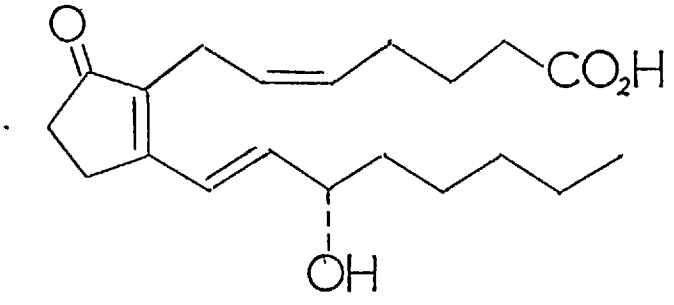
PGA_1



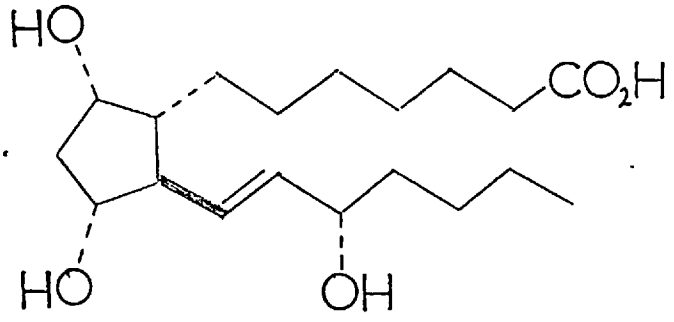
PGA_2



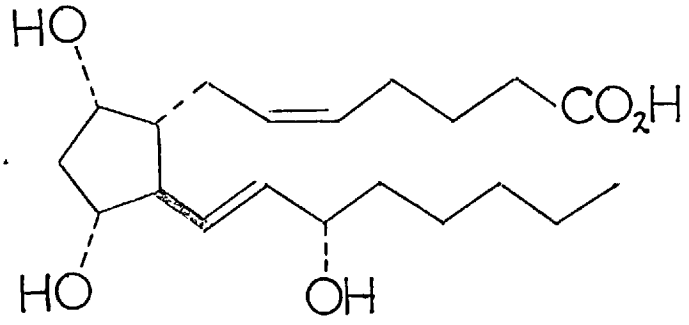
PGB_1



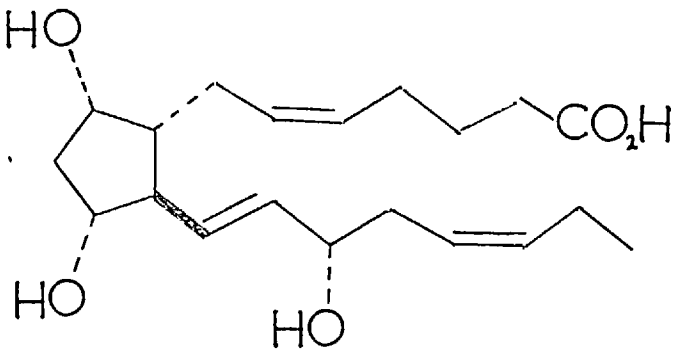
PGB_2



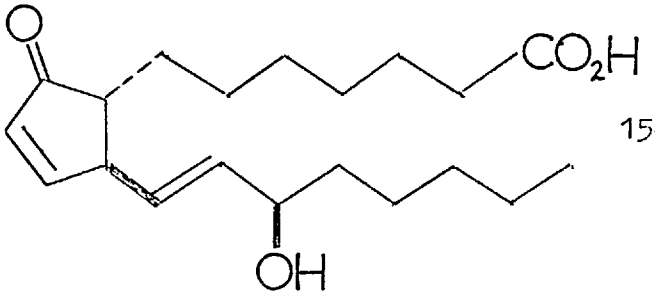
$PGF_{1\alpha}$



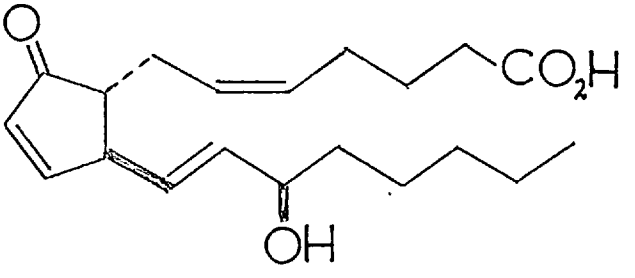
$PGF_{2\alpha}$



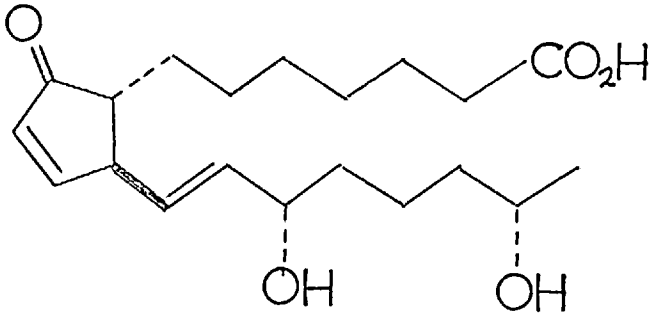
$PGF_{3\alpha}$



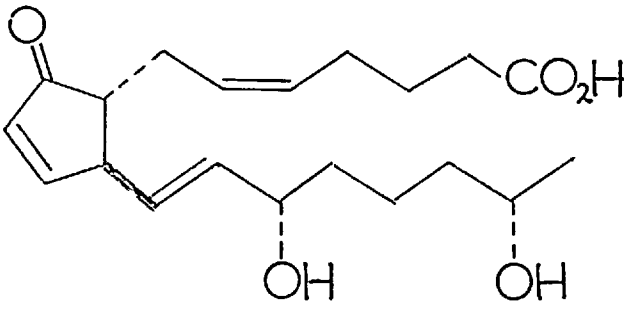
15-β - PGA_1



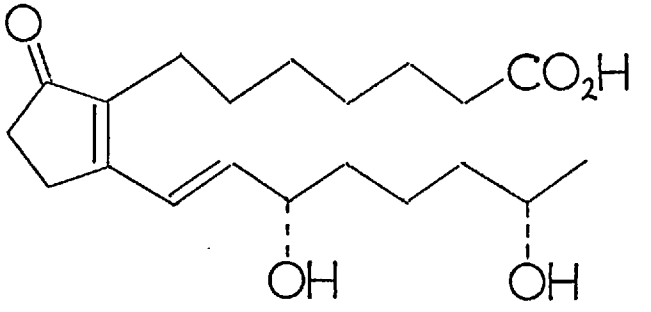
15-β - PGA_2



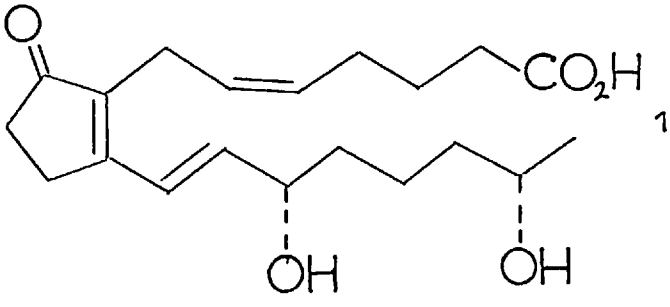
19 - hydroxy- PGA_1



19 - hydroxy - PGA_2



19 - hydroxy - PGB_1



19 - hydroxy - PGB_2

The nomenclature of the prostaglandins is thus based on:-

1) The substituents on the cyclopentane ring (which decides the series)
2) The number of carbon - carbon double bonds in the side chains (which determines the numerical suffix).

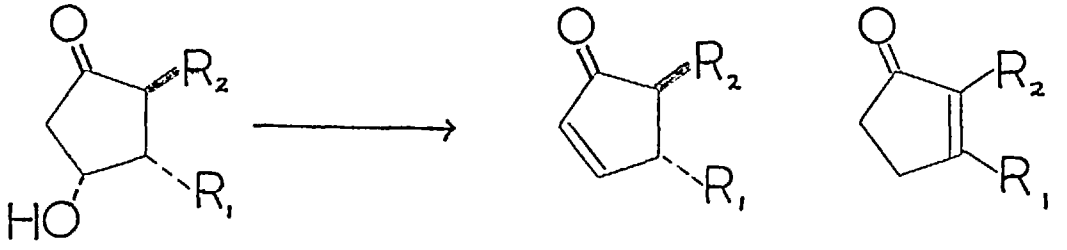
In the PGF series the suffix α indicates the orientation of the 9 - hydroxy group.

As will be shown later many of the prostaglandins are interconvertible.

Synthetic approaches.

The first problem in the synthesis of any of the prostaglandins is the presence of chiral centres; in the case of $PGF_{1\alpha}$ there are five, which neglecting any cis - trans isomerism of the C_{13} - C_{14} double bond, would lead to thirty two isomers in a non-stereo-specific synthesis.

In the PGE series the β - ketol system in the ring is easily dehydrated and in many syntheses the reagents employed often cause dehydration, producing substantial amounts of prostaglandins in the PGA series.



(2) (3a) (3b)

The allylic alcohol system at C_{13}, C_{14}, C_{15} is another sensitive group in the prostaglandin molecule. Isomerisation of the group easily occurs and the double bond often moves into conjugation with the ring double bond (in the PGB series).

The synthetic approaches can be divided into three general groups :-

1) Bicyclic ring systems as precursors.

2) Preparation of the required skeleton by ring closure.

3) Use of a cyclopentane compound as a precursor.

In these groups the syntheses most fully reviewed are those in which a high degree of stereochemical control has been achieved. Those syntheses dealing with the prostaglandins of lesser stereochemical complexity (PGA, PGB) and which neglect stereochemistry will only be reviewed superficially.

In 1) the general idea is to prepare an isomerically pure

bicyclic compound, suitably substituted, one ring of which can be opened in a controlled fashion to produce the prostaglandin.

In 2) the most successful syntheses are those in which the sites of cyclisation are rigidly controlled, and the cyclopentane ring once formed is subject to the same considerations as 3).

In 3) a general feature of the syntheses is that at some stage, an equilibration step yields the desired, thermodynamically more stable all-trans isomers.

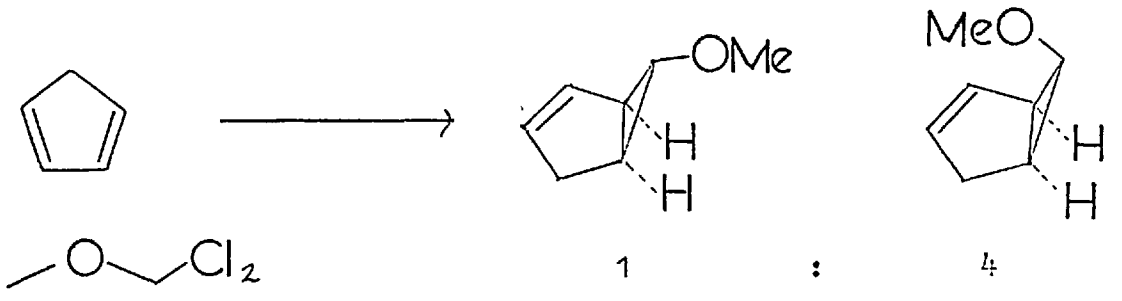
1) Bicyclic Precursors.

An elegant synthesis of PGE_1, $PGF_{2\alpha}$ using 6 - methoxy - bicyclo - (3, 1, 0) - hex - 2 - ene (4) was described by Corey and his co-workers.[3] The reaction of cyclopentadiene and dichloromethyl methyl ether yields the bicyclohexene (4) as a mixture of exo and endo isomers. Treatment of the isomer mixture with dichloroacetyl chloride in triethylamine leads to a position-specific and stereospecific addition of dichloroketene to give the tricyclic ketone (5).

Dechlorination of (5) with zinc-acetic acid yields the tricyclic ketone (6). GLC analysis shows a ratio endo : exo methoxy isomers of 97:3, indicating that the addition of dichloro ketene was preferentially to the endo isomer (4). Baeyer-Villager oxidation of (6) using hydrogen peroxide - acetic acid followed by demethylation of the ether with boron

tribromide gives the hydroxy lactone (7). A controlled oxidation of (7) with chromic acid gives three products, one of which is the hydroxy aldehyde (8); treatment of the crude reaction mixture with the sodio derivative of 2 - oxo - heptyl phosphonate yields after chromatography the specifically trans-enone lactone (9).

This enone lactone is converted into PGE_1 as described later.[4] Although stereochemical control is very good the conversion (7) to (8) is very difficult with the result that the enone lactone (9) is produced in only 12% yield from (7).



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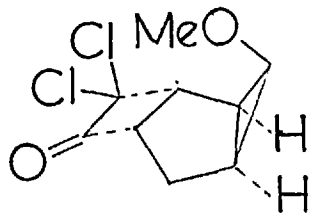

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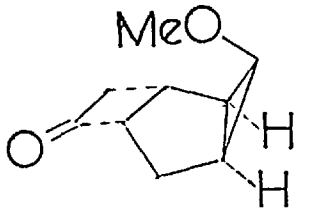

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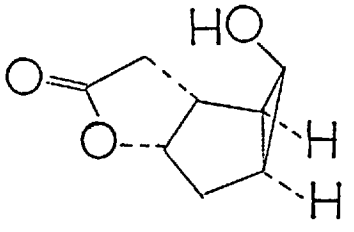

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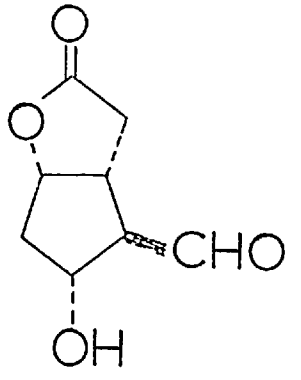

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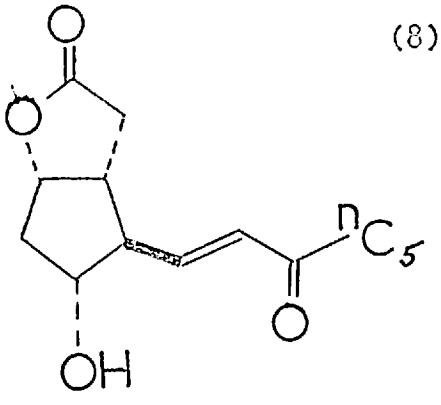


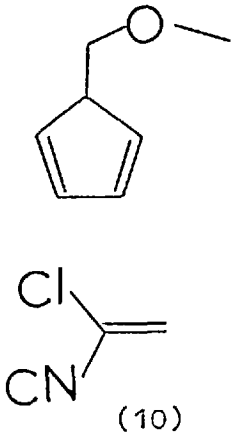
(9)

An alternative synthesis of the enone-lactone (9) as the acetate was also described by Corey[4] using a norbornene precursor.

Diels-Alder addition of 2 - chloro acrylonitrile to the cyclopentadiene ether (10) yields the norbornene (11) as a mixture of isomers. Alkaline hydrolysis of the geminal chloro-nitrile group yields the ketone (12) in which the C_7 ether group is syn to the double bond. Baeyer-Villager oxidation of (12) gives the lactone (13) which is saponified to the hydroxy acid salt (14), then treated with iodine in a buffered base to give the iodolactone (15). The iodolactone (15) is acetylated, deiodinated with tri - n - butyl tin hydride, demethylated with boron tribromide, and the primary alcohol formed oxidised to yield the cyclopentane carboxaldehyde (16). During the whole reaction sequence (12) to (16) the relative stereochemistry has been controlled.

Phosphonate condensation of (16) with the sodio derivative of dimethyl 2 - oxo - heptyl phosphonate gives the acetate (17) of the trans-enone lactone (9) described above. Borohydride reduction of the allylic ketone (17) yields an epimeric mixture of the allylic alcohols, which are separated and the undesired β - epimer recycled by oxidation and reduction, to yield (18). Hydrolysis of the acetate and treatment of the resultant diol with dihydropyran yields the diether (19), which is reduced to

the lactol (20) with di-isobutyl aluminium hydride. A Wittig reaction on (20) yields the bis-tetrahydro pyranyl ether of dl-$PGF_{2\alpha}$ (21). Controlled hydrolysis of (21) affords dl-$PGF_{2\alpha}$ in 90% yield from the bis ether. A two-phase chromic acid oxidation of (21) followed by careful hydrolysis yields dl-PGE_2.



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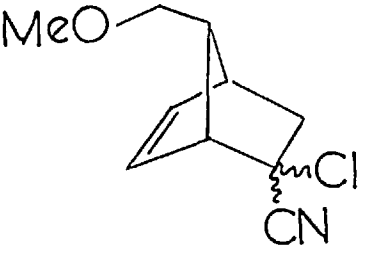

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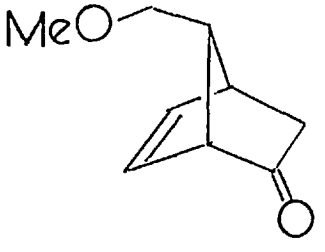

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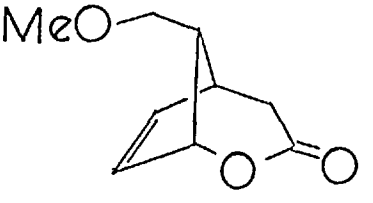

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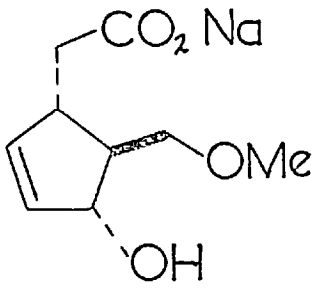

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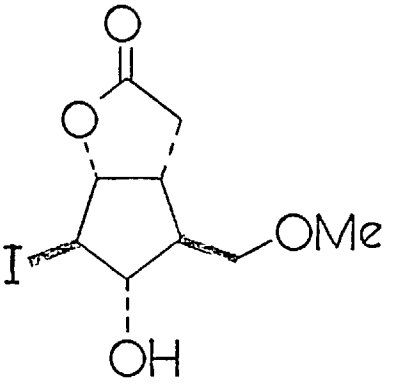

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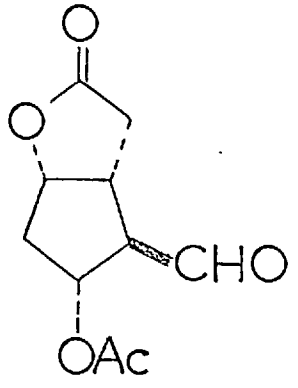

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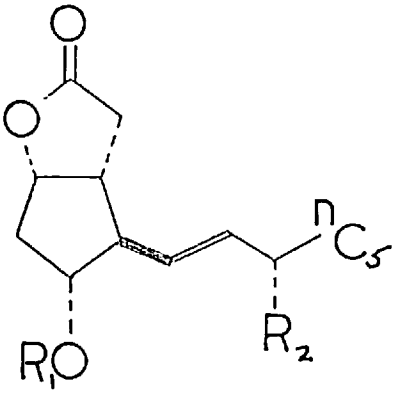
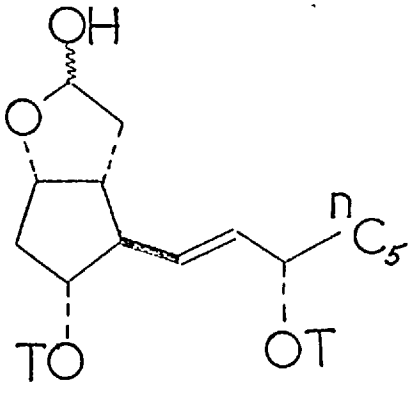


(17) R_1=Ac , R_2 = O

(18) R_1 = Ac, R_2 = OH

(19) R_1= H, R_2= OT



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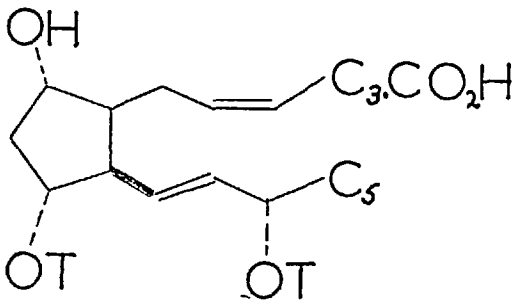


(21)

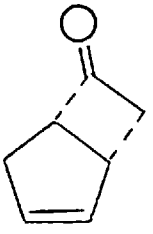
Corey[5] and his co-workers have reported a successful resolution of the hydroxy acid from (14) as the (+)- ephedrine salts, and have used the above reaction sequence to produce $PGF_{2\alpha}$ and PGE_2 in pure d- and l- forms.

Corey and Noyori[6] have described a synthesis of dl- $PGF_{2\alpha}$ from 2 - oxa - bicyclo - (3,2,0) - oct - 6 - ene - 3 - one (22) using well established procedures in the above references [3,4].

Baeyer-Villager oxidation of (22) followed by saponification and treatment of the hydroxy acid with iodine in buffered base yields the iodolactone (23). Saponification of (23) with sodium hydroxide followed by acidification yields the epoxide (24) in which the relative stereochemistry of the epoxide and lactone is cis - syn - cis from the stereocontrolled reactions. Controlled reduction and alkylation of (24) yields the oxido-acetal (25) which is reacted with 1,3 - bis - (methylthio) - allyl lithium to yield a mixture of products containing (26).

Careful hydrolysis of this mixture, followed by chromatographic separation gives the unsaturated aldehyde (27).

Reaction of (27) with n- amyl lithium yields a mixture of epimers, which are separated chromatographically to give (28). Hydrolysis of (28) followed by Wittig reaction of the lactol as in (20) (21) yields dl - $PGF_{2\alpha}$.



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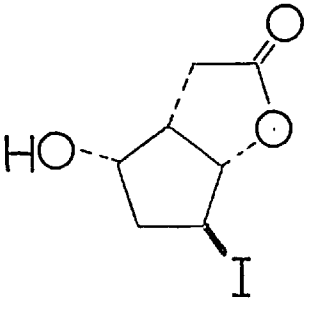

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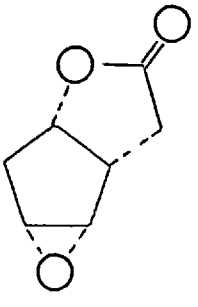

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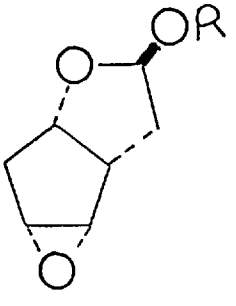

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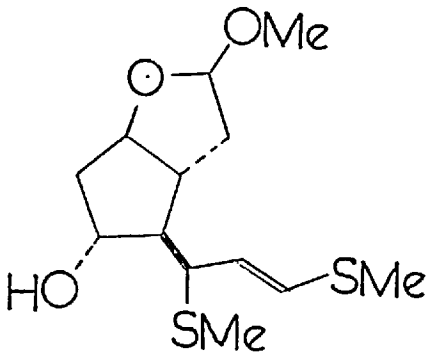

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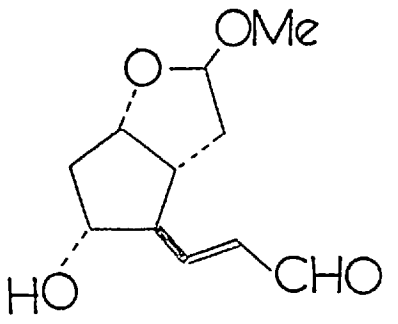

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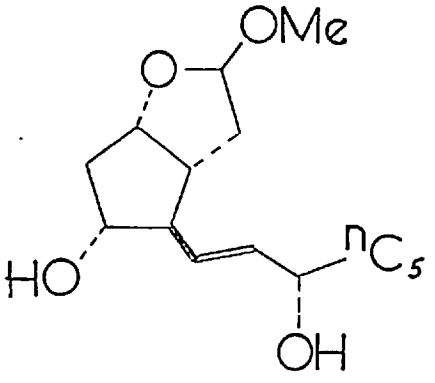
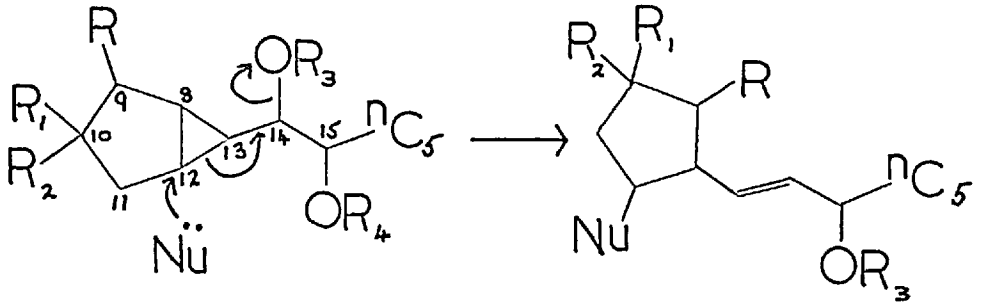


(28)

(3,1,0) - bicyclohexane precursors.

The stereoselectivity of the solvolytic ring opening of cyclopropyl carbinols was rationalised on the basis of the transition states having a geometry resembling that required for a concerted process as suggested by Newmann projection models[7].

Application of the solvolysis to the bicyclic system (29) would produce 'prostaglandin - like' compounds.



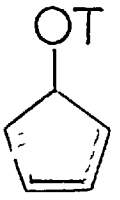
(29) (30)

This approach has some useful features :-

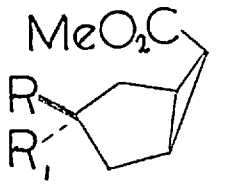
1) Its general applicability ; by varying R, R_1, R_2, R_3.
2) Its control of stereochemistry; the trans relationship of the groups on C_8, C_{12} ; and the preparation of cis and trans C_{13} C_{14} double bonds from the possible threo erythro isomerism at C_{14} C_{15} in (29).

The published literature is concerned with the preparation of pure isomers of compounds similar to (29) and the results of solvolytic rearrangement studied with several different groups R_3.

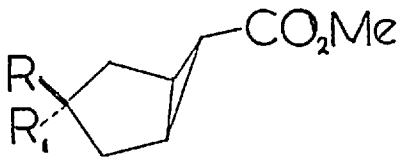
Just and Simonovitch [8,10] first described the preparation of the bicyclic precursors via a carbene addition to the tetrahydropyranyl ether of 3- cyclopentene -1-ol (31).



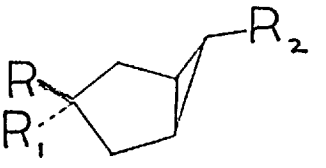
(31)



32a) R=OT, R_1= H
b) R=H , R_1= OT



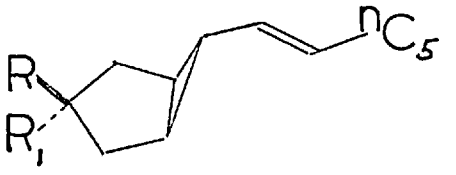
33a) R= OT, R_1=H
b) R=H , R_1= OT



34 a) R= OT, R_1=H, R_2=CH_2OH
b) R=H, R_1 = OT, R_2=CH_2OH
35 a) R=OT, R_1=H, R_2 = CHO
b) R=H, R_1= OT, R_2 = CHO

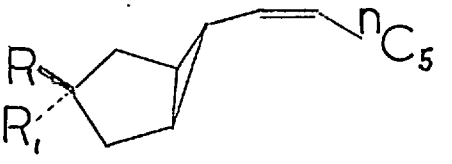
The carbene addition yields the four syn-anti exo - endo isomers (32 a,b; 33 a,b) which can be equilibrated to the pure exo isomers (33 a,b).

Lithium aluminium hydride reduction gave the alcohols (34) which can be carefully oxidised to the aldehydes (35). Wittig reaction yields two isomers from each of the pure aldehydes due to cis - trans isomerism about the double bond.



36 b) R=OT, R_1 = H

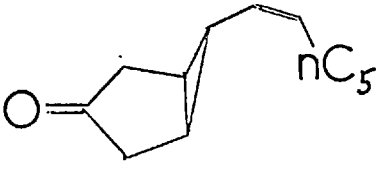
d) R=H, R_1 = OT



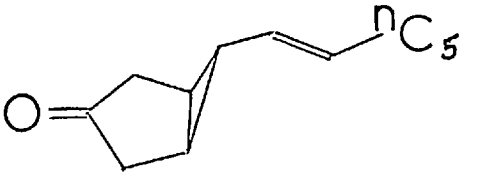
36 a) R= OT, R_1= H

c) R=H, R_1 =OT

The four isomers (36 a,b,c,d) can be separated as the alcohols which can be oxidised to the ketones (37).

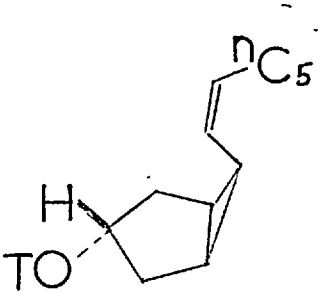


(37a)

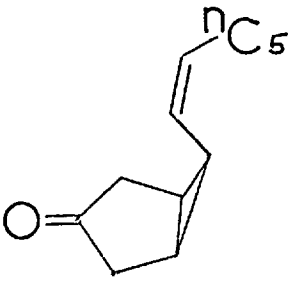


(37b)

Axen and his co-workers [11] have described the synthesis of the endo series; (38) as the pure cis, anti, endo isomer; (39) as the pure cis, endo isomer.

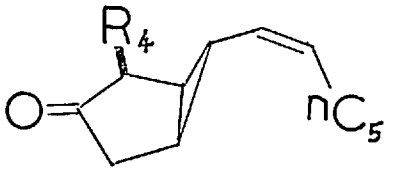


(38)

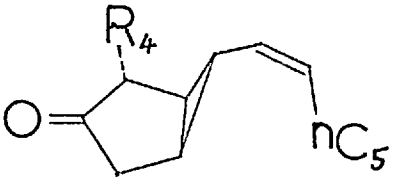


(39)

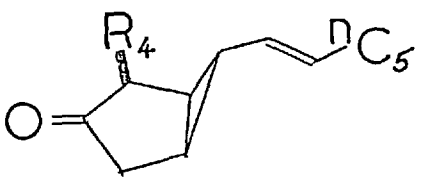
Alkylation of the cyclopentanone nucleus of (37), (39) has been extensively studied.[8-13] After early disagreement it is now accepted that alkylation is not stereospecific and in the exo series both cis (37a) and trans (37b) isomers yield 65% β and 35% α isomers (40).



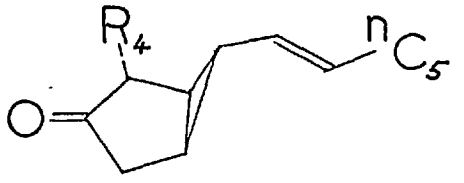
(40a)



(40b)

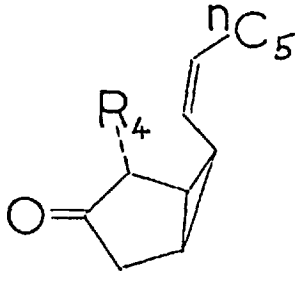


(40c)

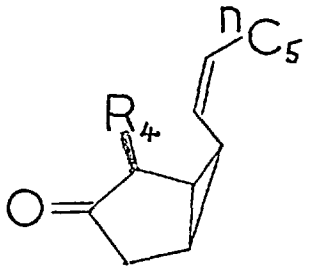


(40d)

The isomers (40 a,b,c,d) are again separable on TLC. In the endo series alkylation is again not stereospecific and gives a ratio of α : β alkylated product of 4 : 1. (40 e,f).

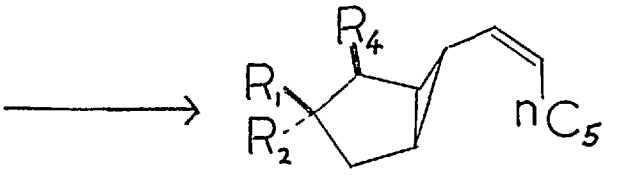


(40e)



(40f)

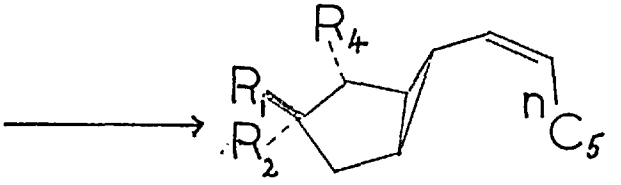
Borohydride reduction of the ketones (40) yields a mixture of isomers which are separable on TLC.[10]

(40a) 

41a) R_1 = OH, R_2 = H 42%

b) R_1 = H, R_2 = OH 58%

Similarly for 40c)

(40b) 

41c), R_1 = OH, R_2 = H 10%

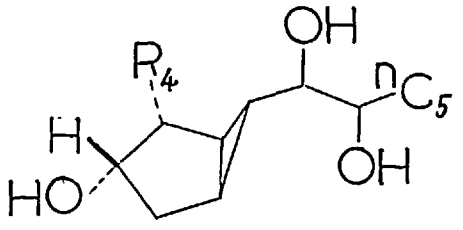
d) R_1 = H, R_2 = OH 90%

Similarly for trans 40d).

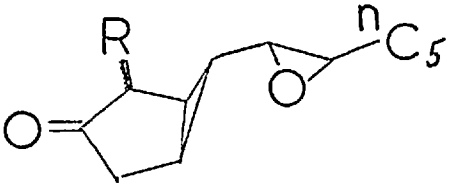
The early work on the transformation of the bicyclic compounds (40, 41) into prostaglandins via the vicinal hydroxy derivatives was a subject of some controversy.

Just[8] and his collaborators claimed that treatment of (40b, R_4 = CO_2H) with hydrogen peroxide in buffered formic acid produced small amounts of dl - PGE_1, as a mixture of C_{15} epimers, whilst (41d, R_4 = $-C_6CO_2H$) similarly produced dl - $PGF_{1\alpha}$ as the C_{15} epimers.

Holden[12] claimed that no rearrangement of (41d) occurred under these conditions but said that the major product was unrearranged vicinal diol (42). However these workers report that solvolysis of (43), of undefined stereochemistry under basic conditions yields the methyl ester of dl - PGB_1 as a mixture of epimers at C_{15}.



(42)

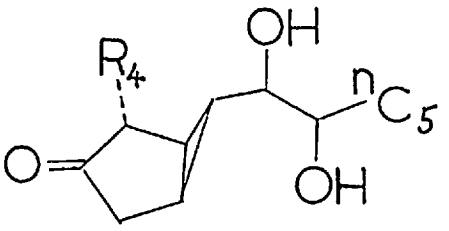


(43)

R_4 = $C_6 \cdot CO_2Me$.

Further investigations by Holden and his co-workers showed that some traces of PGE_1, $PGF_{1\alpha}$ were formed from (40b) by using unbuffered formic acid as solvent.

Schneider and his co-workers[9] found that vicinal hydroxylation of pure (40b,c) with performic acid was quite non-stereoselective whereas treatment of (40b) with osmium tetroxide gave the two erythro vicinal diol racemates (44) which were separable on TLC. Similarly (40c) gave the two threo vicinal diol racemates (45) which were also separated on TLC.



(44) R = C_6. CO_2Me erythro

(45) R = C_6 . CO_2Me threo

Solvolysis of the bis mesylates of the four isomers of (44, 45) gave small amounts of dl - PGE_1 methyl ester and its C_{15} epimer. Dl - PGE_1 could be prepared by using the 1,1,1, - trichloro ethyl ester, which could be easily removed with zinc - acetic acid.

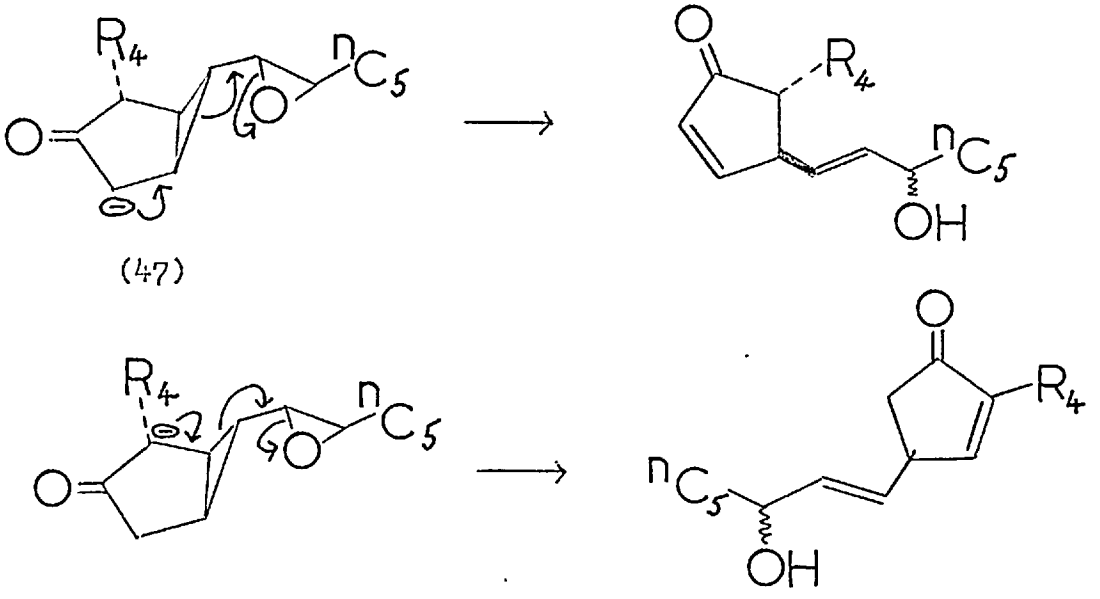
In a similar manner Schneider[9] found that the β - isomers (40a) gave 8 - iso-PGE_1 compounds, and (41d) gave $PGF_{1\alpha}$.

There is still doubt among research groups [9,13] as to whether the original Just[8] solvolysis yields prostaglandins, but in general solvolysis of the bis mesylates has been shown to be a more successful process. Schneider[13] demonstrated the carbonium ion character of the cyclopropyl carbinol system.

Solvolysis of the bis mesylates of the two erythro glycols (44) showed no evidence for a cis double bond at C_{13} - C_{14} in the isolated prostaglandins which suggests that the solvolysis

is not a concerted process. This group[13] also found that the isomers of (44) gave 8 - iso-PGE_1 compounds, and that in general the β - alkylated series gave a uniformly higher percentage of rearranged solvolysis products than the α - series.

Solvolyses [13] of the bis - mesylates of (44) under basic conditions were shown to give PGA, PGB like compounds, presumably via an intermediate epoxide (47).



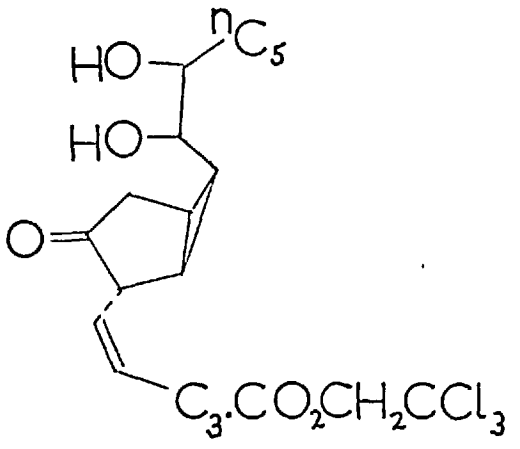
(47)

Axen[11] and his group have shown that the endo isomers (40e, f) can be converted into prostaglandins approximately three times more efficiently than the exo - series. Treatment of (40e), $R_4 = -C_6.CO_2Et$, with osmium tetroxide gave two isomeric glycols, the erythro and 15 - epi erythro isomers which were separated. Solvolysis of the bis mesylates of these isomers gave in both

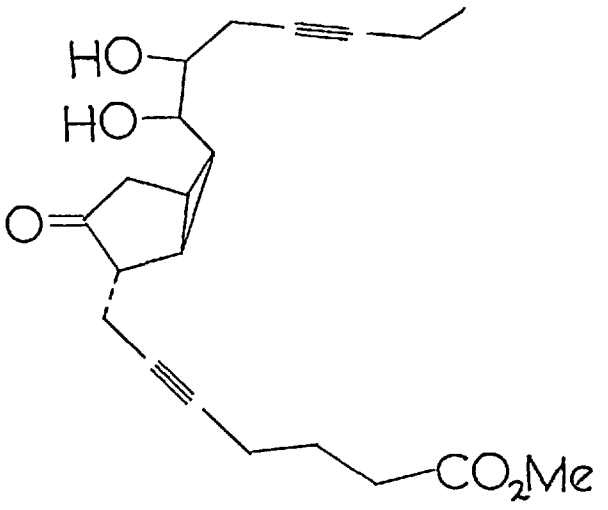
cases dl - PGE_1, ethyl ester as a mixture of C_{15} epimers. Similarly the β - isomer (40f) gave 8 - iso-PGE_1 as a C_{15} epimer mixture.

Schneider[14] has recently reported a synthesis of dl - PGE_2 via the solvolysis of the bis mesylate of (48) and describes its conversion into $PGF_{2\alpha}$.

By a similar procedure (49) has been converted into dl - PGE_3, methyl ester.



(48)



(49)

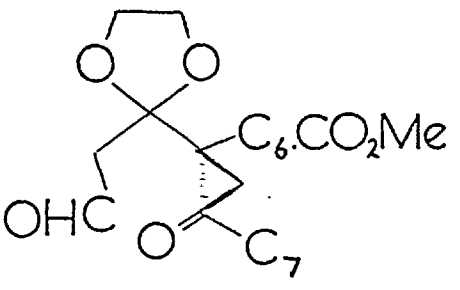
From the published results the following facts are generally agreed :-

1) The solvolysis of these bicyclics could become a useful general synthetic approach.
2) This procedure has the disadvantages at present of,
   (i) Careful chromatography necessary to produce pure isomeric precursors.
   (ii) Low yields of rearranged solvolysis products.
3) From the point of stereochemistry the method is not too successful since it fails to produce the pure double bond isomers as expected from a concerted solvolysis, although the C_8 - C_{12} <u>trans</u> relationship, the C_9,C_{10} chiral centres are preserved.

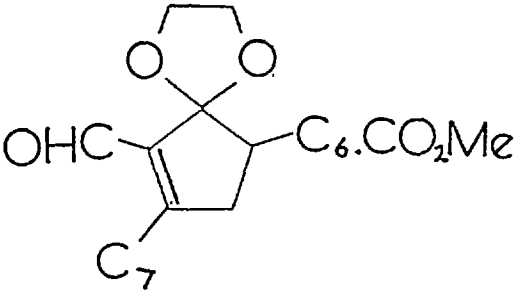
Syntheses involving ring closure.

A successful preparation of the prostanoic skeleton from a C_{20} aliphatic chain must involve some form of control over the site of cyclisation.

Morin's attempt [16] to cyclise the keto aldehyde (50) led to the formation of (51) rather than the desired (52).



(50)



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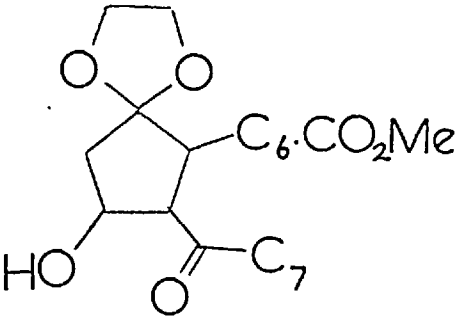

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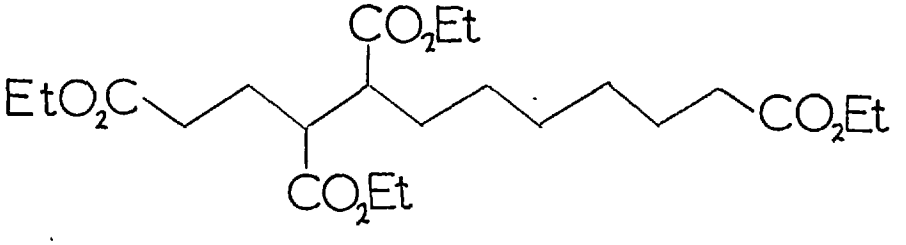
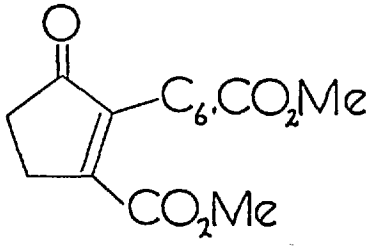


(53)

Finch and Fitt [17] cyclised the tetra ester (53) to produce (54) after five steps. Allylic bromination and acetolysis produced (55) which was converted into the trimethyl silyl ether (56). Cis hydrogenation occurred specifically on the side of the ring opposite to the bulky silyl ether to give (57) with an all cis stereochemistry .



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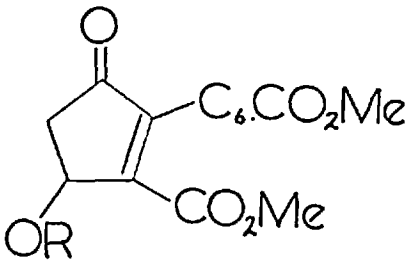
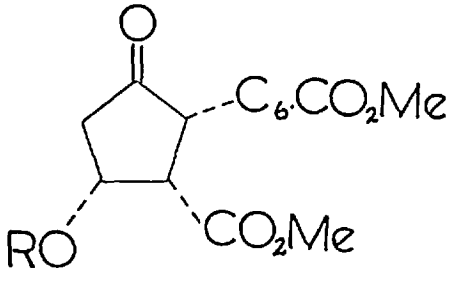
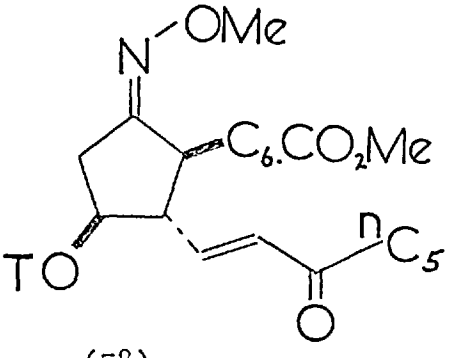


(55) R = Ac
(56) R= SiMe3

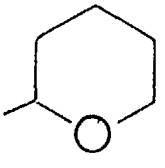


(57) R = SiMe3



(58)

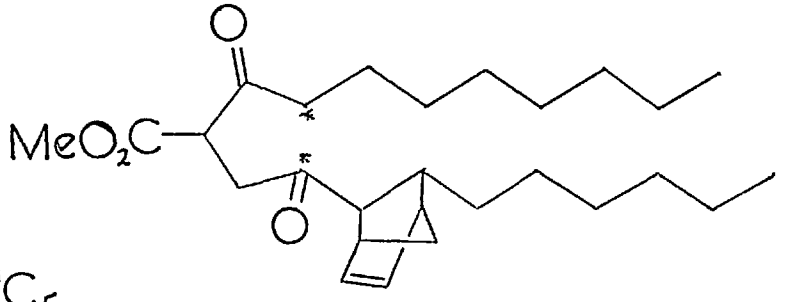
T =



Protection of the carbonyl group as the N - methoxime, followed by an equilibration to give the all - trans isomer

(2β , 5β as drawn) and a series of controlled reactions give (58), which is converted into a mixture of dl - PGE_1 and dl - PGA_1 as their C_{15} epimers, separable on TLC.

Miyano[18] described a synthesis of dl - PGE_{237}, 15 - dehydro - PGE_{237} and 15 - dehydro PGB_1 using the norbornene (59) of established exo - endo geometry. Cyclisation occurs at the positions indicated in (60) because of the hinderance imposed by the bicyclic ring. Pyrolysis of (61) gives the trans olefin (62) by a reverse Diels - Alder reaction.



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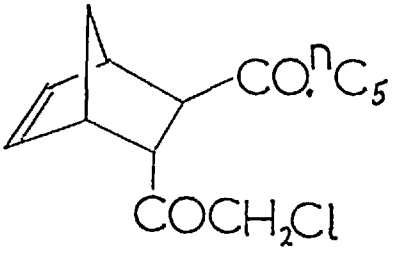
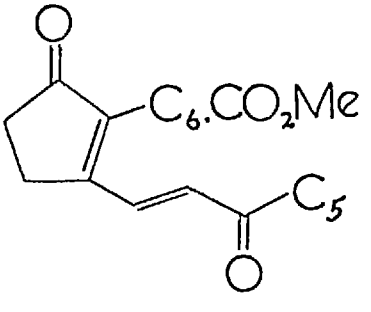
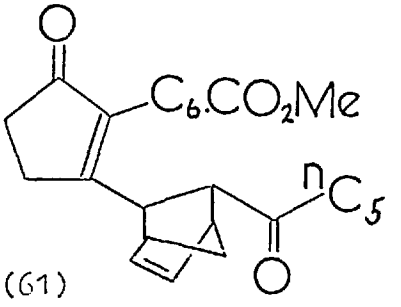


(59)

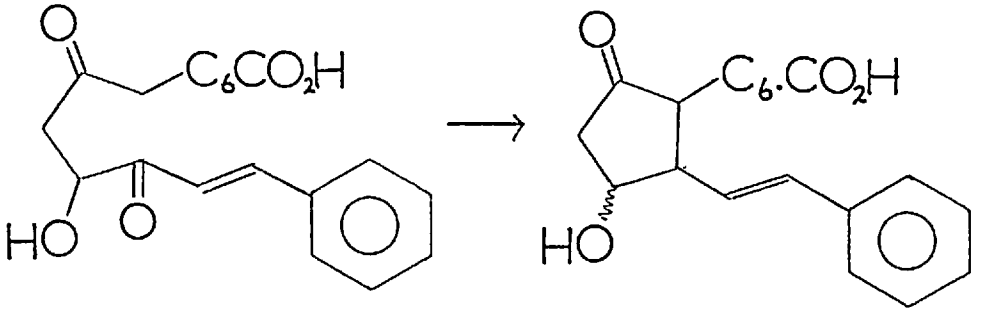


(62)

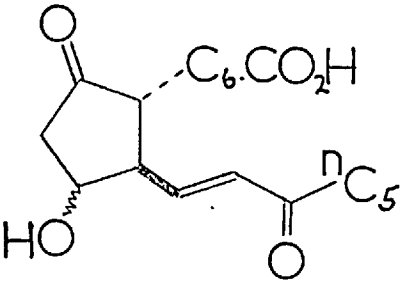


(61)

By a similar procedure Miyano and Dorn [19] prepared 15 - dehydro PGE_1 from the keto acid (63). The C_{11} epimers were separated by partition chromatography together with dehydration products. In this route the reduction of the ring double bond was assumed to give a trans relationship of the side chains.



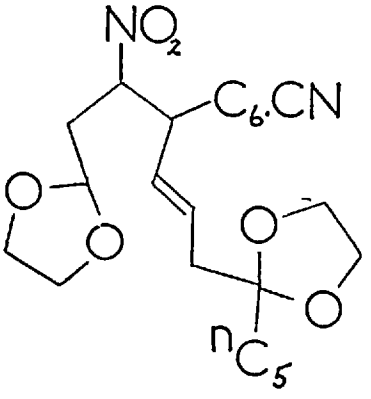
(63)



(64)

Corey [20] described the preparation of the racemic amine (67) by ring closure of the bis ketal (65). Mild base equilibration of the nitro group of (66) followed by removal of any 11β - hydroxy compound chromatographically yielded, after reduction of the nitro group, the amine (67). This amine proved to be a

useful precursor [21,22] and could be resolved as the camphor sulphonic acid salt.



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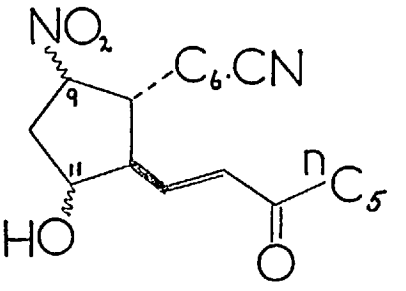
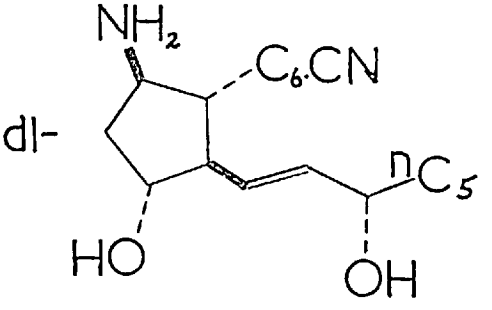
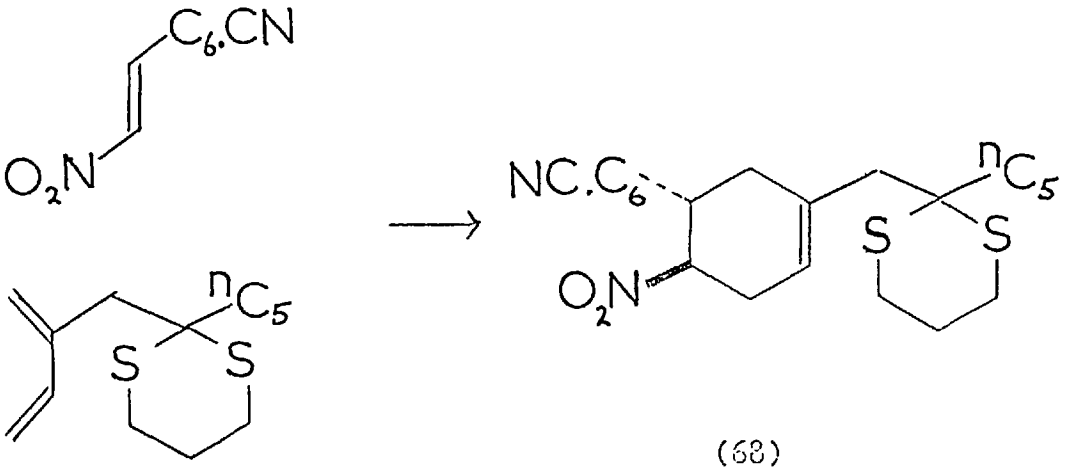


(66)



(67)

In an improved synthesis of (67) the relative trans stereochemistry of the groups on C_8 and C_9 in a similar compound (69) is ensured by the initial Diels - Alder addition to form (68), a small amount of the positional isomer is also formed.



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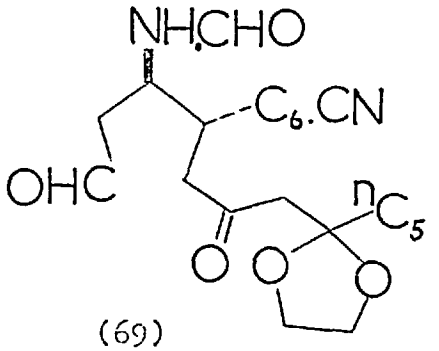
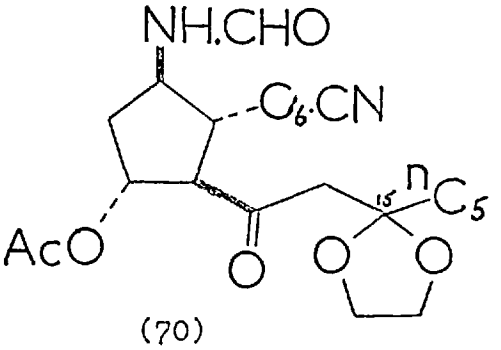


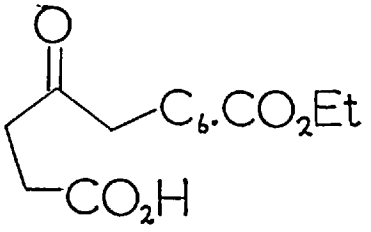
(69)



(70)

Cyclisation of (69) gives the all trans compound (70) as the major product. Conversion of (70) into dl - PGE_1 dl - $PGF_{1\alpha}$, dl - $PGF_{1\beta}$ and PGA_1 was very successful using standard reactions. In a subsequent communication Corey [22] describes the preparation of the free C_{15} ketone of (70) by a non - stereospecific route, the four stereoisomers of which can be separated by chromatography. Conversion of the amine (67) into PGE_1 uses well tried procedures.

A synthesis of dl - PGB_1 was described by Yura and Ide [23] via cyclisation of the half keto ester (71), and formation of the enol ether (72) of the 1,3 dione produced.



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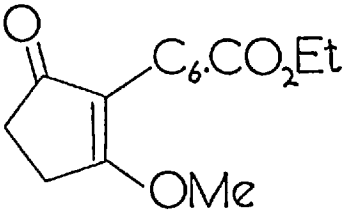
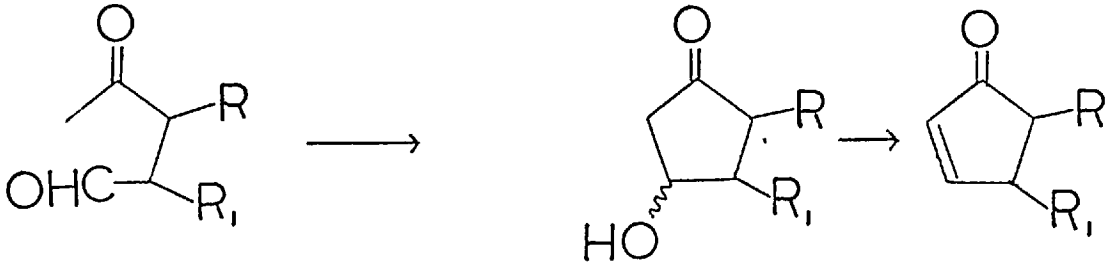


(72)

Strike and Smith [24] synthesised dl - 13,14 - dihydro PGE_1 and the dehydration products dl - PGA_1, dl - PGB_1 by initial aldolisation of the levulinic aldehyde (73). Under the reaction conditions equilibration to give the trans isomer at C_8, C_{12} was assumed to occur.

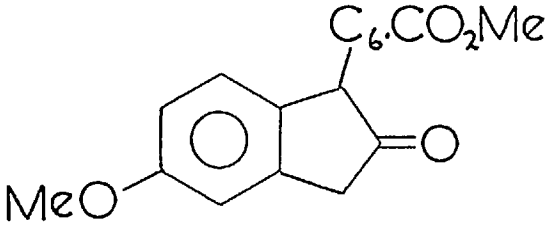


(73)

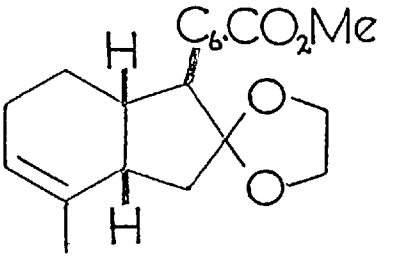
R = $C_6.CO_2Et$, R_1 = C_2 - CH(OT) - $^nC_5$

Wendler [25] and his co-workers published an elegant synthesis of dl - PGE_1 in which stereochemical control at the nuclear chiral centres was achieved by the construction of a cis - hydrindanone system (75) in which the thermodynamically stable exo side chain orientation predominates.

The cis - hydrindanone derivative (75) was prepared from the aromatic compound (74) ; with the preferred orientation of the side chain as shown.

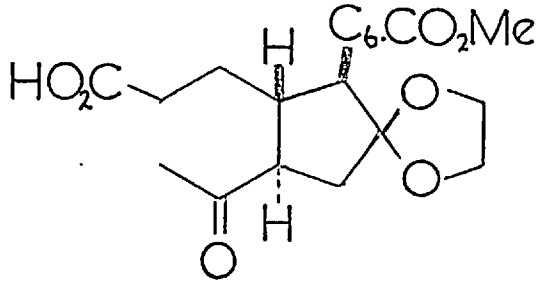


(74)

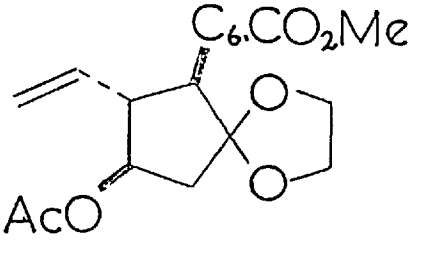


(75)

Oxidative cleavage of the double bond, followed by epimerisation of the acetyl group gave the seco acid (76) which was converted into (77).

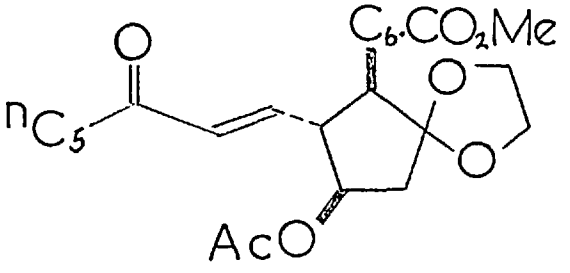


(76)



(77)

Cleavage of the double bond followed by a Wittig condensation of the resultant aldehyde gave (78) which was converted into a mixture of dl - PGE_1 and its C_{15} epimer.

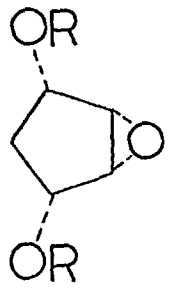


(78)

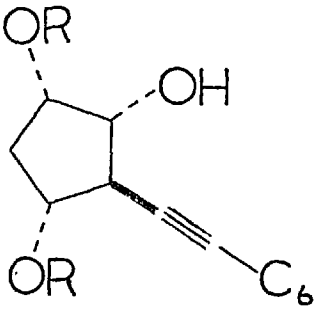
Precursors containing a cyclopentane nucleus.

Most of the syntheses which fall into this category have one common feature, which incidentally is true of the ring closure syntheses once the ring is formed. This feature is that at some stage there is an equilibration step which yields the thermodynamically favoured all trans compounds. The first two syntheses under consideration do not however involve equilibration and the stereochemical control achieved merits special attention. One synthesis due to Fried and his co-workers [26] depends on the unusual reactivity of polyhydroxylated cyclopentanes. The all - cis epoxide (79) is reacted with an organo - aluminium compound to give (80) in which the trans stereochemistry is proved. Appropriate alkylation of the oxygen followed by reduction of the triple bond, debenzylation and allylic oxidation gives dl - 7 - oxa - $PGF_{1\alpha}$ (81). Modification of the reduction step

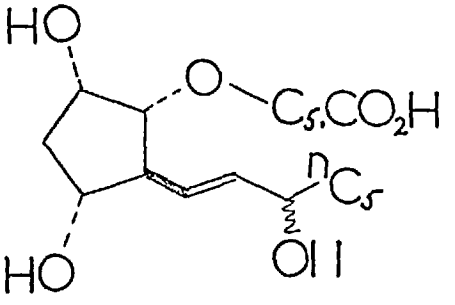
gives the cis isomer (82).



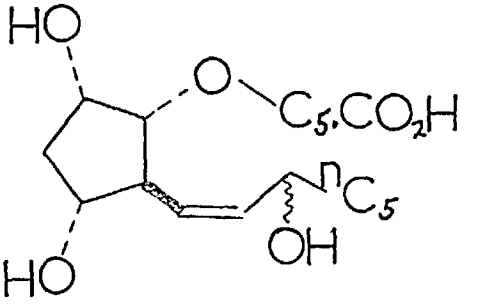
(79) R = $Ph.CH_2$-



(80)



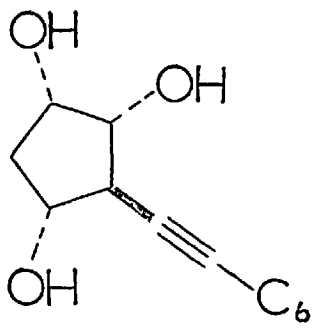
(81)



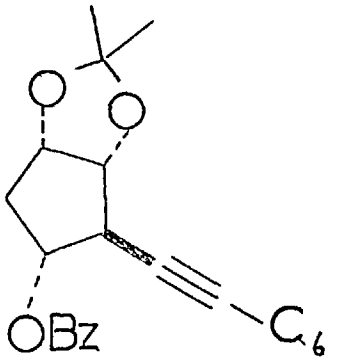
(82)

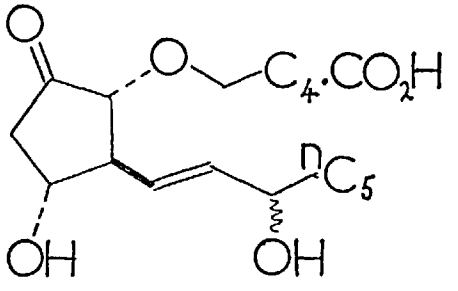
In an essentially similar manner the same group[27] prepared the triol (83) from the all cis trimethyl silyl ether (79, R = $SiMe_3$). Protection of the hydroxy groups as indicated and alkylation gave (84), which was separated from the positional isomer.

After oxidation and ketalisation of the 9 - hydroxy group, essentially similar reactions as in the previous reference yielded dl - 7 - oxa - PGE_1 (85).

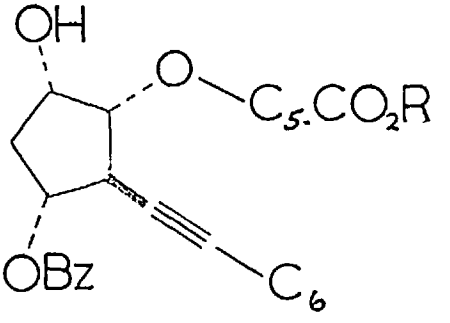


(83)



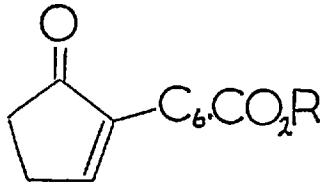


(85)

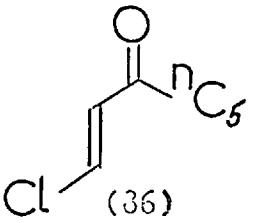


(84)

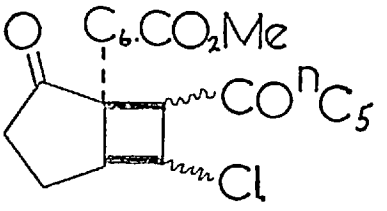
A unique synthesis of 11 - deoxy prostaglandins was described by Bagli and Bogri[28]. The photochemical addition of the vinyl chloride (86) to the ester (87) yields the cis adduct (88) in which the two carbonyl groups are in the orientation shown.



(87) R = Me

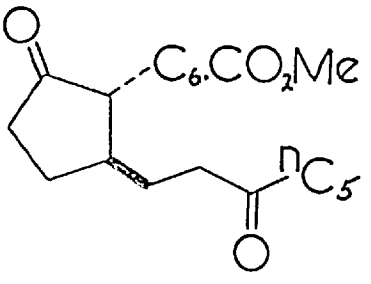


(36)

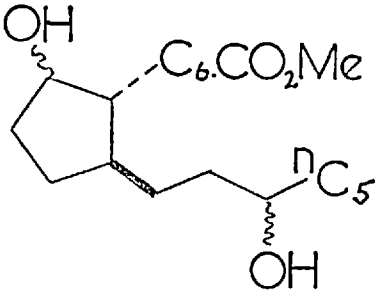


(88)

Treatment of (88) with zinc - acetic acid gave (89) as the major isomer which was reduced with sodium borohydride to give eventually the epimeric mixture dl - 11 - deoxy - $PGF_{1\alpha}$ (90).

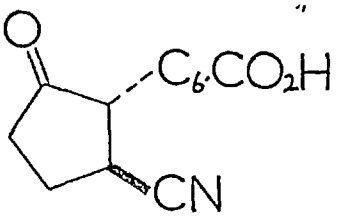


(89)

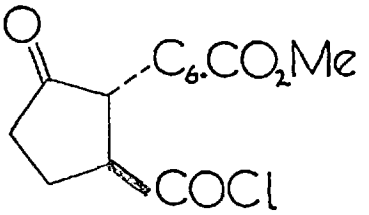


(90)

Bagli and Bogri[29,30] describe the addition of hydrogen cyanide (from its cyanohydrin) to the cyclopentenone acid (87, R = H). The addition was assumed to give the stable trans adduct (91), which after hydrolysis of the cyano group and selective esterification of the side chain acid was converted into the acid chloride (92).

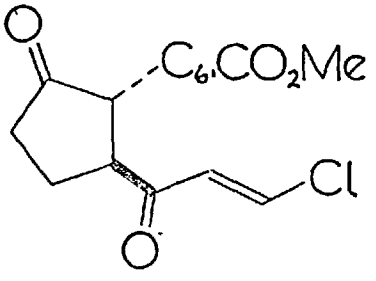


(91)

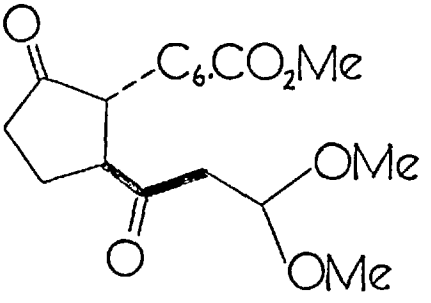


(92)

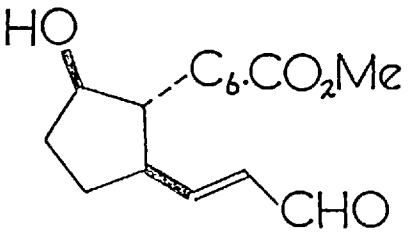
The acid chloride was converted into the acetal (94) via the vinyl chloride (93)[29]. Reduction of the 9 - keto function followed by hydrolysis of the acetal group gave the aldehyde (95) as a mixture of enantiomers in which the isomer with the relative stereochemistry shown was assumed to predominate. Conversion of (95) into dl - 11 - deoxy - 9 - epi-$PGF_{1\alpha}$ (96) was easily achieved via the addition of n - pentyl magnesium bromide and subsequent alkaline hydrolysis.



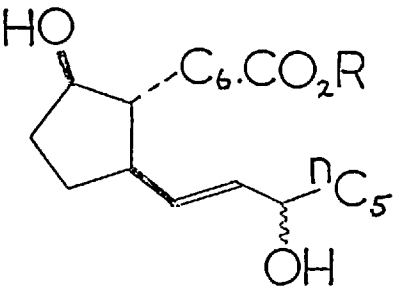
(93)



(94)

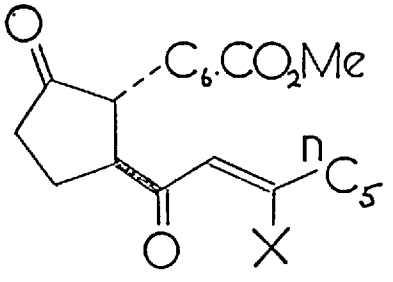


(95)

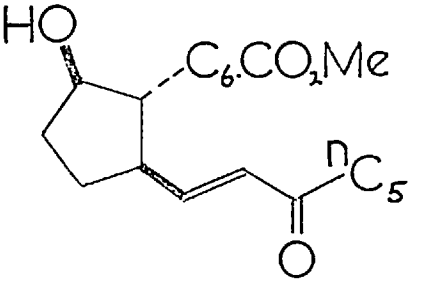


(96a) R = Me
(96b) R = H

Some proof of the stereochemistry of these reactions was offered in a later paper[30], in which an improved synthesis of (96) from (92) was described. Reaction of (92) with 1 - heptyne and aluminium chloride gave the vinyl chloride (97) which was solvolysed to (98).



(97) X = Cl
(98) X = OMe

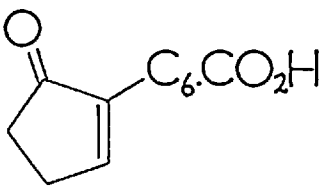


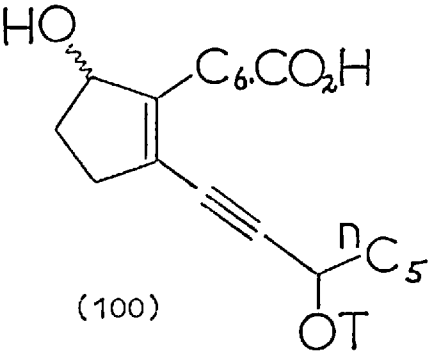
(99) a) R = Me
b) R = H

Borohydride reduction of (98) followed by treatment with acid yields (99a), the 15 - dehydro derivative of (96a), which could be isolated as the acid. Borohydride reduction of (99a) yields

as expected (96a).

Two syntheses of dl - PGB_1, dl - PGE - 237, of no special stereochemical merit were described[31,32] involving addition of Grignard reagents to the acid[31] (87, R = H) and its ester[32] (87, R = Et) as outlined below.



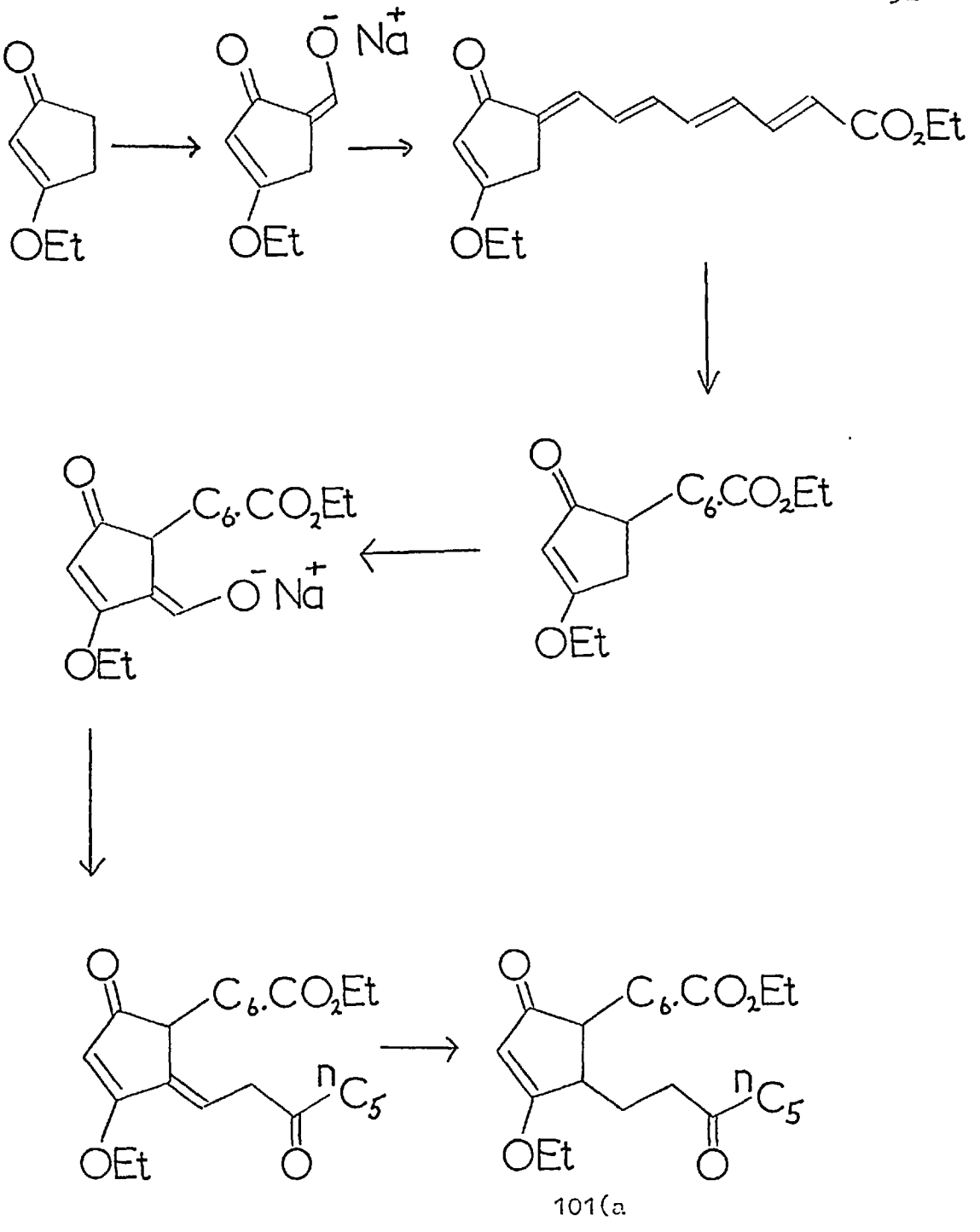


(100)

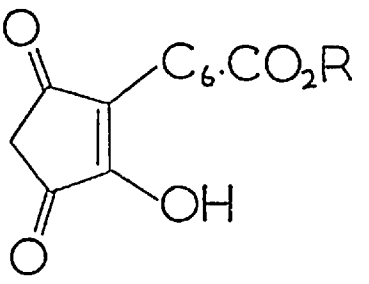
Oppenauer oxidation of (100) followed by hydrolysis of the ether gives the C_{13} - C_{14} alkyne which was selectively reduced, partially to give cis or trans isomers of dl - PGB_1 or completely to give dl - PGE - 237.

The ester was converted by a similar route to (100) and the corresponding cyclopentanone. The selective partial reduction of the alkyne group gave the cis isomer of dl - PGB_1, which can be isomerised to the trans compound.

In an early publication Beal[33] describes the preparation of the ethyl ester of dihydro PGE_1 by successive functionalising of the carbon atoms in a cyclopentane dione enol ether, using sodium hydride - formic ester.



101(a



(102)

(101a) was converted into its benzyl derivative (101b) and hence into dl - dihydro PGE_1 ethyl ester, via a reduction and a hydrogenolysis step. These workers assumed the stereochemistry of the ring junction to be trans.

Two syntheses of dl - PGB_1 from the triketone (102) have been described[34,35] but these are covered in the discussion section of this thesis.

Interconversions.

It has often been found that the conditions used for the preparation of prostaglandins in the PGE series give rise to dehydration products of the PGA series and the isomeric PGB series. Pike[36] and others have studied the conversions within the prostaglandin series which are briefly summarised below.

$PGE_1 \xrightarrow{90\ \%\ AcOH,\ 60^{\circ}C} PGA_1$

$PGE_2 \xrightarrow{90\ \%\ AcOH,\ 60^{\circ}C} PGA_2$

$PGE_1 \xrightarrow{NaOH} PGB_1$

$\underline{epi}\text{-}PGE_1 \xrightarrow{NaOH} \underline{epi}\text{-}PGB_1$

$PGE_1 \xrightarrow{MnO_2} C_{15}$ ketone (selective)

$PGF_1 \xrightarrow{MnO_2} C_{15}$ ketone (selective)

Corey[37] describes the conversion of an optically active $PGF_{2\alpha}$ derivative into $PGF_{1\alpha}$ by selective reduction of the C_5- C_6 double bond and hence into a PGE_1 derivative.

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SYNTHESIS OF 3 - (6' - CARBOXYHEXYL) - 1,2,4, - CYCLOPENTAINE TRIKETONE. (4).

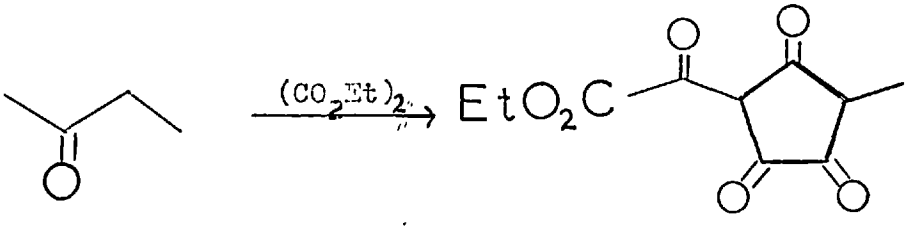
Synthesis and reactions of 3- (6' - carboxyhexyl)- 1, 2, 4, - cyclopentane triketone (4).

Discussion

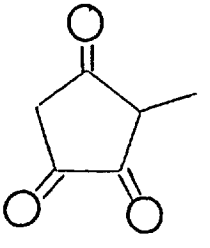
Properties of 3- methyl- 1, 2, 4, - cyclopentane triketone (3)

The synthesis of 3- methyl- 1,2,4, -cyclopentane triketone (3) was described by Orchin and Butz [1].

Condensation of 2- butanone with a twofold excess of diethyl oxalate in the presence of sodium ethoxide gave ethyl -4- methyl- 2,3,5 - triketo - cyclopentenyl glyoxalate (2). After purification, deoxalation of (2) with refluxing 50% phosphoric acid gave the triketone (3) as its monohydrate. The anhydrous triketone was prepared by vacuum sublimation of the hydrate.

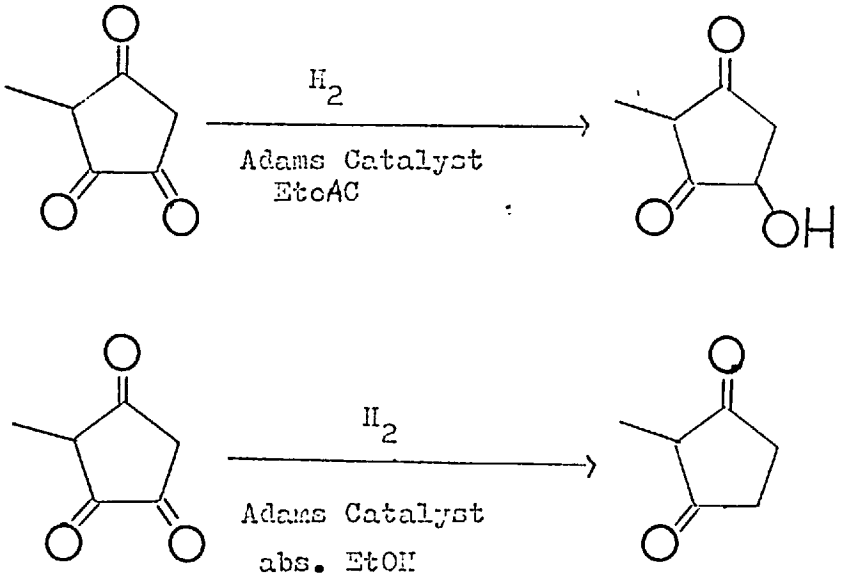


(1) (2)



(3)

The subsequent study of the chemistry of (3) showed that it was a potentially useful compound and the reactions outlined below are of particular relevance to a successful synthesis of dl- PGB_1 discussed later.



The spectra of (3) were recorded to provide useful reference data in the preparation of the title compound (4), and to deduce the structure of the methyl triketone.

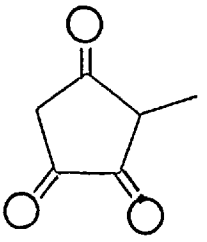
The p.m.r. spectrum of (3) showed the following peaks:-

(i) τ 8·12, 3H, small couplings ~ 1 Hz

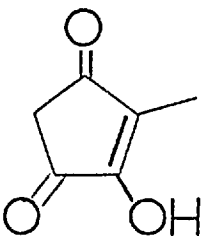
(ii) τ 7·15, 2H, small couplings ~ 1·5 Hz

(iii) τ 3·33, enolic H and hydrate, broad signal.

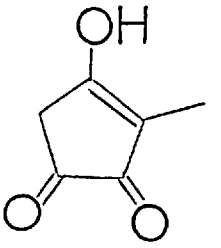
The possible structures of the triketone (3) are:-



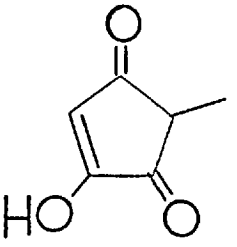
(3a)



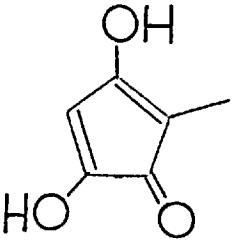
(3b)



(3c)



(3d)



(3e)

(3a), (3d) and (3e) can be eliminated because of the absence of vinylic protons or a doublet signal for the methyl group. The enolic form (3c) can be ruled out since the α- diketone would preferentially exist in the diosphenol form. This requires (3b) to be the correct structure of the triketone, and is confirmed by the recent work of Sheley and Schechter.[2]

The ultra-violet spectrum of (3b) shows the following absorptions:-

(i) λ max $\begin{matrix}\text{EtOH}\\ \text{HCl}\end{matrix}$ 274 mμ

(ii) λ max $\begin{matrix}\text{EtOH}\\ \text{NaOH}\end{matrix}$ 328 mμ

The shift of the maximum to longer wavelength is indicative of an enol - enolate anion system.

The infra-red spectrum of (3b) shows the required absorptions:-

(i) ν max. 3100 cm^{-1} enolic hydroxy group.

(ii) 1742 cm^{-1}, '5' ring C = O stretching.

(iii) 1695, 1660 cm^{-1}, enone stretching frequencies.

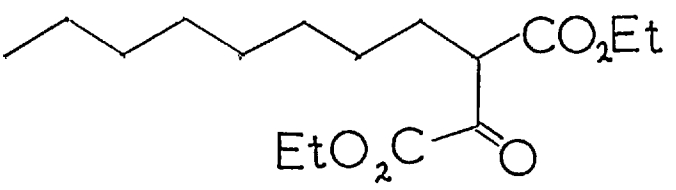
The preparation of the title compound (4) was similar to that of the methyl analogue (3), with certain modifications concerned with the preservation of other sensitive groups present.

The use of ethyl - 9 - keto decanoate (9) as a precursor introduces the possibility of condensation of diethyl oxalate α- to the carboxy ethyl group to give the oxalo ester (5). In order to monitor any formation of (5), the ultra-violet spectrum of a model system, ethyl oxalopropionate (6) was taken.

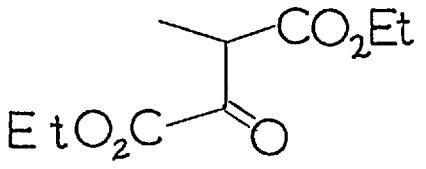
The ultra-violet spectrum of (6) showed the following maxima:-

(i) λ max $\begin{matrix}\text{EtOH}\\ \text{HCl}\end{matrix}$ 261 mμ

(ii) λ max $\begin{matrix}\text{EtOH}\\ \text{NaOH}\end{matrix}$ 281 mμ



(5)



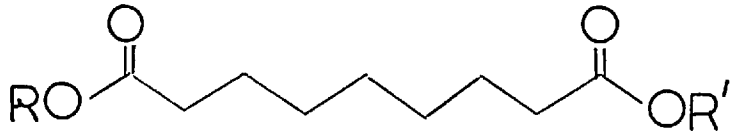
(6)

Preparation of 3- (6' - carboxyhexyl) - 1,2,4 - cyclopentane triketone (4).

Polyazelaic anhydride was refluxed in excess absolute ethanol to give a mixture of azelaic acid, mono-ethyl azelate and diethyl azelate (7). The reaction was followed by infra-red spectroscopy, monitoring the loss of the band at 1815 cm^{-1} (anhydride) and the appearance of the 1735 cm^{-1} (ester) and 1715 cm^{-1} (acid) bands. Base extraction of the acids followed by fractional distillation gave the mono ester in approximately 20% yield based on anhydride. TLC showed the mono ester (7b) to be free of diester (7c) and diacid (7a).

Treatment of the mono ester (7b) with excess thionyl chloride

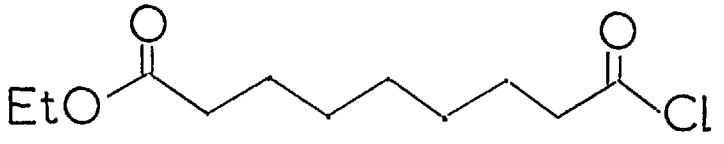
gave the acid chloride (8) in over 90% yield.



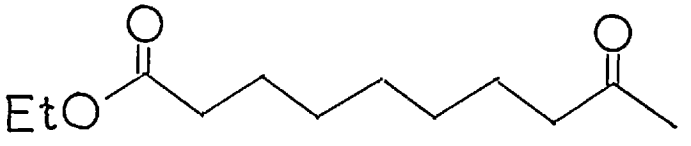
7(a) $R=R_1=H$

(b) $R=Et$, $R_1=H$

(c) $R=R=Et$

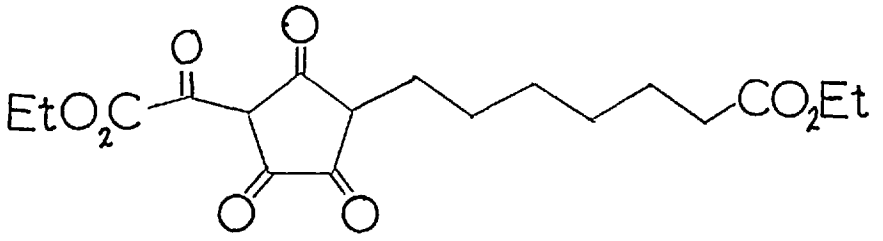


(8)

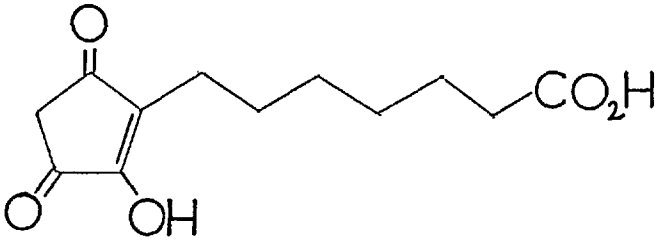


(9)

Ethyl -9- keto decanoate (9) was prepared from (8) using dimethyl cadmium following the method of Mc Kennis and du Vigneaud.[3] The keto ester was easily purified by removal of acidic impurities and distillation. The product was obtained in approximately 60% yield, gave a 2:4 dinitro phenyl hydrazone derivative MPt 72°C, and showed a 3 H singlet at τ 8·02.



(10)



(4)

The keto ester (9), 1 mole, was condensed with diethyl oxalate, 2 moles, in the presence of sodium ethoxide, 2 moles, in ethanol to produce 4 - (6^{1}- ethyl - carboxyhexyl) - 2,3,5 - triketo - cyclopentenyl glyoxalate (10). The reaction was carried out in an atmosphere of hydrogen, generated from the formation of sodium ethoxide <u>in situ</u> from sodium and absolute ethanol. The reaction was complete in 2 hours and on work up the glyoxalate was purified by bicarbonate extraction from the neutral starting materials.

The glyoxalate (10) had the following spectral data:-

Ultra-violet spectrum:-

(i). λ max $\begin{matrix}\text{EtOH}\\ \text{HCl}\end{matrix}$ 258 mμ , 280 mμ

(ii) λ max $\overset{EtOH}{NaHCO_3}$ 279 mμ , 310 mμ

These data indicate an enolic structure for the compound, and shows that no oxalo ester (5) has been formed.

The infra-red spectrum of (10) shows two major peaks:-

(i) ν max 1735 cm^{-1}, ester.

(ii) 1660 cm^{-1}, enolic C = C

The p.m.r. spectrum shows the following peaks:-

(i) τ 5·75, 4H multiplet, possibly two superimposed methylene quartets due to ethyl ester and ethyl oxalo-ester.

The glyoxalate was treated with reluxing hydrochloric acid to yield the title compound, 3 - (6^1- carboxyhexyl)- 1,2,4 - cyclopentane triketone (4). TLC indicated that the triketone was pure, but repeated recrystallisations from methylene chloride - acetonitrile failed to give correct analytical figures. Vacuum sublimation did provide a sample with the correct analysis. The first erroneous values could be attributed to partial hydration of the triketone (4).

The compound had the following physical data:-

MPt 107-8°C

Ultra-violet spectrum:-

is almost identical to the methyl analogue (3b)

(i) λ max $\overset{EtOH}{HCl}$ 278 mμ

(ii) λ max $\overset{EtOH}{NaHCO_3}$ 327 mμ

The p.m.r. spectrum of (4) shows the two proton singlet at ca. τ 7·1 as in the methyl analogue and indicates the same enolic structure:-

(i) τ 7·08, 2H singlet, methylene group of β - diketone

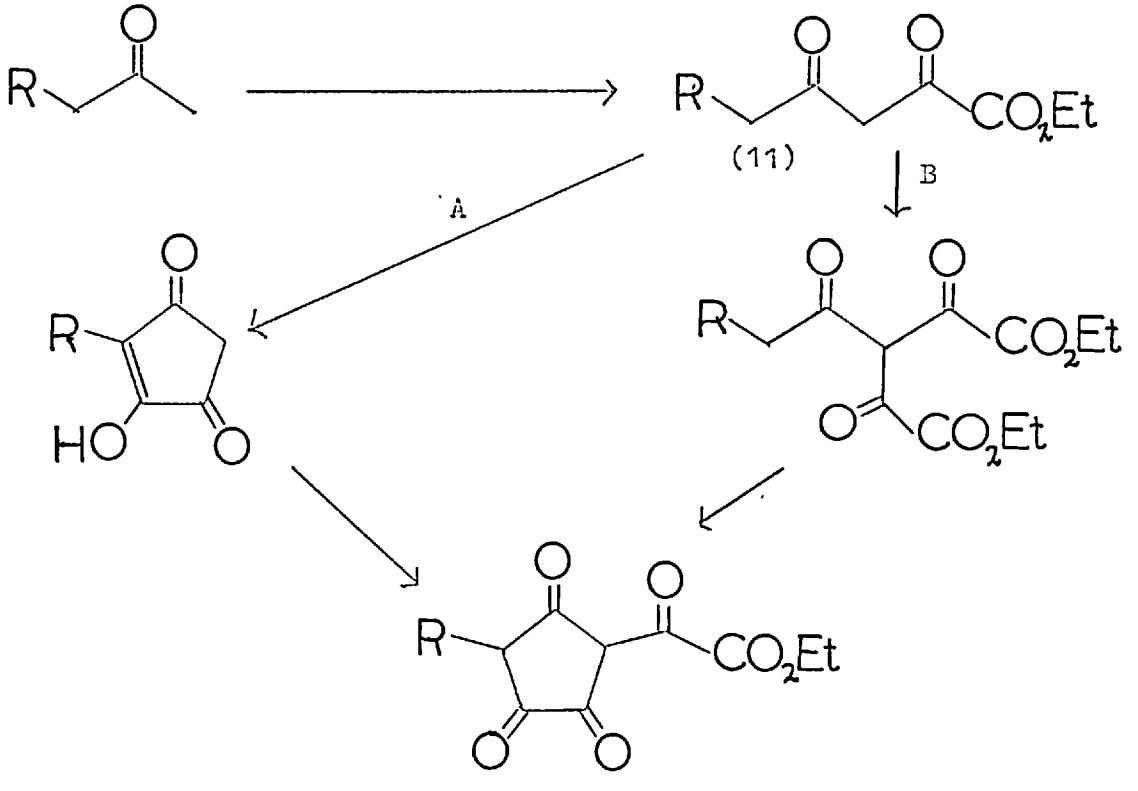
(ii) τ 7·32 - 8·8, 12 H envelope, side chain protons.

(iii) τ - 0·1, 2 H broad, acid and enol protons.

Infra-red spectrum:-

ν max 1738 cm^{-1}, 1705 cm^{-1}, 1694 cm^{-1}, 1650 cm^{-1}.

The desired triketone (4) having been produced, attempts were made to improve the synthesis. The first attempted improvement was to try and form the triketone without formation of the intermediate glyoxalate. The two possible synthetic pathways are shown, assuming initial formation of the β - diketone (11).



Pathway A; the triketone intermediate condenses with excess diethyl oxalate to form the glyoxalate.

Pathway B; a second molecule of diethyl oxalate condenses prior to ring closure.

If the reaction proceeds via path A then a 1:1 mixture of methyl ketone and diethyl oxalate could lead to the selective preparation of the desired triketone.

The condensation reaction was tried with an equimolar mixture of reactants; however p.m.r. and ultra-violet spectra of the products showed that in all cases a mixture of glyoxalate (10) and enolic compounds similar to (11) were formed. The products were not investigated further. A condensation experiment with 2 moles of keto ester (9) to 1 mole diethyl oxalate yielded a bicarbonate soluble product, as white crystals MPt. 83°C, with the following p.m.r. spectrum:-

(i) τ - 0·22, 1 H, broad.

(ii) τ 3·6 , 1 H singlet, vinyl proton of enol.

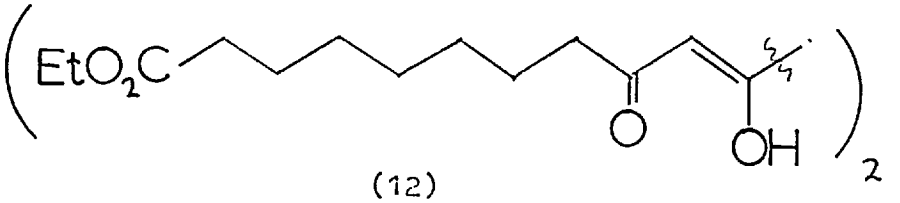
(iii) τ 5·9 , 2 H quartet J = 7 Hz, ethyl ester.

(iv) τ 6·2 - 6·9, 4 H envelope, methylene groups.

(v) τ 8·0 - 9·0, 13 H envelope and triplet J = 7 Hz, methyl group of ethyl ester.

Since this compound did not have the cyclopentane triketone structure it was not investigated further, on the basis of the pmr. data a possible structure is (12), formed from the condensation of two molecules of keto ester (9) with 1 molecule of diethyl

oxalate. This compound was shown to be pure on TLC (alumina - benzene/ether/formic acid) and gave a red colour with ethanolic ferric chloride.



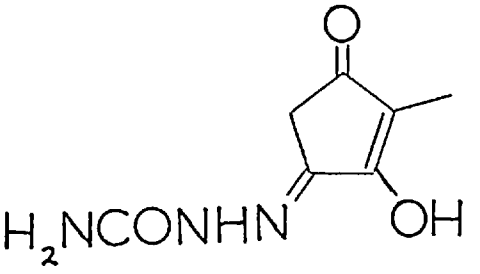
(12)

Our initial condensation experiments used the same sodium ethoxide concentration as Orchin and Butz[1], (sodium (1g.) in ethanol (14 mls)). The effects of reducing the base concentration were investigated, maintaining the ratio, diethyl oxalate (2 moles), keto ester (1 mole), sodium ethoxide (2 moles). The results of the experiments showed that successive dilution of the base to approximately six times its original value resulted in the increased formation of β - diketones of the type (11). P.m.r. spectra of these reaction mixtures showed the presence of vinyl protons at τ 3·6, 3·7 and ultra-violet spectra indicated the presence of some enolic compounds. These products were not further investigated.

Some attempted deoxalations.

Attempts were made to remove the oxalate group from (10) without hydrolysing the ester. All these attempts were

unsuccessful using both acidic and basic media. Disappearance of the glyoxalate was monitored by ultra-violet spectrum. The use of hydrazine and other nitrogen bases introduces the possibility of addition of excess reagent to the triketone once formed, since the methyl compound (36) readily forms a semicarbazone (13). The products from these reactions were studied using p.m.r. spectra.

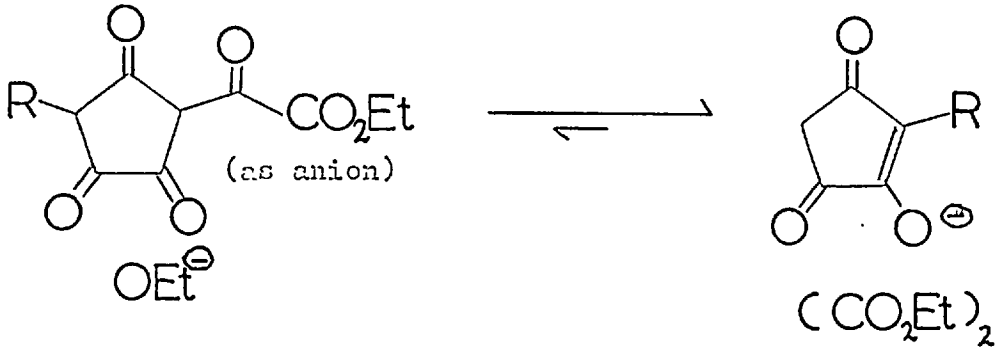


(13)

The results of these experiments are best shown in tabular form:-

Reagent	Spectral Data - Inference.
1) 10, 20, 30, 40, 50% phosphoric acid- 85°C 2 hrs.	UV., p.m.r. indicate complete deoxalation - partial ester hydrolysis
2) $BF_3.Et_2O$ in ethanol	UV - no deoxalation.
3) 2% HCl in ethanol - reflux 2 hrs.	UV - no deoxalation.
4) 1 equiv. sodium ethoxide in ethanol room temperature	p.m.r. - mainly starting material UV - max. 325 mμ indicates partial formation of the anion of (4)
5) 1N NaOH 16hrs. room temperature.	UV - no deoxalation.
6) 1:1 Na_2CO_3 - $NaHCO_3$	UV - no deoxalation
7) N_2H_4 - H_2O in 4:1 pyridine - acetic acid 2 hrs.	UV - no deoxalation p.m.r. - starting material

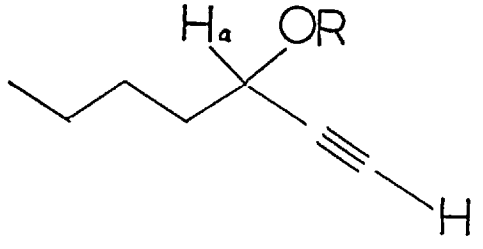
The glyoxalate (10) was treated with 1 equivalent of sodium ethoxide in ethanol to try and establish the following equilibrium :-

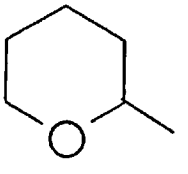


In all cases the product obtained was largely starting material.

Synthesis of 1 - octyne - 3 - ol.

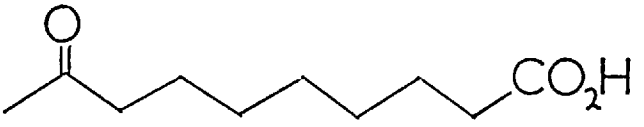
Following the synthesis of the title compound (4) the octynol (14a) was prepared by the addition of sodium acetylide to hexanal, since it was hoped to use this as a precursor for the prostaglandin side chain.



14(a) R=H (b) R = 

The octynol readily gave a tetrahydro pyranyl ether (14b).

Publications received at the time of the completion of this work confirmed the potential of the title compound (4). Collins[4] prepared the triketone (4) from the keto acid (15) by an essentially similar route.



(15)

The spectral data published for (4) was in complete agreement with our own:-

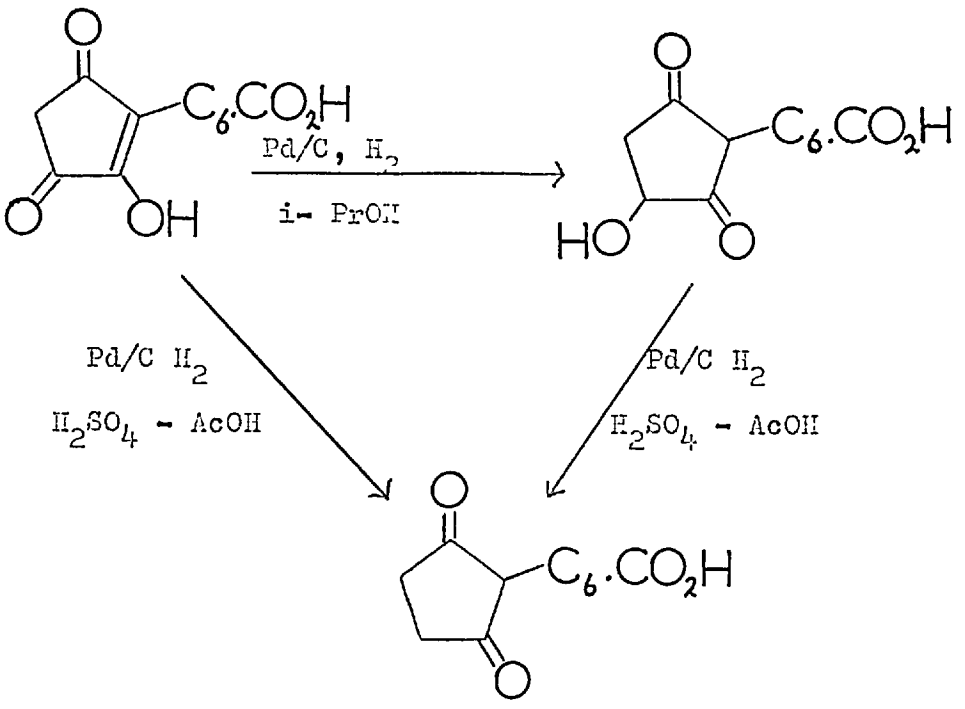
Ultra-violet spectrum,

(i) λ max aq. HCl. 278 mμ (ε = 10,400)

Infra - red spectrum,

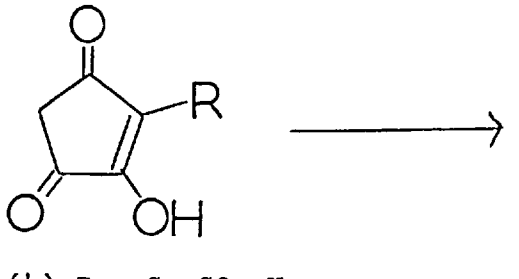
(i) ν max 5·75, 5·91, 6·03 cm^{-1}.

(4) was found to undergo the same reductions as the methyl analogue (3b).



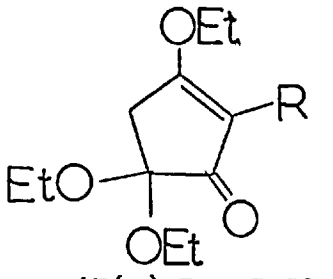
(16)

The dione (16) was converted into dl - PGB_1 in 5 steps. More relevant to a possible synthesis of $PGF_{1\alpha}$ via precursors such as (4) and (14) was the preparation of the orthoformic esters of cyclopentane triketones by Vandewalle[5] and his co-workers. The title compound and its methyl analogue were converted into the orthoformic esters (17). Subsequent reaction of (17b) with a hexynyl lithium compound gave (18) which was converted into (19).



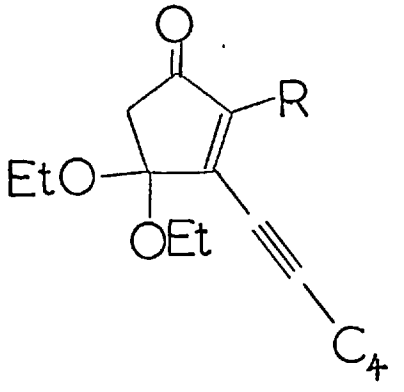
(4) R = C_6CO_2H

(5b) R= Me

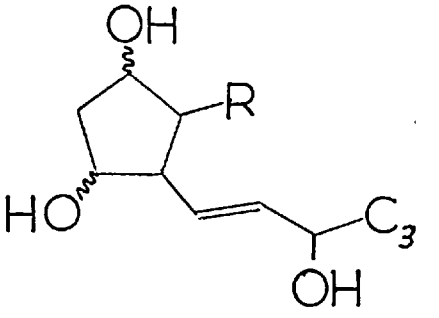


17(a) R = C_6CO_2H

(b) R = Me



(18) R = Me



(19) R = Me

General experimental Data.

MPts were determined on a Kofler Block and are uncorrected.

Infra-red spectra were recorded on a UNICAM SP 200.

Ultra-violet spectra were recorded on a UNICAM SP 800.

P.m.r. spectra were recorded on a Varian A-60 or HA-100.

Gas-liquid chromatograms were recorded on a Perkin-Elmer F11.

Preparative TLC plates were made of Merck silica GF_{254}.

EXPERIMENTAL

1) Preparation of the mono ester (7b)

Polyazelaic anhydride (100g) and absolute ethanol (400 ml) were refluxed until infra-red spectra indicated complete solvolysis of the anhydride. Excess ethanol was distilled off and the residue dissolved in ether (500 mls). Azelaic acid (7a) and the mono ester (7b) were extracted from the ethereal solution with sodium bicarbonate solution, and after careful acidification with concentrated hydrochloric acid re-extracted into ether (500 mls). The ethereal solution was dried (magnesium sulphate) and the ether removed under reduced pressure. The residue was left on a vacuum pump for several hours during which time azelaic acid separated from the oily mixture. The residue was filtered and fractionated to give the mono ester (7b) (26·5g, 21%). B.Pt. 178 - 9° C, (5·5 mm.);

B.Pt. 119 - 20° C, (0·06 mm)

Infra - red spectrum :-

ν max. liquid film 1735 cm^{-1} (ester), 1710 cm^{-1} (acid)

P.m.r. spectrum :-

(i) τ - 1·35 , 1H singlet, acid proton.

(ii) τ 6·07, 2H quartet J = 7 Hz, ethyl ester

(iii) τ 8·82, 3H triplet J = 7 Hz, ethyl ester

(iv) τ 7·5 - 9·0, 14 H envelope, methylene protons.

2) Preparation of the acid chloride (8).

Mono ethyl azelate (7b) (45g) and thionyl chloride (36 mls) were stood at 50°C for 2 hours, and then at 80°C for 2 hours. Distillation of excess thionyl chloride and fractionation of the residue gave (8) (32g, 94%). B.Pt.158°C (15 mm).

Infra-red spectrum :-

ν max. liquid film 1735 cm^{-1} (ester), 1796 cm^{-1} (acid chloride)

P.m.r. spectrum :-

(i) τ 5·95, 2H quartet, J = 7 Hz, ethyl ester

(ii) τ 7·15, 2H distorted triplet J = 6 Hz, methylene group adjacent to acid chloride.

(iii) τ 8·78, 3H triplet J = 7 Hz, ethyl ester

(iv) τ 7·5 - 9·0, 12 H envelope, methylene protons.

3) Preparation of ethyl - 9 - keto decanoate (9).

Methyl magnesium iodide (0·14 mole) was prepared from magnesium turnings (3·36g, 0·14 mole), methyl iodide (4·5g, 0·19 mole) in ether (200 ml) under nitrogen. The Grignard solution was cooled in ice and anhydrous cadmium chloride (2·8g, 0·15 mole) was added slowly in one portion. The cadmium Grignard solution was stirred for 5 minutes and a solution of the acid chloride (8) (18g, 0·07 mole) in ether (60 ml) was added. The reaction mixture was refluxed for 4 hours and excess Grignard reagent destroyed with sodium bicarbonate solution. The ethereal

solution was washed with aqueous sodium bicarbonate, dried (magnesium sulphate), and the ether distilled off. Fractionation of the residue gave the keto ester (9) (10·4g, 57%) BPt. 145-8°C (10mm).

2:4 dinitro phenyl hydrazone MPt 72°C.

Infra-red spectrum:-

ν max liquid film, 1710 - 1740 cm^{-1} broad, 1190 cm^{-1}

P.m.r. spectrum :-

(i) τ 5·98, 2H quartet J = 7Hz, ethyl ester.

(ii) τ 8·82, 3H triplet J = 7Hz, ethyl ester

(iii) τ 8·02, 3H singlet, methyl ketone

(iv) τ 7·5 - 9·0, 14H envelope, methylene protons.

4) Preparation of the glyoxalate (10).

Sodium (0·92g; 0·04 mole) was dissolved in absolute ethanol (14 mls) in a flask sealed with a serum cap containing a hypodermic needle to allow gas to escape, while maintaining an atmosphere of hydrogen. The resulting sodium ethoxide solution was cooled to room temperature and stirred magnetically. A solution of the keto ester (9) (4·5g, 0·02 mole) and diethyl oxalate (6·4g, 0·044 mole) was added dropwise and the mixture stirred for 2 hours. The reaction mixture was acidified carefully with 5% sulphuric acid and the ethanol removed under reduced pressure. The crude glyoxalate was dissolved in ether (30 ml) and then extracted into sodium bicarbonate solution. The solution was carefully acidified with concentrated hydrochloric acid and the glyoxalate extracted

into ether (50 ml) with salting out. The ether was dried (sodium sulphate) and evaporated under reduced pressure to give pure glyoxalate (10) as a pale yellow oil (3·2g).

Infra- red Spectrum ;

ν max.liquid film. 1735 cm^{-1} (broad), 1660, 1200 cm^{-1}

UV; λ max. H.Cl 258, 280 mμ , $NaHCO_3$ 279, 310 mμ .

P.m.r. spectrum :-

(i) τ 5.8 , 4H, multiplet.

(ii) τ 7.75, 4H, broad,

(iii) τ 8.0 - 9.0, 14 H.

5) Preparation of the cyclopentane triketone (4).

The glyoxalate (300 mgs) was refluxed for 2 hours with 2N hydrochloric acid (20 mls). The solution was extracted with chloroform (4 x 20 mls) with salting out. The chloroform was dried (sodium sulphate) to give the crude triketone (4) (115 mgs). Vacuum sublimation gave an analytical sample MPt 107 - 8°C.

Analysis, Found C = 60·03%, H = 6·54%

($C_{12}H_{16}O_5$ requires C = 60%, H = 6·72%)

6) Preparation of the compound (12).

The same procedure as in the preparation of the glyoxalate (10) was used, with the following reactants,

Sodium	(92 mgs, 0·004 mole)
Diethyl oxalate	(290 mgs, 0·002 mole)
Keto ester (9)	(430 mgs, 0·002 mole)
Ethanol	(1·5 mls.)

The product was recrystallised from benzene yield 120 mgs, MPt 83°C.

Infra-red spectrum:-

γ max. liquid film. 1700 - 1740 cm^{-1} (broad), 1645, 1608 cm^{-1}.

Ultra-violet spectrum:-

1) λ max $\begin{matrix}\text{EtOH}\\\text{HCl}\end{matrix}$ 287 $m\mu$

2) λ max $\begin{matrix}\text{EtOH}\\\text{NaHCO}_3\end{matrix}$ 314 $m\mu$

7) Preparation of 1 - octyne - 3 - ol (14a).

Sodium (11·5g, 0.5 mole) was converted into sodium acetylide as described in the literature. Hexanal (50g, 0·5 mole) in ether (50 ml) was added during 30 minutes, and the mixture stirred for 3 hours. Ammonium chloride (30g) was added in portions over 15 minutes. The liquid ammonia was allowed to evaporate and ether (100 ml) was added. The mixture was filtered and the filter cake washed with ether (300 ml). Ether (approx. 200 mls) was distilled off to expel any remaining ammonia and the residual ether washed

with sodium bisulphite solution to remove any unreacted aldehyde. The ethereal solution was dried (sodium sulphate, potassium carbonate) and the ether distilled off. Fractionation of the residue (from potassium carbonate) gave the ethynyl carbinol (24·5g, 40%) BPt 174°C. (14 mm)

P.m.r. spectrum:-

(i) τ 5·65, 1H multiplet, proton on carbon bearing hydroxyl group.

(ii) τ 7·3, 1H broad, hydroxyl proton

(iii) τ 7·55, 1H multiplet, ethynyl proton

(iv) τ 8·0 - 9·3, 11 H envelope, chain protons.

8) Preparation of the tetrahydropyranyl ether (14 (b)

1 - octyn - 3 - ol (3g) and dihydropyran (2·4g) were placed in a flask fitted with a reflux condenser, and 1 crystal of p - toluene sulphonic acid was added. The contents of the flask heated up as the exothermic reaction proceeded. The flask was allowed to cool to room temperature and the reaction mixture stirred for 1 hour with anhydrous potassium carbonate. The reaction mixture was filtered and the filtrate warmed under reduced pressure to remove excess dihydropyran. Yield of the ether (14b) (4·1g)

REFERENCES.

1) M. A. Orchin and L. W. Butz, J. Amer. Chem. Soc., 65, 2296.

2) C. F. Sheley and H. Schechter, J. Org. Chem., 35 (7), 2367, (1970).

3) McKennis and du Vigneaud, J. Amer. Chem. Soc., 68, 832, (1946).

4) P. Collins, C. J. Jung, R. Pappo, Israel J. Chem., 6, 839, (1968).

5) M. Vandewalle, V. Sipido, H. De Wilde, Bull. Soc. Chim. Belges, 79, 403, (1970).

6) 'A Course in Modern Techniques of Organic Chemistry' by Elvidge and Sammes, p. 168.

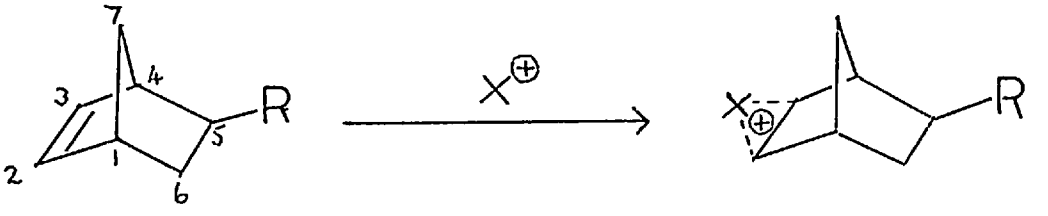
ADDITION REACTIONS TO SUBSTITUTED NORBORNENES.

A study of some addition reactions to norbornenes.

The use of bicyclic compounds as precursors for the synthesis of the prostaglandin skeleton has been fully discussed in the review. In this section the results of some investigations into the chemistry of norbornene compounds are discussed.

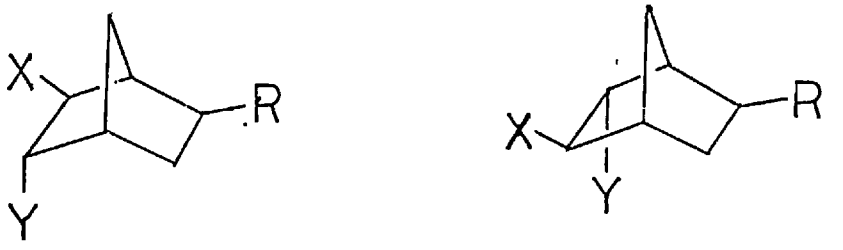
Reactions of substituted norbornenes with N - Bromosuccinimide.

The reaction of a substituted norbornene with an electrophile can proceed in three ways after initial formation of the ion (2)



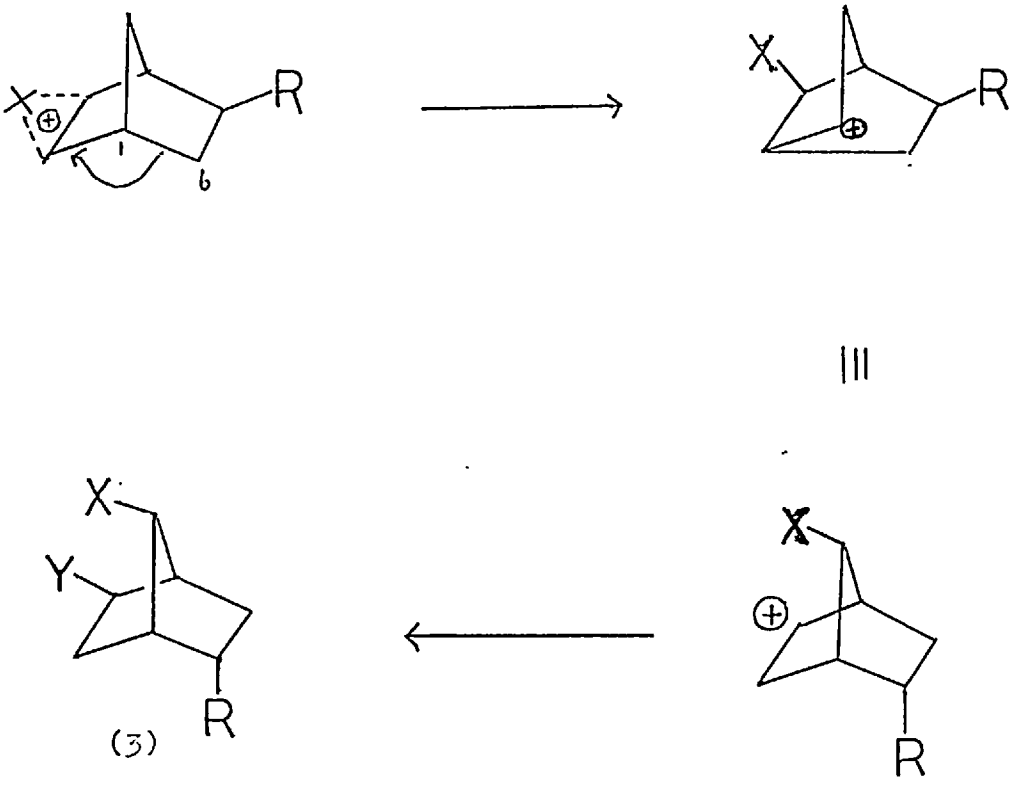
(1) (2)

(a) Solvation of the ion to give a 1, 2 - disubstituted product :-

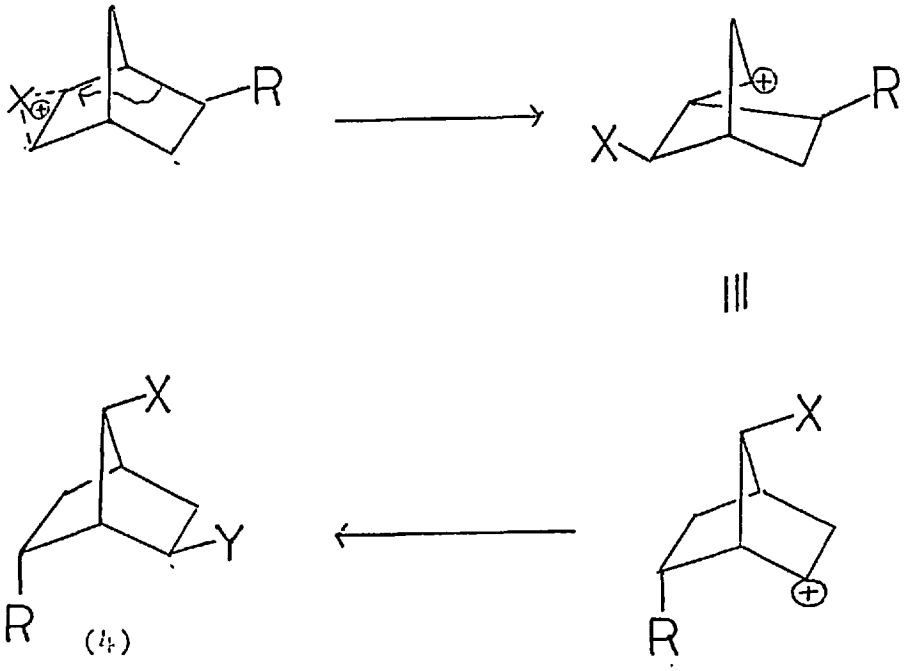


b) Skeletal rearrangement, which after solvation of the carbonium ion gives a 1, 3 - adduct. There are two possible skeletal rearrangements which lead to different positional isomers; in both rearrangements exo solvation of the final carbonium ion is assumed, and the group -R formally inverts its configuration as a consequence of the structural rearrangement.

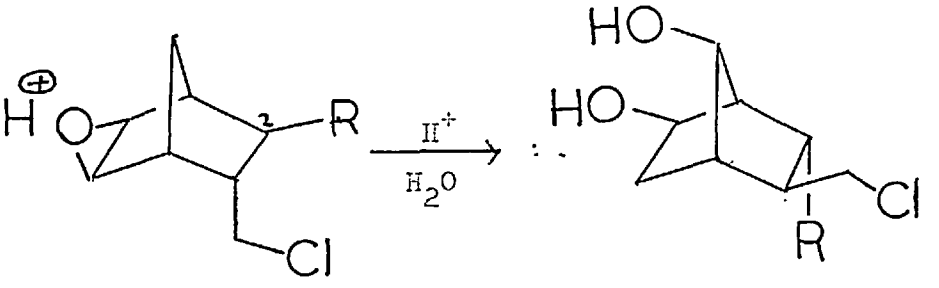
Path 1, migration of the 1 - 6 bond,



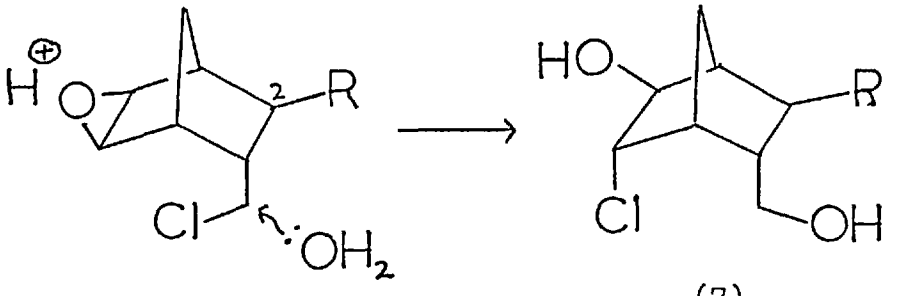
Path 2, migration of the 4 - 5 bond,



Examples of 1,2 - and 1,3 - additions have been reported, but there is little evidence for the regioselectivity of these reactions apart from the work of Christol[1] and his co-workers who have investigated the rearrangement occurring during the acid catalysed opening of an epoxide, and have studied the effects of various 2- exo substituents -R (5) on the amount of rearranged product formed (6) compared with the product of endo participation of the chloromethyl group (7).

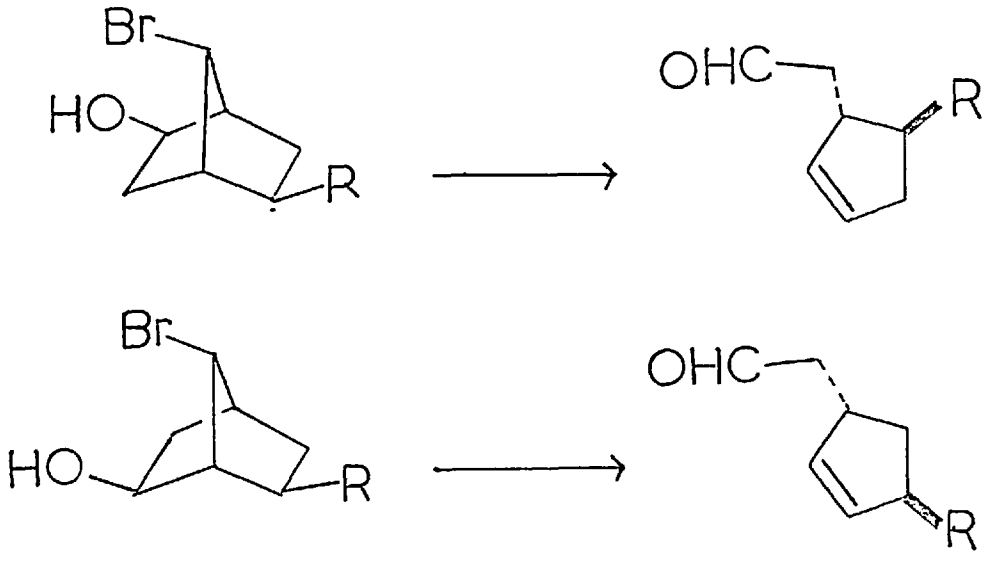


(5) (6)



(7)

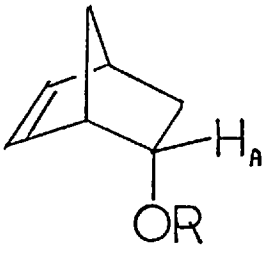
It was necessary to investigate these addition reactions and to try and establish the substitution of the product because of the possible use of 1,3 - bromhydrins derived from substituted norbornenes as general precursors for stereo-controlled syntheses of prostaglandins. As an example, dehydrobromination of the two bromhydrins with concomitant ring opening could yield the cyclopentenes with the substitution and stereochemistry shown.

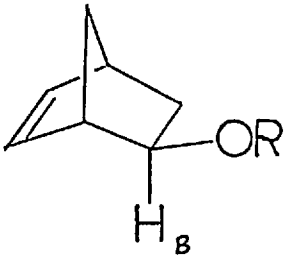


The first stage of the investigation was the preparation of some substituted norbornenes, with as high a degree of isomeric purity as possible.

Preparation of some substituted norbornenes.

2 - norbornene - 5 - acetate was prepared by the addition of vinyl acetate to cyclopentadiene as described in the literature.[2] The p.m.r. spectrum showed that the product after distillation contained approximately 70% of the endo (8a) and 30% of the exo acetates (8b) as estimated by measurement of the integrals of the exo proton, H_A (τ 4·65) and the endo proton, H_B (τ 5·25) in (8a,b).

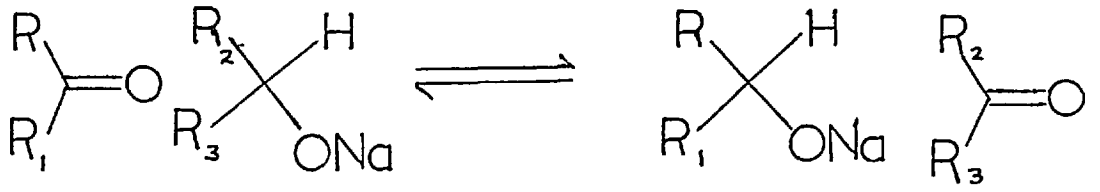




(8a) R = Ac (8b) R = Ac

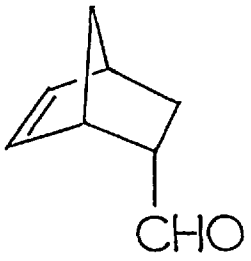
(9a) R = H (9b) R = H

Saponification of the acetate mixture (8a,b) with sodium hydroxide gave the corresponding alcohols (9a,b). Spectra of the re-acetylated alcohol mixture showed that no structural rearrangement or equilibration had occurred during the saponification. An equilibration of the alcohol mixture to enrich it in exo isomer (9b) was attempted using Roberts' modification of the Doering procedure[3], which involves the reflux of the alcohol mixture with sodium and fluorenone to establish the following equilibrium, with the formation of the thermodynamically more stable exo - norbornenol:-

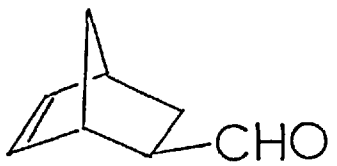


However a low yield of the isomer mixture (9ab) was obtained. Hydroboration of norbornadiene[4] yielded a mixture of alcohols which was shown by GLC and p.m.r. spectra to contain 92% of the exo alcohol (9b) and 8% of the endo isomer (9a).

2 - norbornene - 5 - carboxaldehyde was prepared by the Diels-Alder addition of acrolein to cyclopentadiene.[5] The reaction proceeded rapidly at room temperature and a p.m.r. spectrum of the product after distillation indicated a mixture of isomers. Two aldehyde signals were present in the p.m.r. spectrum, and assuming that the endo aldehyde (10a) is the major product formed, the signal at τ 0·66 can be assigned to this isomer and indicates that it comprises 75% of the mixture. The signal at τ 0·3 can therefore be assigned to the exo isomer (10b). The reaction was repeated at -78°C to try and improve the selectivity of the reaction, but the same mixture of exo and endo isomers was obtained.

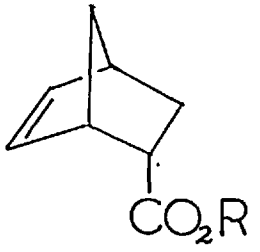


(10a)

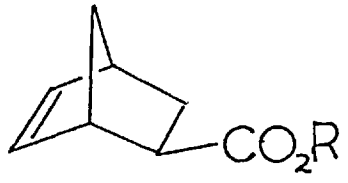


(10b)

Methyl 2 - norbornene - 5 - carboxylate was similarly prepared by the addition of methyl acrylate to cyclopentadiene as described by Roberts.[6] GLC analysis of the purified product showed a mixture of two isomers approximately 75% <u>endo</u> (11a) and 25% <u>exo</u> (11b). The reaction was repeated at -78°C as in the aldehyde preparation but GLC showed no change in the ratio of isomers.



(11a) R = Me
(12a) R = H



(11b) R = Me
(12b) R = H

The ester mixture (11a,b) was equilibrated with refluxing sodium methoxide - methanol to try and prepare pure <u>exo</u> ester (11b). GLC indicated that after approximately 2 hours an

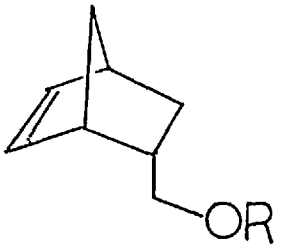
equilibrium mixture was established containing 60% exo ester (11b).

Addition of acrylic acid to cyclopentadiene[7] gave a mixture of endo-2 - norbornene - 5 - carboxylic acid (12a) and the exo isomer (12b). GLC of a portion of this mixture esterified with diazomethane showed the same ratio of isomers as in the direct addition of methyl acrylate.

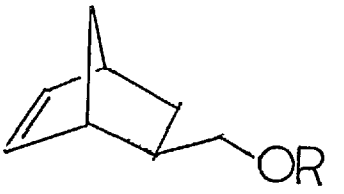
Treatment of the acid mixture (12a,b) in buffered sodium hydroxide solution[6] with iodine gave the known iodolactone (13) from the endo acid (12a). The exo acid (12b) did not react and was readily separated. GLC of an esterified portion showed it to contain no endo isomer. The iodolactone (13) had a p.m.r. spectrum consistent with the assigned structure.

Reduction of the iodolactone with zinc dust in aqueous ethanol reformed the norbornene carboxylic acid, shown by GLC of an esterified portion to be pure endo isomer (12a).

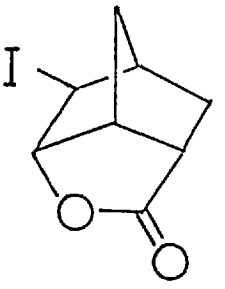
Reduction of the pure acids (12a, 12b) with lithium aluminium hydride gave the corresponding alcohols (14a, 14b) which on treatment with acetic anhydride - pyridine formed the acetates (15a, 15b).



(14a) R = H
(15a) R = Ac



(14b) R = H
(15b) R = Ac

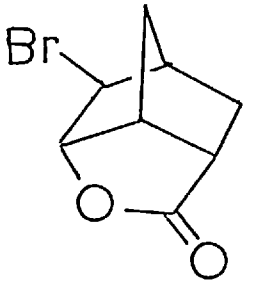


(13)

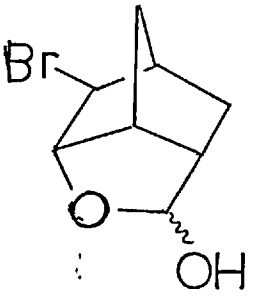
Reactions of N - bromosuccinimide with endo norbornenes showing intramolecular solvation.

Treatment of the endo acid (12a) with NBS in aqueous acetone gave the expected bromolactone (16) as the only product. Its p.m.r. spectrum was almost identical to that of the iodolactone (13) and on reaction with zinc - aqueous ethanol it yielded the endo acid (12a), identified by TLC, and infra-red and p.m.r. spectra.

Reaction of the isomer mixture of 2 - norbornene - 5 - carboxaldehyde (10a,b) with NBS in aqueous acetone gave on work up a semi solid containing two compounds. Crystallisation purified one of the products, MPt 96-8°C, which was assigned the bromolactol structure (17) on the basis of its infra-red spectrum and reduction with zinc-aqueous ethanol to endo - 2 - norbornene - 5 - carboxaldehyde (10a).



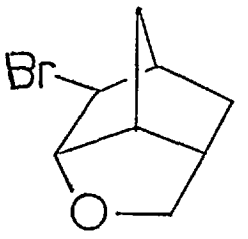
(16)



(17)

Oxidation of the bromolactol (17) at 0°C with Jones' reagent gave the bromolactone (16) identified by its infra-red and p.m.r. spectra.

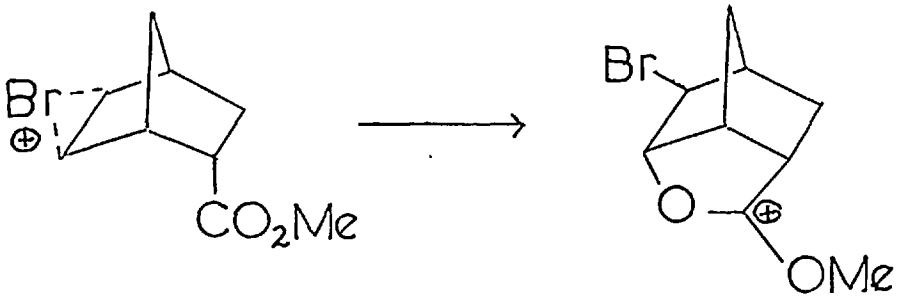
Endo - 2 - norbornene - 5 - methylcarbinol (14a) on treatment with NBS in aqueous acetone gave the expected bromoether (18) which was treated with refluxing zinc-aqueous ethanol to reform the endo alcohol (14a) identified by its spectral data.



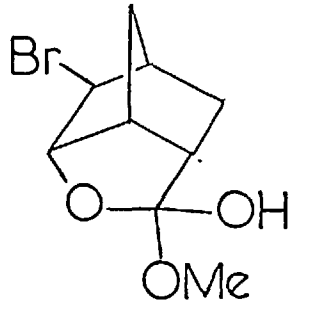
(18)

1,3 addition of NBS to norbornene acids and esters.

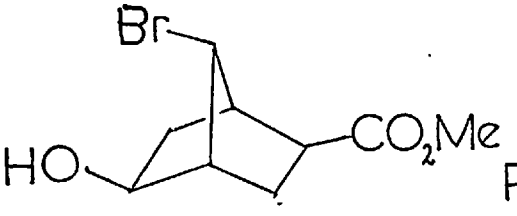
Treatment of endo methyl 2 - norbornene - 5 - carboxylate (11a) with NBS in aqueous acetone was shown by TLC to produce two products which were separable chromatographically. The first was identified as the bromolactone (16) and is presumably formed as shown:-



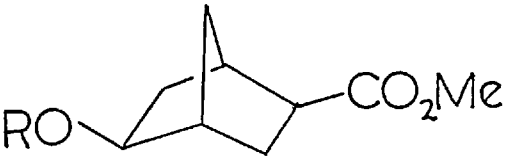
(16) ←



The second product was shown to be a bromhydrin of the ester (11a) by analysis of its 3,5 - dinitrobenzoate derivative and was arbitrarily assigned the structure (19) on the basis of the p.m.r. spectrum which supports the assignment of a 1,3 - adduct.

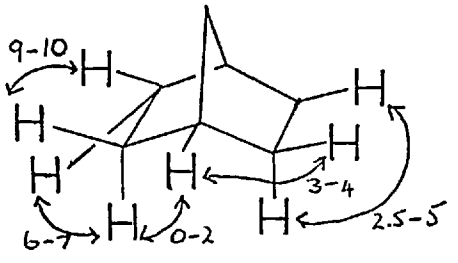


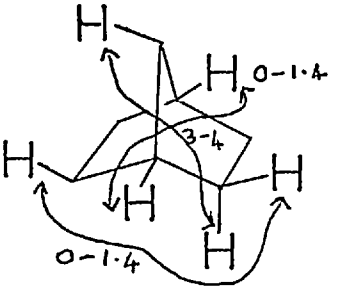
(19)



(20) R = H

(21) R = Ac



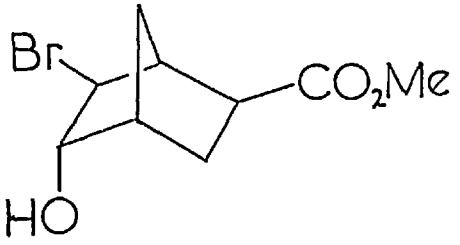


Couplings of norbornane protons.

(22)

The methine carbinol proton signal showed a width at half height, $W_{\frac{1}{2}}$ = 15 Hz, which favours the assignment of the 1,3 adduct structure.

The width at half height of this proton in the spectra of all the bromhydrins prepared is a strong piece of evidence for the assignment of the 1,3 adduct structures. A simple addition of the couplings quoted in (22) shows that for a 1,2 bromhydrin eg (23), the $W_{\frac{1}{2}}$ value varies between 5·5 and 11 Hz ; for a 1,3 adduct, however, the value varies between 11·5 and 18 Hz.



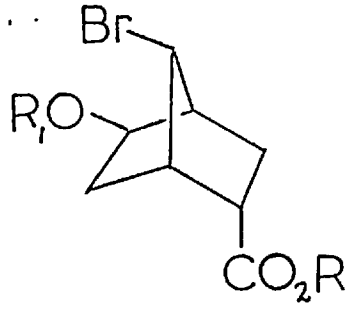
(25)

No evidence for the position of the ester group can be obtained from the spectrum, the assignment of the chosen positional isomer structure is purely arbitrary.

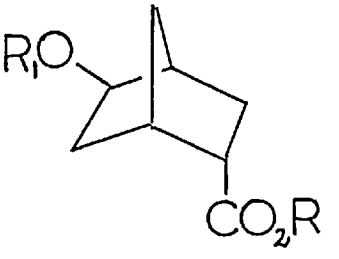
Reduction of (19) with zinc - aqueous ethanol yielded the corresponding hydroxy ester (20). This result establishes that the 1,2 - adduct has not been formed since it would have yielded an olefin by the removal of the elements of HOBr on zinc reduction. Acetylation of (20) gave the corresponding acetate (21). The p.m.r. spectrum of the acetate showed the presence of a second compound, since the methyl ester (τ 6·3) and acetate signals

(τ 7·98) were accompanied by minor signals at approximately 0·02 ppm lower field.

Treatment of the exo ester (11b) with NBS in aqueous acetone gave an oily product which showed a single spot on TLC. This compound was shown to be a bromhydrin of the ester (11b) by analysis of a 3,5 - dinitrobenzoate derivative and was tentatively assigned the structure (24).



(24) R = Me, R_1 = H
(25) R = Me, R_1 = Ac
(26) R = R_1 = H.



(27) R = Me, R_1 = H
(28) R = Me , R_1 = Ac.

The p.m.r. spectrum of the acetate (25) again supported the assignment of a 1,3 - bromhydrin structure. The proton adjacent to the acetoxy group appeared as a 'distorted triplet', $W_{\frac{1}{2}}$ = 15 Hz, and the proton adjacent to the bromine atom (τ 6·05), $W_{\frac{1}{2}}$ = 5 Hz.

Zinc reduction of the bromhydrin (24) gave the hydroxy ester (27) thereby confirming the assignment of a 1,3 - adduct

structure.

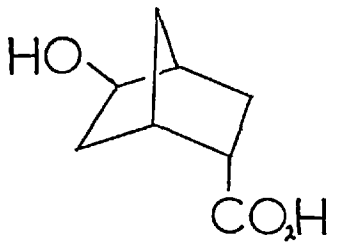
The p.m.r. spectrum of the acetate (28) indicated the presence of a second compound as with the exo isomer (21). The methyl ester (τ 6·3) and acetate signals (τ 7·98) showed additional minor signals at approximately 0·02 ppm lower field. These additional signals in the p.m.r. spectra of both isomers are explained by the presence of a second isomeric compound and are discussed later.

Refluxing the two isomers (21, 28) with sodium methoxide - methanol followed by reacetylation removes the extra signals in the ester and acetate regions in both cases, the p.m.r. spectra of the crude equilibrated products from both isomers were almost identical.

This inconclusive evidence suggests that during equilibration or subsequent work up the minor isomer is removed.

The exo acid (12b) was treated with NBS in aqueous acetone to give a single compound which was assigned the 1,3 - bromhydrin structure (26). Esterification with diazomethane, followed by acetylation gave an ester acetate which was shown by infra-red and p.m.r. spectra to be identical to (25) derived directly from the ester (11b). Reduction of (26) with zinc - aqueous ethanol yielded a crystalline product, which was shown to consist of two compounds by TLC. The major compound which formed approximately 92% of the total reaction mixture was assigned the

hydroxy acid structure (29).



(29)

P.m.r. spectrum of a sample purified by TLC showed the absence of vinylic protons and confirmed the assignment of the 1,3 - structure to (26). A sample of hydroxy acid (29) was recrystallised for analysis from the crude reaction mixture because of partial formylation during TLC (benzene - ether - formic acid).

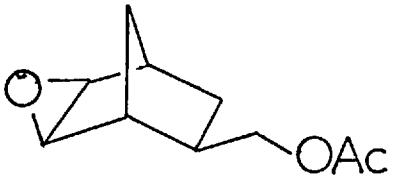
The minor bicarbonate - soluble product was not completely characterised, however, the p.m.r. spectrum showed the presence of vinyl protons.

At this stage the data described give no clue as to the isomeric purity of the products obtained, although their elemental composition has been established. Some evidence for isomeric purity was obtained by conversion of the hydroxy esters into the products obtained by similar reaction of the 2 - norbornene - 5 - methyl carbinol acetates (15a, 15b).

Preparation of a mixture of 2,5 - and 2,6 - disubstituted norbornyl diacetates (31,32,35,36).

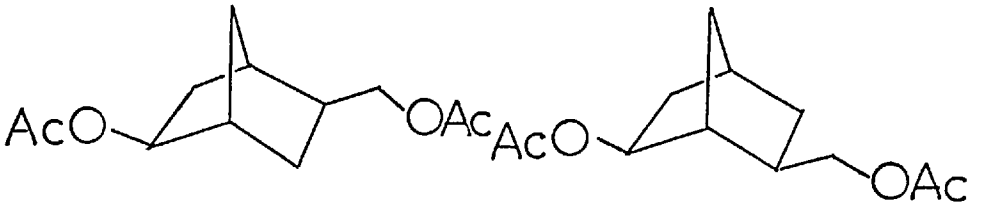
Brown[8] has recently prepared both α - and β - epoxides of substituted norbornenes and shown that they can be quantitatively reduced without rearrangement to the alcohols with lithium-ethylamine. This method was used to prepare the required mixtures of positional isomers, which would be formed by the two possible skeletal rearrangements on 1,3 addition.

Treatment of exo - 2 - norbornene - 5 - methyl carbinol acetate (15b) with m - chloroperbenzoic acid gave an epoxide which was assigned the β - configuration (30) on the basis of Brown's data. This epoxide showed a single peak on GLC analysis and had a p.m.r. structure consistent with the assigned structure.



(30)

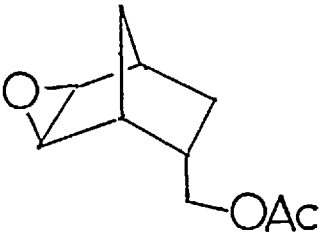
Reduction of the epoxide (30) with lithium - ethylamine and acetylation of the reaction mixture gave a product which was shown by GLC to contain two compounds, accepted as the two positional isomers (31,32).



(31) (32)

The p.m.r. spectrum was that expected for the mixture of diacetates and showed the two isomers by the presence of two acetate signals at (τ 7·92, 7·97) and the shape of the signals due to the protons adjacent to the acetoxy groups.(33)

(33)

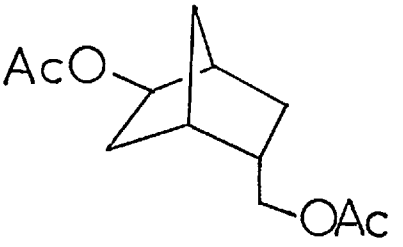


(34)

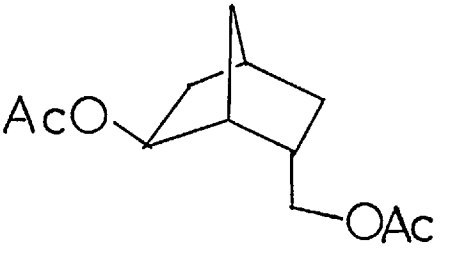
Epoxidation of the endo isomer (15a) gave the corresponding β - epoxide (34) which gave a single peak on GLC and showed a p.m.r. spectrum consistent with the assigned structure.

Reduction of the epoxide (34) with lithium-ethylamine followed by acetylation gave a product which GLC showed to

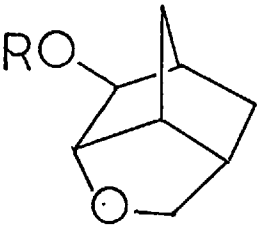
consist of three compounds. The two peaks with comparable retention times to the exo isomers were accepted as the 'endo' diacetates (35,36).



(35)



(36)



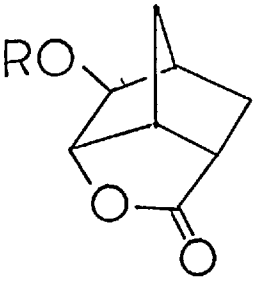
(37) R = H
(38) R = Ac

The third compound was thought to be the acetoxy ether (38) arising from an intramolecular attack on the epoxide. The structure of (38) was subsequently proved by epoxidation of the endo alcohol (14a). TLC showed that a single crystalline product was produced, which analysis showed had the correct

elemental composition for the assigned hydroxy ether (37). The p.m.r. spectrum of (37) was consistent with the assigned structure, the protons adjacent to the oxygen atoms appeared as a complex signal, τ 5·9 - 6·6 (5H). Acetylation of (37) gave the corresponding acetate (38), which a p.m.r. spectrum indicated was the acetoxy ether, since on acetylation a single proton had moved to lower field, τ 5·65. GLC showed the acetoxy ether to be pure and it was characterised by accurate mass measurement. GLC enhancement experiments showed that the third peak in the acetylated reduction product of the endo epoxide (34) was indeed the ether (38).

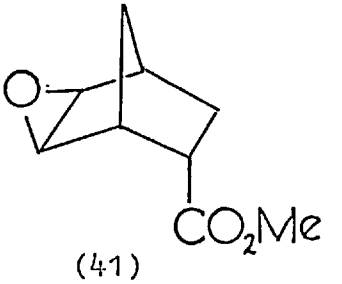
Reaction of the endo norbornene compounds, (10a,12a,14a) with NBS showed that intramolecular cyclisation by nucleophilic attack on the initial bromonium ion was the sole reaction product.

The opening of the epoxide ring during the preparation of the ether (37) prompted the investigation of the epoxidation of the endo acid (12a). A single bicarbonate-insoluble product was obtained, which analysis showed to have the correct elemental formula for the hydroxy lactone (39).

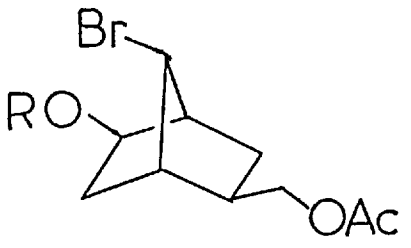


(39) R = H

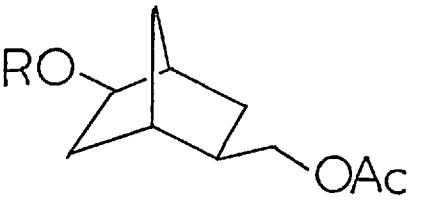
(40) R = Ac



(41)



(42) R = H
(43) R = Ac



(44) R = H
(31) R = Ac

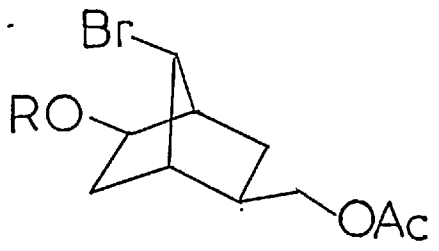
The infra-red in chloroform solution, ν max 3410, 1775 cm^{-1}, supported the assignment of structure.

Reaction of the hydroxy lactone with acetic anhydride - pyridine gave a single crystalline compound which was shown by analysis to have the empirical formula of the mono acetate (40). This structure was confirmed by its p.m.r. and infra-red spectra. The crude reaction mixture from the epoxidation was treated with diazomethane, after work up a p.m.r. spectrum showed that no epoxy ester was present (41).

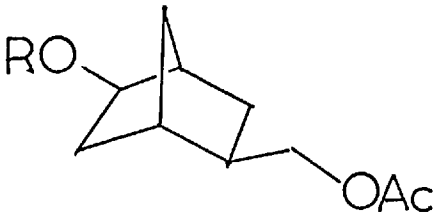
1,3 addition of NBS to the acetates (15a,15b).

Treatment of the endo acetate (15a) with NBS in aqueous acetone gave on work up an oil which showed as a single spot on TLC. Analysis of the 3,5 - dinitrobenzoate derivative showed this to be a bromhydrin, which was tentatively assigned the

structure (42). A p.m.r. spectrum of the corresponding acetate (43) indicated the 1,3 - bromhydrin structure, the methine carbinol acetate proton showed the expected coupling, $W_{\frac{1}{2}}$ = 15Hz, τ 5·2.



(42) R = H
(43) R = Ac

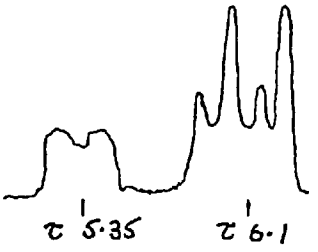


(44) R = H
(31) R = Ac

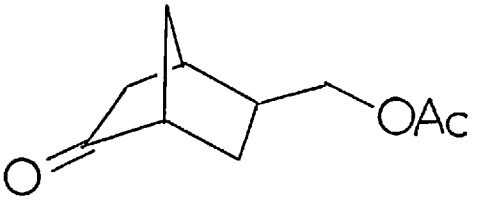
Reduction of the bromhydrin (42) with zinc-aqueous ethanol gave the corresponding hydroxy acetate (44). Acetylation of (44) gave a product which TLC showed to contain two compounds. The minor product, accounting for less than 10% of the total, was not characterised but a p.m.r. spectrum showed it to be an olefin.

The major product was assigned to the diacetate (31). GLC of the diacetate, however, showed the presence of two compounds in the ratio 19:1 which were found to correspond to the positional isomers obtained from the epoxide (30). The p.m.r.

spectrum of the diacetate showed the presence of two isomers (31,32), being identical in all general features to that of the mixture derived from the epoxide (30) and showing the predominance of one of the isomers (45),

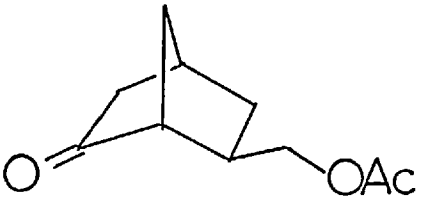


(45)



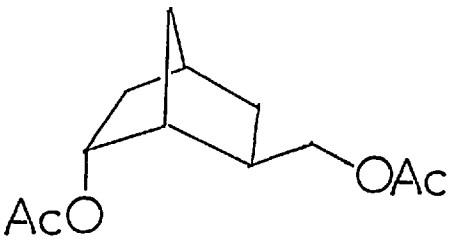
(46)

Oxidation of the hydroxy acetate (44) with Jones reagent gave smoothly the corresponding keto acetate (46), which a p.m.r. spectrum showed contained a second isomer assigned arbitrarily to (47). The presence of an additional minor signal 0·02 ppm to higher field indicates

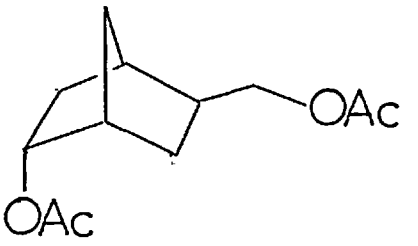


(47)

that the complex signals obtained in the p.m.r. spectrum of the diacetates (31,32) were rightly assigned to the positional isomers and not to any products (48,49) arising from endo solvation in the NBS reaction sequence



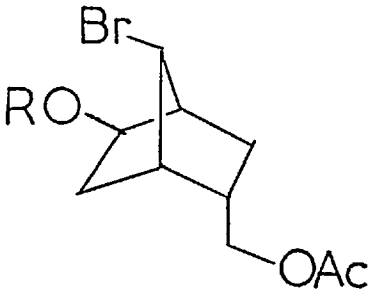
(48)



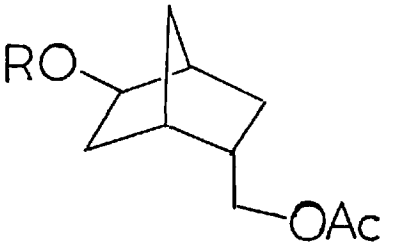
(49)

or from the reduction of any α - epoxide.

Treatment of the exo isomer (15b) with NBS in aqueous acetone gave a product which showed as a single spot on TLC. Analysis of a 3,5 - dinitrobenzoate derivative again showed it to be the corresponding bromhydrin. The bromhydrin was assigned the 1,3 - adduct (50), the methine carbinol acetate proton in the diacetate derivative (51) showed the expected coupling, $W_{\frac{1}{2}}$ = 15 Hz.



(50) R = H
(51) R = Ac



(52) R = H
(35) R = Ac

Reduction of the bromhydrin (50) with zinc-aqueous ethanol gave the corresponding hydroxy acetate (52), again the absence of any vinyl protons in the p.m.r. spectrum justified the assignment of the 1,3 - adduct (50). TLC of the diacetate showed the presence of two compounds. Chromatography yielded the two fractions, the minor component accounting for less than 10% of the mixture recovered was not identified. The major component was arbitrarily assigned to the diacetate (35) which was found on GLC to contain two compounds in the ratio of 20:1, which were shown to correspond to the two positional isomers (35,36) derived from reduction and acetylation of the epoxide (34).

Unlike the exo series the p.m.r. spectrum of these diacetates did not give any additional evidence on the purity of the products, nor was any comparison possible with the spectrum of

the reduced epoxide because of the presence of the acetoxy ether (38).

Conversion of the hydroxy esters (20,27) into the corresponding diacetates.

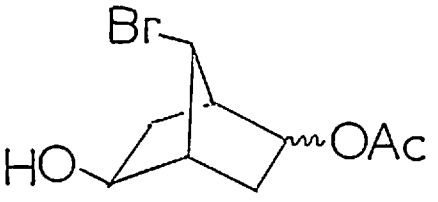
The exo ester (20) was reduced with lithium aluminium hydride and the crude reaction mixture acetylated. Chromatography of the mixture yielded a diacetate as the major product (> 90%) which was shown by GLC, infra-red and p.m.r. spectra to be identical to that assigned structure (31) derived from the endo acetate (15a) and was of the same isomeric purity within the limits of experimental error.

In a similar manner, reduction of the endo isomer (27) and acetylation gave the diacetate (35) as the major product (> 90%) from chromatographic separation. GLC, infra-red and p.m.r. spectra showed the product to be identical to that obtained from the exo acetate (15b).

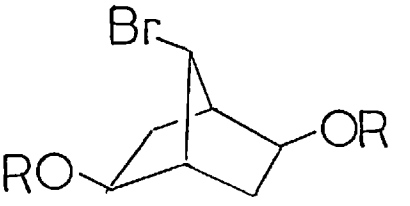
Correlation of the diacetates derived from the esters (11a, 11b) and acetates (15a,15b) with those derived from the epoxides (30,34) shows that the skeletal rearrangement of the initial bromonium ion (2) is highly specific. The assignment of the 2,5 disubstituted structure to the major products is purely arbitrary, although evidence is presented later to support this assignment.

1:3 addition of NBS to norbornenyl acetate (8a,b) and related compounds.

Treatment of 2 - norbornene - 5 - acetate (8a,b; 70% endo isomer) with NBS in aqueous acetone gave an oil which was assigned the 1,3 bromhydrin structure, since zinc reduction produced no olefin, and was assumed to contain 70% of the exo, exo isomer. (52a) on the basis of p.m.r. and the composition of the starting material.



(52a)

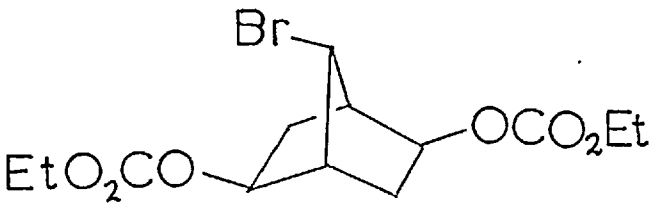


(53) R = H
(54) R = Ac
(56) R = THP ether, T

Initial attempts to hydrolyse the acetate (52a) with aqueous sodium hydroxide led to destruction of the molecule. The acetyl group could be removed however with sodium carbonate in aqueous dioxan to give a low yield of a crystalline compound, MPt. 163°C, and which analysis showed to have the elemental composition of the bromo diol (53). The bromo diol (53) was assumed to be predominantly the exo, exo isomer and had a p.m.r. spectrum consistent with the assigned structure. The methine carbinol protons, τ 6·2, $W_{\frac{1}{2}}$ 15 Hz, confirmed the assignment of the 1,3 bromhydrin

structure, together with the zinc reduction of the bromo diol to the corresponding diol (57) described later. Direct reaction of the corresponding alcohol mixture (9ab, 70% endo isomer) gave the bromo diol in higher yield.

Treatment of the bromo diol with acetic anhydride - pyridine gave the diacetate derivative (54), again the methine carbinol acetate protons showed the broad couplings in the p.m.r. spectrum characteristic of the assigned structure, (τ 5·3, $W_{\frac{1}{2}}$ height 15 Hz).

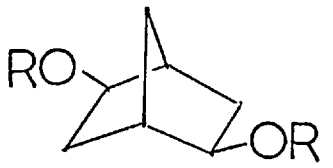


(55)

In a similar manner, the bromo diol gave the dicarbonate ester (55) on reaction with ethyl chloroformate - pyridine, which TLC showed to be pure. It was characterised by accurate mass measurement, and had infra-red and p.m.r. spectra consistent with the structure (55)

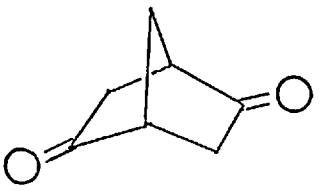
The bromo diol (53) gave a bis - tetrahydropyranyl ether on treatment with excess dihydropyran - conc. acid (56). No information was obtained from its p.m.r. spectrum, which showed the expected ratio of 'high field' to 'low field' protons.

Reduction of the bromodiol (53) with zinc - aqueous ethanol or with lithium - ammonia gave the corresponding diol (57). The absence of vinyl protons in the p,m.r. spectrum of the diol (57) proved the assignment of the 1:3 adduct structure to (53). The diol gave the correct analysis and was assumed to be almost exclusively the exo-exo isomer after recrystallisation. (MPt. 177-181°C).

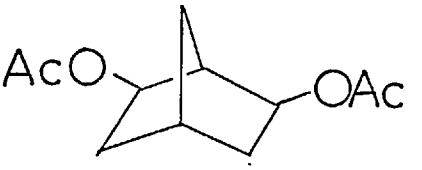


(57) R = H

(58) R = Ac



(59)

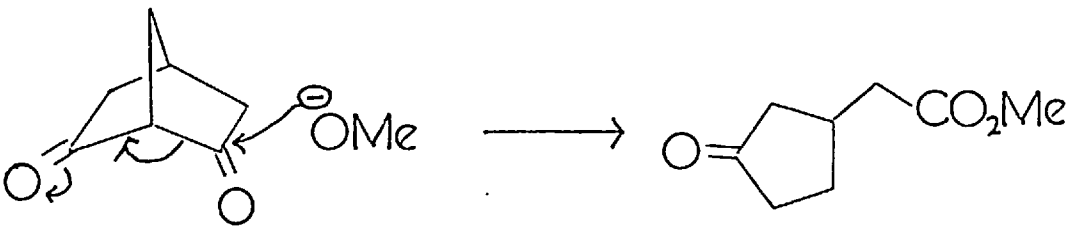


(60)

Acetylation gave the corresponding diacetate derivative (58) which GLC showed to contain a small amount of another compound, however poor separation of the peaks prevented a quantitative estimation. The symmetry of the p.m.r. spectrum of (58) strongly supported the 2:5 diacetate structure rather than the 2,6 isomer (60). The bridgehead protons appeared at τ 7·6 (width $\frac{1}{2}$ height 8 Hz) whereas in (60) the two bridgehead protons would be expected to show different chemical shifts.

Oxidation of the diol (57) with Jones Reagent gave a single crystalline product which was assigned the dione structure (59). The dione was characterised by an accurate mass measurement, had the same melting point (142°C) and a comparable infra-red spectrum to that reported for bicyclo-(2,2,1) - heptane - 2,5 - dione by Meinwald[9].

The dione (59) was stirred with a solution of sodium methoxide - methanol for 24 hours. The quantitative recovery of the dione from the reaction further supported the assignment of the 2,5 disubstitution since the β -diketone system of the 2,6 isomer (60) might be expected to react by fission one of the rings:-

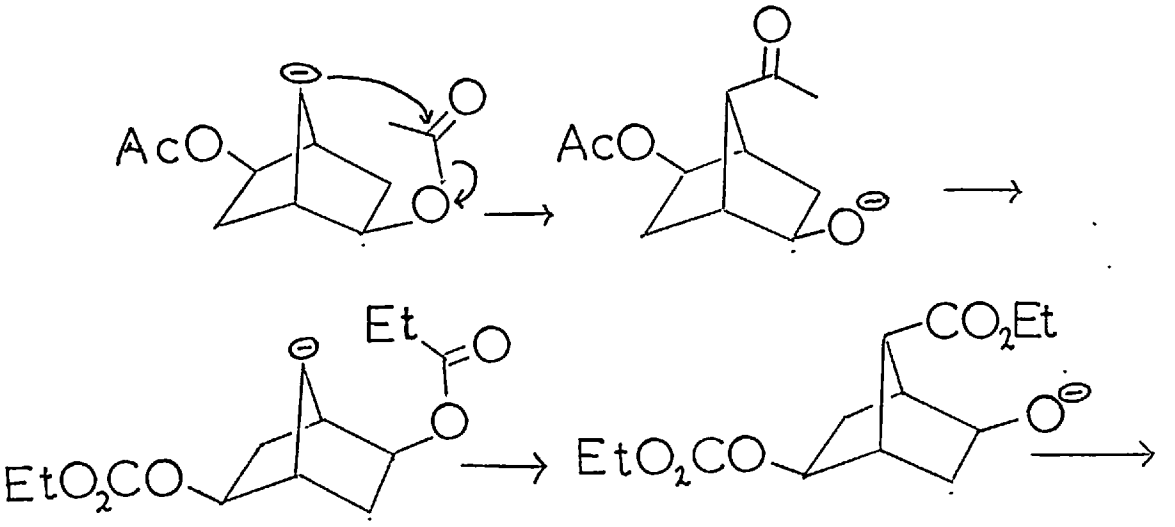


(61)

Some reactions of the bromodiol (41) and derivatives.

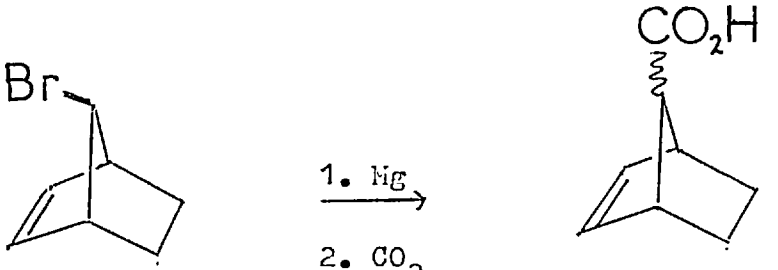
In a later section attempts to prepare a 7 - alkyl norbornane skeleton are discussed. The first attempt to prepare such compounds was by reducing the diacetate (54) and the dicarbonate esters (55) with lithium-ammonia. It was hoped that during reduction migration of a group to C_7 might

occur, as shown below :-



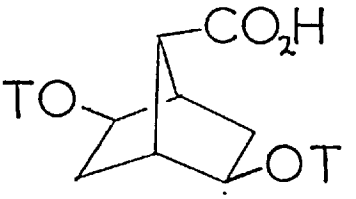
In both cases the only product obtained was the diol (57) which was acetylated and shown by infra-red, p.m.r. spectra to be identical to authentic diacetate (58).

The Grignard derivative of 7 - bromo - 2 - norbornene (62) had been made and successfully carbonated,[10] and so an attempt was made to prepare the Grignard reagent of the bis ether (56).



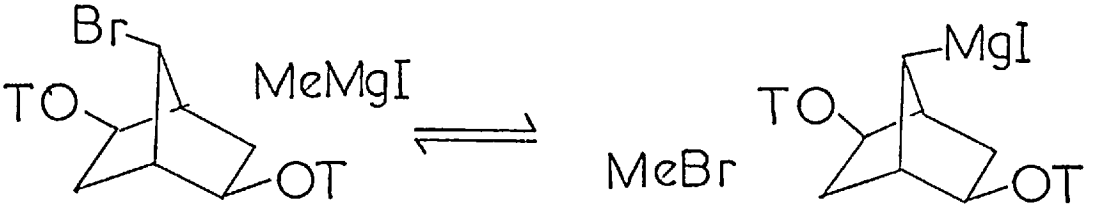
(62)

However all attempts to prepare the Grignard reagent resulted in a good recovery of the starting material, and no acid (63) was detected after carbonation of the reaction mixture.



(63)

An 'exchange reaction' was tried, by first preparing methyl magnesium iodide and adding the ether (56) :-



In principle the left to right reaction should be favoured since the norbornane Grignard is the more stable. The geometry of the bicyclic system imposes a hybridisation on C_7 nearer S + p^3 than Sp^3, which, allowing for the bonds being those concerned in the two C-C and 1 C-H bonds, means that the formal negative charge on the carbon atom of

a Grignard reagent is located in a orbital with a large amount of 's' character, which can best stabilise the charge.

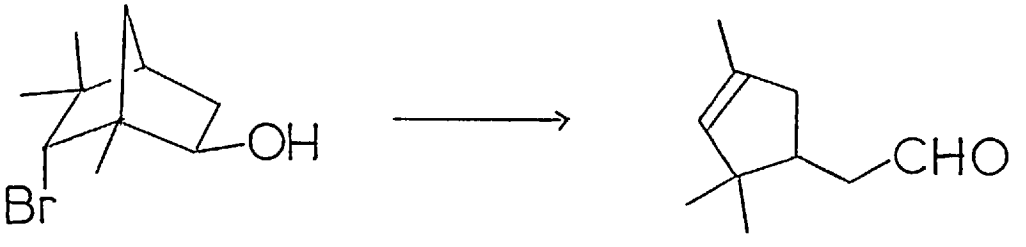
However, refluxing the bromo ether (56) with methyl magnesium iodide in both THF and diethyl ether, and carbonation of the reaction mixture yielded only the starting material in good yield.

Some attempts to ring open by dehydrobromination

The instability of the bromodiol (53) to sodium hydroxide suggested that more controlled reaction conditions might effect dehydrobromination with concomitant ring opening.

Treatment of the bromodiol (53) with 1 equivalent of aqueous sodium hydroxide at room temperature again gave a mixture of products derived from a complete breakdown of the bromodiol. Surprisingly the bromodiol proved stable to potassium hydroxide in t - butanol, and was recovered in high yield.

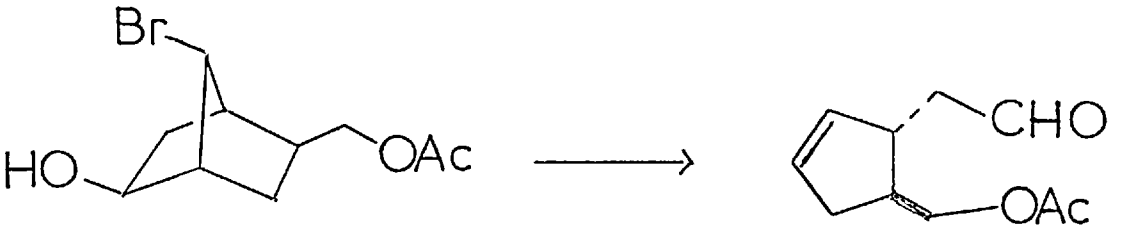
The desired ring opening had been carried out on a camphane derivative [11] using silver acetate in acetic acid at 80°C.



However the bromhydrin (42) was not affected by these reaction conditions and was recovered in high yield. It is possible that reaction did not occur because of the 'cis' relationship of the bromine and hydroxyl groups.

In a basic medium, silver perchlorate in a solution of sodium methoxide in methanol, the bromhydrin (42) was shown by TLC to undergo complete reaction.

The crude reaction mixture was treated with diazomethane to esterify any acids formed by any silver ion oxidations A p.m.r. spectrum showed that the required cyclopentene (52)



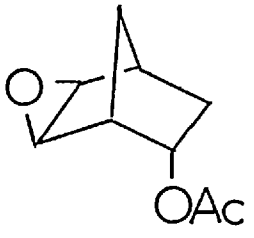
(42) (52)

had not been formed, and indicated the presence of methoxy groups in the product. The reaction was not investigated further.

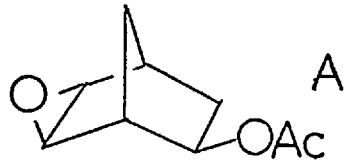
Some attempts to establish the structure of the hydroxy acid(29).

Initial experiments were concerned with the conversion of the acid (29) into a compound related to the dione (59).

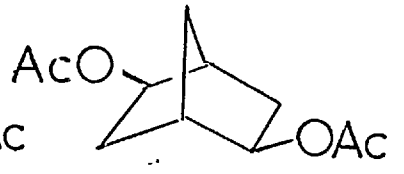
As a first step the four isomeric diacetates (65cdef) were prepared from the norbornenyl acetates (8ab) via the epoxides (65ab) as described previously for the epoxide (30). However all attempts to separate the four isomers on GLC failed.



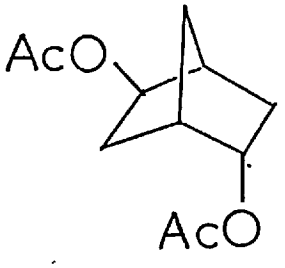
(65a)



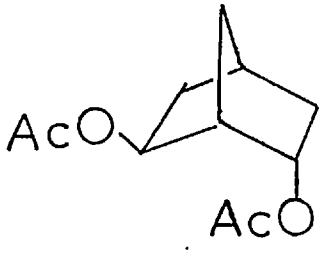
(65b)



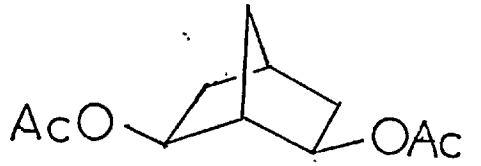
(65c)



(65d)

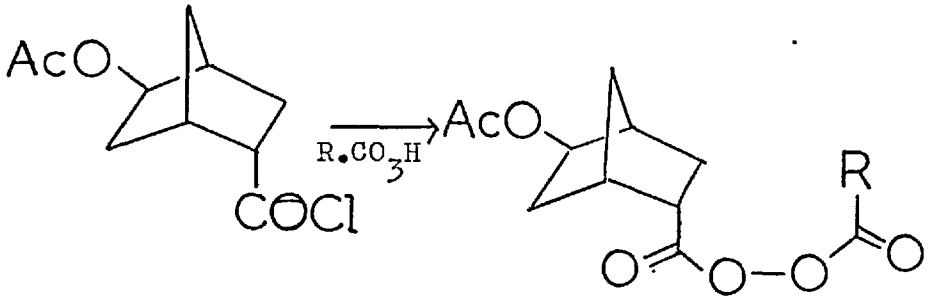


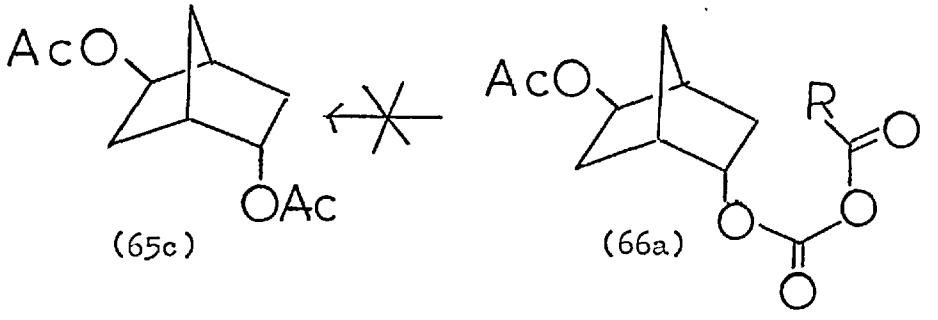
(65e)



(65f)

Next the hydroxy acid (29) was converted into the acid chloride (66), which was treated with m- chloroperbenzoic acid as described by Denney[12] for the carboxy inversion reaction:-



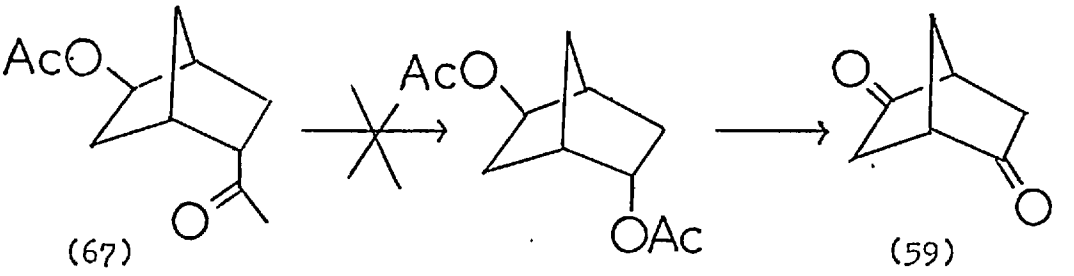


(65c) (66a)

Treatment of the reaction mixture with alkali to saponify any mixed anhydride (66a) followed by acetylation of the neutral product gave a low yield (<10%) of an acetate whose p.m.r. spectrum was not consistent with the structure of any of the required diacetates (65 cdef).

This approach was abandoned and the hydroxy acid (29) was converted into the ketone(67) in low yield by reaction with methyl lithium. The ketone was treated with pertrifluoroacetic acid in buffered methylene chloride as described by Emmons[13] for the Baeyer- Villager oxidation of methylketones. TLC showed the presence of several compounds. The crude mixture was reduced with LAH and then oxidised with Jones' reagent.

TLC showed again several products, none of which was the dione(59) as shown by reference to an authentic sample.

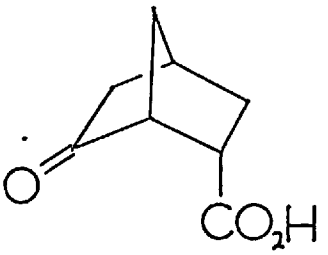


(67) (59)

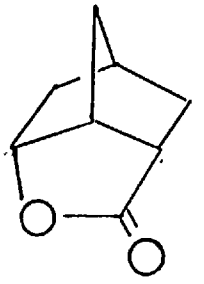
A more successful approach was found which involved reduction of the anions of norbornane keto acids. Beckmann[14,15] had shown that endo-6-keto norbornane- 2 -carboxylic acid(68) could be reduced, as its anion, with sodium borohydride in methanol, to give the lactone (69) as the only isolable product. The intermediate hydroxy acid (70) was shown to be unstable with respect to the lactone(69). The physical and spectral data for both (68) and (69) are available and provided useful reference data.

Oxidation of the hydroxy acid (29) with chromium trioxide gave smoothly the keto acid(71), which was reduced with sodium borohydride as described[14,15]. The product did not have the spectral data reported for the lactone(69). Its infra-red spectrum showed a peak at 1705 cm^{-1}, cf. lactone(69) 1779 cm^{-1}. Traylor[16] reported the p.m.r. data of the lactone(69) in a later publication. The "quartet" at τ6.31 was absent in the spectrum of the reduced keto acid (71).

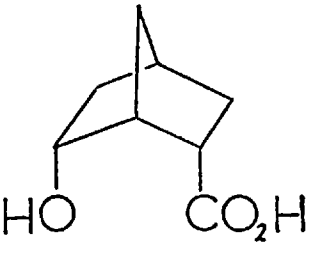
On this basis the hydroxy acid obtained from borohydride reduction was tentatively assigned structure (72)



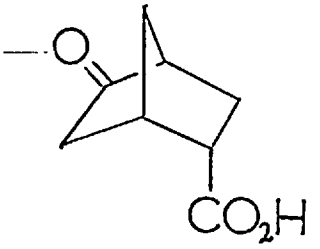
(68)



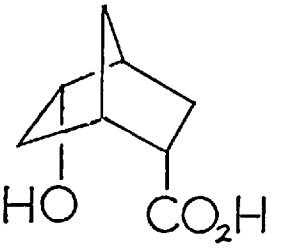
(69)



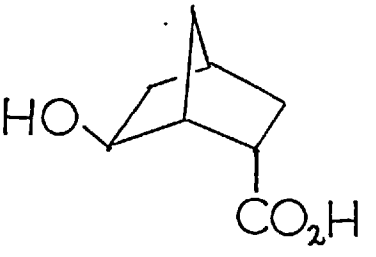
(70)



(71)



(72)



(73)

These results strongly indicate that the hydroxy acid(29) is indeed the 2,5 isomer as described. The argument for this assignment is dependant upon the acceptance of the following assumptions, since the acid(29) has not been correlated with a known compound.

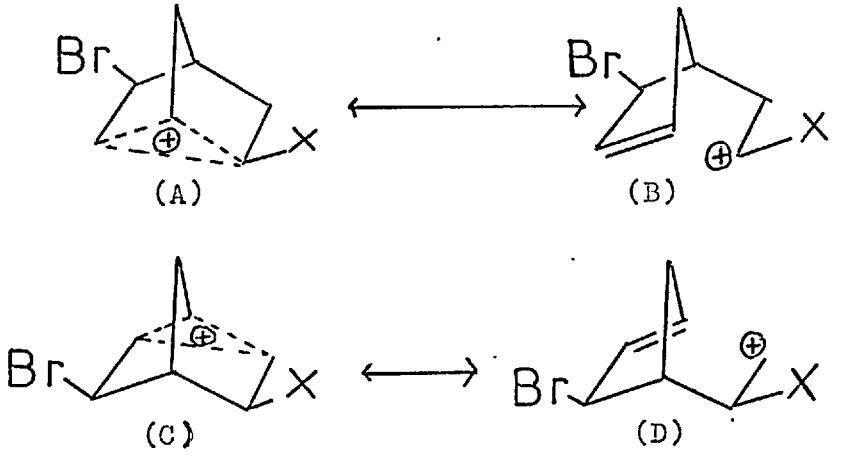
(i) Borohydride reduction of (71) does give the di-endo hydroxy acid (72). Slight evidence for this comes from the p.m.r. spectrum of (72) which differs from that of its isomer (29) in that the exo- methine carbinol proton (τ 5.9) is 0.3 ppm lower field than that shown for the endo- methine carbinol proton in (29).

(ii) The structures (29,73) are the only possibilities for the hydroxy acid derived from the NBS addition, reduction sequence, on the basis of the previous correlation experiments.

Summary and conclusion.

The skeletal rearrangement which occurs when a 5-substituted-2-norbornene reacts with a bromonium ion has been shown to be a highly regioselective process. The evidence presented strongly suggests that the major 1,3- adducts formed in the compounds studied are those in which the bond adjacent to the carbon bearing substituent does not move (Path 1, page 86).

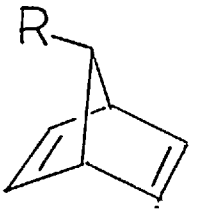
If one can dismiss the possibility of 1,2- proton transfer occurring after rearrangement and before solvation some attempt should be made to rationalise the preferred migration of the 1,6- bond in terms of its electron density as compared to the 4,5- bond. For electron-withdrawing substituents (X= OH, CO_2R) this is reasonable because X will tend to destabilise the non-classical structures (A,B) in favour of (C,D) in both <u>exo</u>- and <u>endo</u>- configurations.

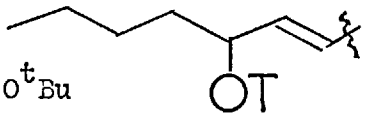


For the cases (X= CH_2OAc) this theory is not so attractive, and others would have to be considered. Structural features of the substituents as well as solvent effects could be major factors, although the balance of all these factors has yet to be worked out.

Attempted preparation of some 7 - alkyl norbornadienes

The title compounds were considered to be useful precursors for the synthesis of the prostaglandin skeleton. The preparation of the allylic ether (74) was the ultimate target since one of the required side chains has already been introduced.



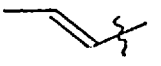
(74) R = 

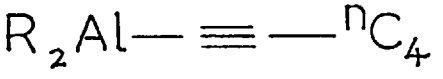
(75) R = O^{t}Bu

(76) R = Me

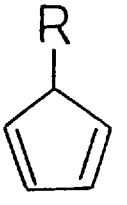
(77) R = Ph

(78) R = n- C_7H_{13}

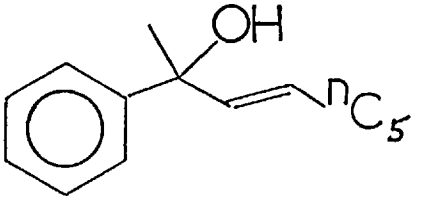
(79) R = n- C_5 



(80)



(81)



(82)

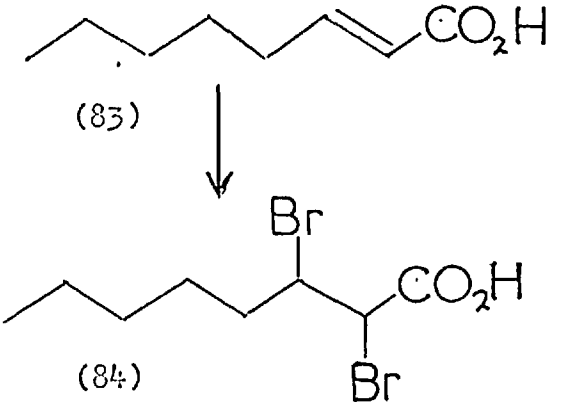
The preparation of substituted norbornadienes by the method used to prepare norbornadiene itself (the addition of acetylene to cyclopentadiene) was not attempted, since a mixture of isomers would be produced due to isomerisation of the required alkyl cyclopentadiene (81) prior to reaction.

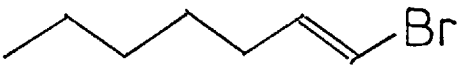
Story[17] has reported the preparation of the methyl- and phenyl- norbornadienes (76,77) from the butoxy ether (75). In this procedure the Grignard reagent PhMgI, MeMgI, was prepared in ether and the solvent replaced with benzene. The ether (75) is refluxed with the Grignard reagent in the hydrocarbon solvent to give the product in high yield.

This method was used to try and prepare the norbornadiene (79) from the ether (75) and a vinyl Grignard (from 85)

The ether (75) was prepared by the method described[17] and repetition of the preparation of the phenyl derivative (77)[17] gave the product in high yield

1- heptenyl - 1 - bromide (85) was prepared via the α/β - dibromoacid (84) as described in the literature[18].



(84) ⟶  (85)

The preparation of the Grignard reagent from (85) necessitated the use of THF instead of diethyl ether, the solvent was easily replaced by benzene as in the original procedure. However, on work up most of the ether (75) was recovered. The same result was obtained using toluene as the hydrocarbon solvent whilst refluxing xylene proved to be too vigorous conditions and led to a complete destruction of the reactants.

P.m.r. spectra of the crude reaction mixtures from these experiments showed that no vinyl halide was present, and assuming satisfactory formation of the Grignard, the failure to prepare the required compound (79) would be due to any of the following factors :-

(i) <u>The use of THF to prepare the vinyl Grignard</u>,

No evidence is available on the mechanism of the reaction

and it is possible that the reaction requires some diethyl ether to remain co-ordinated to the magnesium after the change of solvent.

This possibility was partially disproved by the preparation of the 7- phenyl compound (77), having first made the Grignard in THF.

(ii) Steric effects,

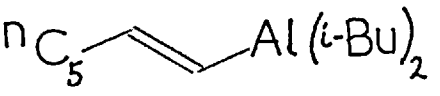
The failure of the reaction could be due to steric effects imposed by the length of the carbon chain in the Grignard. However, this possibility was eliminated by the successful preparation of the hydrocarbon (78) from the corresponding 'saturated' Grignard n- heptyl magnesium bromide.

(iii) Stability of the vinyl Grignard to the reaction conditions,

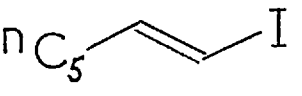
The Grignard reagent of (85) was prepared in THF and refluxed for the same time as is required to change the solvent in the reaction. Acetophenone was added to react with any Grignard present. On work up, no alcohol (82) was detected and the ketone was recovered in high yield. This result leads us to question the stability of the Grignard reagent under these conditions.

Hutton[19] has recently shown that the ether (75) does

not react with acetylenic aluminium compounds of the type (80). The same result has been found with vinyl alanes. Compound (86) was prepared <u>in situ</u> from 1 - heptyne in toluene and diisobutyl aluminium hydride, and the ether added. After two days reflux in toluene a good yield of the ether (75) was recovered.



(86)



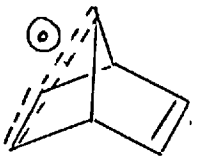
(87)

Treatment of the alane (86) with iodine in THF as described gave 1 - heptenyl - 1 - iodide[20] (87). This method of preparing vinyl halides proved to be far superior to that used to prepare the bromide (85).

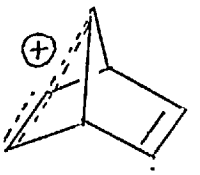
The Grignard prepared from the iodide (87) was refluxed with the ether (75) in benzene containing a little hexa methyl phosphoric triamide. On work up after 2 days a high yield of starting material was obtained.

The mechanism of the formation of the 7 - alkyl norbornadienes (76,77,78) is open to debate, however a strong possibility is a radical coupling mechanism. Support could be claimed from the method of preparation of the ether itself,

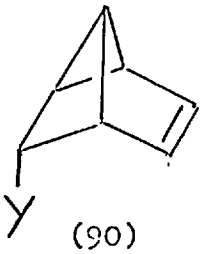
which is certainly a radical reaction involving t - butyl perbenzoate and Cu_2Br_2. The interesting feature of this reaction is the absence of any positional isomers of (75), and it is possible that the '7 - radical' is stabilised by a double bond in a non-classical structure as shown (88).



(88)



(89)



(90)

This non-classical structure has been proposed for the 7 - cation (89) by Story[17] to explain the unusual reduction product obtained (90, Y = H) on reducing 7 - chloro norbornadiene with LAH.

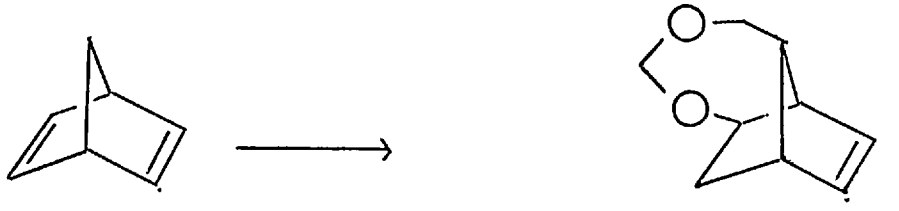
Kharasch[21] has shown that radical coupling of Grignard reagents can be effected using cobaltous bromide as catalyst.

The ether (75) was refluxed in benzene with the vinyl Grignard derived from (87) in the presence of $CoBr_2$ for 2 days. On work up, a p.m.r. spectrum showed that all the ether (75) had been consumed but indicated that several compounds had been produced none of which had the spectrum expected of the required hydrocarbon product. A Control

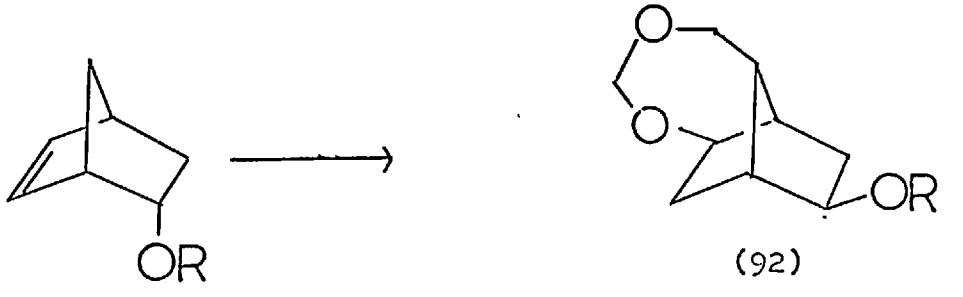
experiment showed that most of these products were obtained from the Grignard alone. The experiment was repeated at room temperature for 2 days but gave the ether (75) in good yield.

Investigation of a modified Prins reaction.

Several projected syntheses of the prostaglandins involve, as a first step, the conversion of norbornadiene or a norbornenol derivative into the compounds (91,92) by a Prins reaction invòlving 1,3- addition of the reagent.



(91)



(92)

98/100% formic acid was chosen as the acidic medium for our investigations.

Treatment of norbornadiene with a suspension of excess paraformaldehyde in formic acid gave on work up a mixture of formates, which were hydrolysed with aqueous sodium carbonate and acetylated. Preparative TLC of the acetates yielded two products.

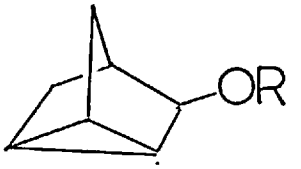
The minor product was shown by a p.m.r. spectrum and an accurate mass measurement to be nortricyclanol acetate (94) arising from an addition of formic acid to norbornadiene.

P.m.r. spectrum (94),

(i) τ 5.35, 1H

(ii) τ 7.95, 3H

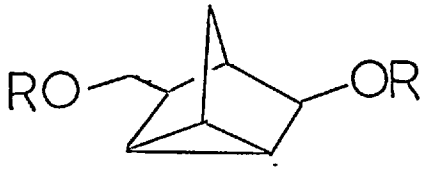
(iii) τ 8.0-9.0, 8H, envelope.



(93) R = CHO

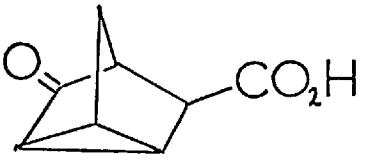
(94) R = Ac

The major product was shown by a p.m.r. spectrum and an accurate mass measurement to be the diacetate (95). (P.m.r. see experimental)



(95) R = Ac

(96) R = H



(97)

Oxidation of the alcohol (96) with Jones reagent gave a crystalline compound which analysis showed to have the empirical

formula corresponding to the keto acid (97).

Treatment of norbornadiene with hexanal in formic acid gave an unexpected product which a control experiment showed was not derived from hexanal alone. This product was not a formate, since it was not hydrolysed by sodium carbonate, and showed a carbonyl stretching frequency of 1725 cm^{-1} in its infra-red spectrum. A p.m.r. spectrum did not give any evidence for a structure, mass spectrometry indicated that the elemental formula corresponded to a combination of 1 molecule of hexanal, 1 molecule of norbornadiene, and 1 molecule of carbon monoxide. The product was not investigated further.

Treatment of norbornadiene with chloral in formic acid gave a mixture of two formates which were separable chromatographically.

The minor product was shown to be nortricyclanol formate (93) by a p.m.r. spectrum and mass measurement.

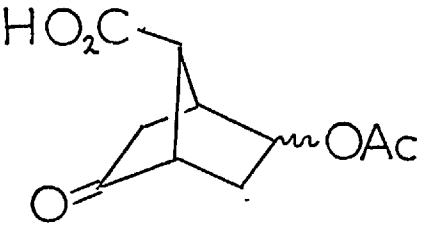
The major product which was also a formate was not completely characterised, a control experiment showed that it was derived from the solvent and norbornadiene during the removal of excess chloral and formic acid by distillation during work up.

Hydrolysis of the formate gave a crystalline alcohol which analysis showed to have the empirical formula required for a norbornane diol. This formate could be prepared by warming nortricyclanol formate (93) with formic acid. Oxidation of the alcohol with Jones reagent gave the corresponding ketone which by comparison of its spectral data with the spectra of authentic samples was shown not to be norbornane-1,2-dione, or the 2,5- dione (59).

Treatment of norbornadiene with chloral in formic acid avoiding heating during work up gave only nortricyclanol formate (93).

Treatment of the norbornenyl acetates (8ab) with paraformaldehyde in formic acid gave a mixture of formates which were not separable on TLC. The reaction mixture was treated with ammonia-methanol to selectively remove the formyl groups, and the resulting alcohols oxidised with Jones reagent.

Two fractions were obtained, a bicarbonate soluble fraction which was shown by mass spectrometry to have the formula required for the keto acid (98), or an isomer,



(98)

The neutral fraction was shown to contain a lactone, but no further information was obtained.

EXPERIMENTAL.

1. Preparation of cyclopentadiene.

Commercial dicyclopentadiene was passed through a column of alumina (grade I) to remove peroxides. The dimer was then distilled from iron powder through a 12 cm fractionating column, maintaining the still head thermometer at 40 - 45°C. The distillate was collected in a tared vessel cooled in cardice/acetone, and fitted with a calcium chloride guard tube. At intervals a few drops of distillate were allowed to evaporate from a ground glass surface, the absence of any substantial amount of residue indicating a low concentration of dimer.

2. Preparation of 2 - norbornene - 5 - acetate (8a,8b).

The acetate was prepared by the method of Alder and Rickert[2].

BPt 73 - 77°C (14mm)

P.m.r. spectrum indicated 70% endo, 30% exo isomer, as described in the discussion.

3. Preparation of the alcohols (9a,b).

The acetate (8a,b, 5g), was refluxed for 6 hours with sodium hydroxide (5g) in water (40 mls). The solution was salted out and extracted with ether. The ether was dried (sodium sulphate)

and evaporated under reduced pressure. Vacuum sublimation (30 mm) gave the alcohol mixture. (3·3g, 92%).

MPt 103-7°C.

4. Attempted equilibration of the alcohols (9a,b)

The method used was that described by Roberts[3]. The alcohols (250 mgs) yielded (70 mgs) of product after sublimation.

5. Hydroboration of norbornadiene.[4]

Norbornadiene (100 ml) and sodium-dry ether (200 ml) were mixed together and stirred at 0°C under nitrogen. A solution of diborane (40 ml of a 1·8 M solution) was added over 1 hour. The reaction mixture was allowed to rise to room temperature, excess norbornadiene and ether were evaporated under reduced pressure to yield a glue-like residue of the alkyl boron complex. The residue was dissolved in ether (250 mls), 3N caustic soda solution (28 mls) and 30% hydrogen peroxide solution (28 mls) were added with stirring maintaining the temperature between 20°C and 40°C. The solution was stirred vigorously for 1 hour. The ethereal layer was dried (sodium sulphate) and evaporated to give the product (20g)

GLC, 3^1 4% PEG-A column 92% exo isomer (9b)

8% endo isomer (9a)

6. Preparation of the aldehyde (10a,b).

The method used was that described by Alder and Stein.[5] Distillation gave the aldehyde as a mixture of isomers, BPt 70-72°C (20 mm).

7. Preparation of the ester (11a,b).

The ester was prepared by the method of Roberts[6]

BPt 63-64°C (5·2 mm).

GLC on a 2 metre 13% carbowax column at 80°C shows the isomers present in a ratio exo:endo of approximately 1:3.

8. Equilibration of the esters (11a,b).

The esters (11a,b, 2·5g,) were refluxed with a solution of sodium methoxide (300 mgs sodium) in methanol (16 mls). At ½ hour intervals small aliquots of the mixture were removed, acidified (dilute sulphuric acid) and the methanol evaporated. The residue was dissolved in ether, which was dried (sodium sulphate), and evaporated under reduced pressure.

GLC under the conditions used in experiment 7 showed an equilibrium value for the isomer ratio to have been reached after 2 hours :-

Exo : endo 3:2

9. Preparation of the acids (12a, 12b).

The acid mixture (12a,b) was prepared by the method of Diels and Alder[7].

BPt 136 - 8°C. (22 mm).

Treatment of the acid mixture (8g) with iodine solution in a buffered base using the method of Roberts[6] gave the crystalline exo acid (12b) MPt 43-5°C (1·8g) and the iodolactone (13), MPt 58-9°C, (8·6g), with the following p.m.r. spectrum:-

(i) τ 4·92, 1H $W_{\frac{1}{2}}$ = 8 Hz, doublet, proton adjacent to the iodine atom,

(ii) τ 6·17, 1H $W_{\frac{1}{2}}$ = 4 Hz, doublet, proton adjacent to the oxygen atom,

(iii) τ 6·88, 1H $W_{\frac{1}{2}}$ = 11 Hz multiplet, proton adjacent to the carbonyl function,

(iv) τ 7·1 - 9·0, 6H envelope.

The exo acid (12b) was esterified with diazomethane, GLC under the conditions used in experiment 7. showed the acid to be free of endo isomer.

The iodolactone (7·6g) was refluxed with zinc dust (6g) in 85% ethanol (50 mls) for 12 hours. The excess zinc was filtered off and the bulk of the solvent removed under reduced pressure. Water (15 mls) was added and the reaction mixture extracted with ether with salting out. The ether was dried

(sodium sulphate) and evaporated to give the endo acid (12a) which crystallised on standing (3·3g).

A portion esterified with diazomethane was shown by GLC to contain no exo isomer.

10. Preparation of the alcohol (14a)

The endo acid (12a), (1·3g MW = 138), in ether (10 mls) was added to a slurry of lithium aluminium hydride, 1·2g MW = 38, in ether (20 mls). The mixture was refluxed for 2 hours and excess reagent destroyed by the dropwise addition of saturated sodium sulphate solution. The ether was decanted from the granular residue and evaporated to yield the endo alcohol (1·1g).

11. Preparation of the alcohol (14b).

The same method was used as in experiment 10.

The exo acid (840 mgs) was reduced with lithium aluminium hydride (500 mgs) to yield the alcohol (706 mgs).

12. Preparation of the endo acetate (15a).

The alcohol (14a, 815 mgs, MW = 134) was treated with excess acetic anhydride (2g, MW = 102) and pyridine (2g) and the mixture allowed to stand for 12 hours. Ether (50 ml) was added

and the ethereal solution washed with dilute hydrochloric acid, sodium carbonate solution, water and saturated brine. The ether was dried and evaporated under reduced pressure to give the endo acetate (1·07g).

13. Preparation of the exo acetate (15b).

The procedure used was as described in experiment 12. above. The exo alcohol (14b, 580 mgs) gave the corresponding exo acetate (735 mgs).

14. Preparation of the bromolactone (16).

The endo acid, 12a, (320 mgs MW = 138) was dissolved in aqueous acetone and cooled to 0°C. NBS (420 mgs, MW = 178) was added in small portions over 1 hour and the solution stirred for 10 hours. The bulk of the solvent was removed under reduced pressure on a warm water bath and the residue extracted with ether. The ether was washed with 2N sodium hydroxide, water and saturated brine ; and dried (sodium sulphate).

Evaporation of the ether gave the bromolactone as a colourless oil (390 mgs).

TLC silica - chloroform/ethyl acetate 1 spot.

Infra-red spectrum ν max (liq.film) 1780, 1170, 1012 cm^{-1}.

P.m.r. spectrum :-

(i) τ 5·05, 1H doublet, J = 5 Hz, proton adjacent to the bromine atom.

(ii) τ 6·14, 1H doublet, J = 2·5 Hz, proton adjacent to the oxygen atom.

(iii) τ 6·73, 1H multiplet proton adjacent to the carbonyl function.

(iv) τ 7·0 - 9·0, 6H envelope.

15. Reduction of the bromolactone (16).

The bromolactone (410 mgs) was reduced with zinc (500 mgs) in 85% ethanol as described in experiment 9 for the iodolactone, to give endo- 2 - norbornene - 5 - carboxylic acid (110 mgs).

16. Preparation of the bromolactol (17).

The aldehydes (10a,b, (640 mgs MW = 122) were treated with NBS (965 mgs MW = 178) as described in experiment (14). Work up gave a semi-solid, (2 spots TLC silica - chloroform/ethyl acetate) which was recrystallised from benzene - pet.ether) to give the bromolactol (320 mgs).

MPt 96-98°C.

Infra-red, ν max ($CHCl_3$) 3550, 3400, 1715, 1685 cm^{-1}.

Analysis, found C = 44·2%, H = 4·9%

$C_8H_{11}O_2Br$ requires C = 43·8%, H = 5·0%

Accurate mass, $M^{\cdot+}$ calculated 217·993965

$M^{\cdot+}$ found 217·994293

17. Reduction of the bromolactol (17)

The bromolactol (400 mgs) was reduced with zinc (300 mgs) as described in experiment 9 to yield the endo aldehyde (10a) (146 mgs).

18. Oxidation of the bromolactol (17).

The bromolactol (283 mgs MW = 219) was dissolved in acetone (20 mls) and the solution cooled to 0°C. 6N chromic acid (from chromium trioxide (10g), conc. sulphuric acid (16g), water (50 mls)) was added dropwise until a slight excess of reagent was present. The solution was stirred for 2 hours. The presence of excess chromic acid was detected with starch-potassium iodide paper. Methanol (0·4 ml) was added and the solution stirred for 15 minutes. Anhydrous potassium carbonate (1g) was added and the solution stirred for a further 1 hour. The solution was filtered, and evaporated under reduced pressure to yield pure bromolactone (210 mgs).

19. Preparation of the bromoether (18)

The endo alcohol 14a, (500 mgs, MW = 124) was treated with NBS (720 mgs, 1·1 equivalent, MW = 178) as described in

experiment 14 to give the bromoether (510 mgs).

TLC silica - chloroform (1), ethyl acetate (4) 1 spot.

P.m.r. spectrum :-

(i) τ 5·45, 1H distorted doublet J = 5 Hz, proton adjacent to the bromine.

(ii) τ 6·22, 3H multiplet, protons adjacent to the oxygen atoms.

(iii) τ 7·0 - 9·0, 7H envelope.

20. Reduction of the bromoether (18)

The bromoether (150 mgs) was reduced with zinc (250 mgs) in 85% ethanol (6 mls) as described in experiment 9 to give the endo alcohol, 14a, (80 mgs)

21. Preparation of the bromhydrin (19)

The endo ester 11a, (800 mgs, MW = 152) was treated with NBS (960 mgs, MW = 178, 1 equivalent) as described in experiment 14 to yield a crude product (900 mgs)

Preparative TLC, silica - chloroform gave the bromolactone (16), (205 mgs) ; and the bromhydrin (19) (430 mgs) as an oil.

3:5 dinitrobenzoate derivative of (19), MPt 162-4°C

Analysis $C_{15}H_{15}N_2O_6Br$ requires C = 43·4%, H = 3·4%, N = 6·4% ; found C = 43·3%, H = 3·5%, N = 6·7%

P.m.r. spectrum of (19) :-

(i) τ 4·5, exchanges with D_2O, hydroxyl proton.

(ii) τ 5·7 - 6·2, 2H complex signal, protons adjacent to bromine and hydroxyl functions.

(iii) τ 6·3, 3H singlet, methyl ester.

(iv) τ 7·1 - 8·8, 7H envelope.

22. Reduction of the bromhydrin (19).

The bromhydrin 19, 540 mgs was reduced with zinc (1·5g) in 85% ethanol (20 mls) as described in experiment 9 to give the hydroxy ester (20) (295 mgs)

Acetate derivative (21) (experiment 12)

P.m.r. spectrum ; acetate τ 7·98 (7·96), ester τ 6·3 (6·28).

23. Preparation of the bromhydrin (24)

The exo ester 11b, (1·29g) was treated with NBS (1·6g) as described in experiment 14 to give the bromhydrin (2·02g)

TLC silica - chloroform - ethyl acetate

3:5 - dinitrobenzoate derivative, MPt 165-8°C

Analysis, $C_{15}H_{15}N_2O_6Br$ requires C = 43·4%, H = 3·4%, N = 6·4% ; found C = 43·3%, H = 3·3%, N = 6·6%

Acetate derivative (experiment 12) (25),

P.m.r. spectrum of (25)

(i) τ 5·35, 1H 'distorted triplet', proton adjacent to the acetoxy group.

(ii) τ 6·05, 1H, proton adjacent to the bromine

(iii) τ 6·3 (6·32), 3H singlet, methyl ester

(iv) τ 7·0 - 8·8, 10H, ring protons and acetate.

Infra-red ν max (liquid film) 1735 (broad), 1250 cm^{-1}

24. Reduction of the bromhydrin (24).

The bromhydrin (2g) was reduced with zinc (1g) in 85% ethanol (20 mls) as described in experiment 9 to give the hydroxy ester (27) (1·13g)

Acetate derivative (28) ;

P.m.r. spectrum of (28) :- acetate τ 7·98 (7·96),

ester τ 6·3 (6·28)

25. Equilibration of the isomers (21, 28)

The hydroxy ester (21, 200 mgs) was refluxed in sodium methoxide (from sodium (100 mgs)) and methanol (4 mls) for 3 hours. The solution was acidified (dil. hydrochloric acid) and the solvent evaporated. The residue was extracted with ether, and the ether dried (sodium sulphate) and evaporated under reduced pressure to yield the product.

The isomer (28) was similarly equilibrated.

The equilibrated isomers were acetylated as in experiment 12.

26. Preparation of the acid (26).

The exo acid, 12b, (312 mgs, MW = 138) was dissolved in aqueous acetone (40 mls) and cooled to 0°C. NBS (410 mgs, MW = 178) was added in small portions and the solution stirred for 12 hours. The bulk of the solvent was removed under reduced pressure and the residue extracted with ether. The ethereal solution was extracted with aqueous sodium bicarbonate. The bicarbonate solution was acidified dropwise with concentrated hydrochloric acid to pH 1, salted out, and extracted with ether. The ether was dried (sodium sulphate) and evaporated under reduced pressure to yield the product as an oil (320 mgs).

27. Reduction of the acid (26).

The acid 26, (1·1g) was reduced with zinc (2g) as described in experiment 9 to yield the crude hydroxy acid (610 mgs) (29). The crude hydroxy acid was recrystallised from nitromethane, MPt 101-4°C.

(Analysis $C_8H_{12}O_3$ requires C = 61·5%, H = 7·7%

Found C = 61·6%, H = 7·5%.)

TLC of crude reaction product, silica - benzene (20), ether (10), formic acid (5) shows two compounds;

Major isomer (440 mgs), partially formylated acid (29)

P.m.r. spectrum ;

(i) τ 1·9, formate proton.

(ii) τ 2·3, acid and hydroxyl protons

(iii) τ 5·25, 6·2, 1H total, protons adjacent to formate and hydroxyl groups respectively.

(iv) τ 7·0 - 9·0, 9H envelope.

Minor isomer, p.m.r. spectrum ;

(i) τ 3·8, 2H multiplet, vinyl protons

(ii) τ 6·95, 2H multiplet,

(iii) τ 7·5 - 9·3, 6H envelope, D_2O exchange under the envelope.

28. General procedure for epoxidation.

The olefin (1 equivalent) was dissolved in methylene chloride (ca. 300 mgs olefin to 25 mls solvent) and cooled to $0^{\circ}C$. M - chloroperbenzoic acid (1·1 equivalents, calculated for peracid content of reagent) was added in small portions over 30 minutes with stirring. The solution was stirred for 3 hours, then checked for the presence of excess peracid with starch-potassium iodide paper.

The solution was then shaken with aqueous sodium metabisulphite until the organic layer gave a negative peracid

test. The methylene chloride was washed with sodium bicarbonate solution, dried (sodium sulphate) and evaporated under reduced pressure to yield the product (average yield ca 90%).

a) The exo acetate (15b), (217 mgs), gave the corresponding epoxide (30), (205 mgs).

GLC, 3^1 4% PEG - A column, 130°C, 1 peak

P.m.r. spectrum (30),

(i) τ 6·0 (1H), 6·13 (1H), methylene protons adjacent to the acetate group.

(ii) τ 6·9 (2H), singlet, protons attached to the epoxide.

(iii) τ 7·5 - 9·3, 10H, acetate (7·93) and other protons.

b) The endo acetate (15a), (252 mgs) gave the corresponding epoxide (34), (254 mgs).

GLC 3^1 4% PEG - A column, 130°C, 1 peak.

P.m.r. spectrum (34)

(i) τ 5·83 (1H), 5·95 (1H), methylene protons adjacent to the acetate.

(ii) τ 6·8, 2H multiplet, protons attached to the epoxide.

(iii) τ 7·3 - 9·4, (7H), envelope

(iv) τ 7·92, 3H, singlet, acetate group.

c) Epoxidation of the endo alcohol (14a), (184 mgs) gave the hydroxy ether (37), MPt 126-30°C, (164 mgs)

(Analysis $C_8H_{12}O_2$ requires C = 68·6%, H = 8·6% ; found C = 68·8%, H = 8·8%).

An analytical sample prepared by sublimation.

P.m.r. spectrum (37) ;

(i) τ 5·9 - 6·6, 5H, multiplet.

(ii) τ 7·2 - 9·2, 7H multiplet.

Acetate derivative (experiment 12) (38)

GLC, 3^1 4% PEG - A, 130°C. 1 peak.

M^+ 182·094299, (calculated 182·094292)

P.m.r. spectrum (38) ;

(i) τ 5·65, 1H, $W_{\frac{1}{2}}$ = 3Hz, proton adjacent to acetate

(ii) τ 5·8 - 6·4, 3H envelope, protons adjacent to oxygen atom

(iii) τ 7·2 - 9·1, 7H envelope, ring protons

(iv) τ 7·95, 3H singlet, acetate.

d) The endo acid (12a), (458 mgs) gave the hydroxy-lactone, (39), MPt 149-153°C, (440 mgs)

Analytical sample prepared by sublimation.

(Analysis $C_8H_{10}O_3$ requires C = 62·3%, H = 6·5% ;

found C = 62·7%, H = 6·6%).

Infra-red spectrum (39),

ν max ($CHCl_3$) 3410, 1775, 1010 cm^{-1}

Acetate derivative (experiment 12) (40)

MPt 76-78°C (sublimation provided analytical sample).

(Analysis $C_{10}H_{12}O_4$ requires C = 61·2%, H = 6·2% ;
found C = 60·8%, H = 6·2%.)

Infra-red spectrum (40) ;

ν max ($CHCl_3$) 1780, 1740, 1014 cm^{-1}.

P.m.r. spectrum (40)

(i) τ 5·4, 2H multiplet

(ii) τ 6·7, 1H multiplet

(iii) τ 7·2 - 9·0, ring protons (6H).

(iv) τ 7·95, 3H singlet

29. General procedure for reduction of the epoxides.

Lithium (5 fold excess) was cut into small pieces and stirred at 0°C (in a multinecked flask protected with a drying tube) with ethylamine (ca 25 mls to 200 mgs lithium) until a permanent blue colour was obtained. The epoxide, dissolved

in ether, was added dropwise. This often caused decolourising of the reaction mixture. The reaction was stirred until the blue colour returned (at least 4 hours). Ethanol was added dropwise to destroy any lithium amide and the reaction mixture allowed to stir at room temperature to evaporate the ethylamine. Water was added and acidified carefully with conc. hydrochloric acid. The solution was salted out and extracted with ether. The ether was dried (sodium sulphate) and evaporated to yield the product, general yield approximately 50%.

The crude products were acetylated as in experiment 12.

(a) The epoxide (30), (90 mgs), yielded (48 mgs) of product (31, 32) after acetylation.

GLC, 3^1 4% PEG - A, 140°C, 2 peaks.

P.m.r. of the mixture (31, 32)

(i) τ 5·35, 1H multiplet, methine acetoxy proton.

(ii) τ 6·1, 2H multiplet, methylene protons adjacent to the acetate group.

(iii) τ 7·5 - 9·2, ring protons

(iv) τ 7·92, 7·97, acetates.

(b) The epoxide (34), (240 mgs) yielded acetylated product (132 mgs), (35,36,38)

GLC, as (a), 3 peaks.

30. Preparation of the bromhydrin (42).

The endo acetate (1·07g, MW = 166) was reacted with NBS (1·21g, MW = 178) as described in experiment (14) to yield the bromhydrin (42), (1·35g)

TLC silica - chloroform/ethyl acetate, 1 spot.

3:5 - dinitro benzoate derivative ; MPt 137-8°C,

(Analysis $C_{17}H_{17}N_2O_8Br$ requires C = 44·7%, H = 3·7%, N = 6·1% ; found C = 45·0%, H = 3·8%, N = 6·5%.)

Acetate derivative (43),

Infra-red spectrum, ν max (liq.film). 1740, 1240, 1035 cm^{-1}.

P.m.r. spectrum (43),

(i) τ 5·2, 1H multiplet, methine carbinol acetate proton.

(ii) τ 5·8 - 6·2, 3H multiplet, proton adjacent to bromine, and methylene group adjacent to acetate.

(iii) τ 7·2 - 9·0, 7H envelope, ring protons.

(iv) τ 7·92, 6H, singlet, acetates.

31. Reduction of the bromhydrin (42).

The bromhydrin (1·35g) was reduced with zinc (3g) as described in experiment 9 to yield the crude product (44), (796 mgs)

3:5 - dinitrobenzoate derivative, MPt 106-7°C,

Analysis, $C_{17}H_{18}N_2O_8$ requires C = 54·0%, H = 4·8%, N = 7·4%; found C = 53·5%, H = 4·7%, N = 6·8%.

Acetate derivative (31), purified by TLC, silica - methylene chloride, 90% yield, lower R_F compound

Infra-red spectrum,

ν max (liquid film), 1740, 1240, 1035 cm^{-1}

P.m.r. spectrum (31),

(i) τ 5·35, 1H multiplet.

(ii) τ 6·1, 2H multiplet.

(iii) τ 7·5 - 9·2, 9H envelope.

(iv) τ 7·92, 7·97, 6H singlets.

GLC, as experiment 29(a), see discussion.

32. Oxidation of the hydroxy acetate (44)

The hydroxy acetate (44), 217 mgs was oxidised with Jones reagent as described in experiment 18 to yield the ketone (46), (184 mgs)

TLC silica, 1:1 chloroform-methylene chloride.

Infra-red spectrum,

ν max (liq.film) 1745 (broad), 1240, 1035 cm^{-1}

P.m.r. spectrum,

(i) τ 6·0, 2H multiplet

(ii) τ 7·4, 2H multiplet

(iii) τ 7·5 - 9·1, 7H envelope

(iv) τ 7·91, 7·93, 3H, singlets.

33. Preparation of the bromhydrin (50)

The exo acetate, (15b) (735 mgs), was treated with NBS (800 mgs) in aqueous acetone as described in experiment 14 to yield the bromhydrin (50), (988 mgs)

TLC silica - chloroform-ethyl acetate, 1 spot.

3,5 - dinitrobenzoate derivative, MPt 102-4°C

Analysis $C_{17}H_{17}N_2O_8Br$ requires C = 44·7%, H = 3·7%, N = 6·1% ; found C = 44·6%, H = 3·7%, N = 6·4%.

34. Reduction of the bromhydrin (50)

The bromhydrin (960 mgs) was reduced with zinc dust (2g) as described in experiment 9 to yield the crude product (642 mgs) (52).

Acetate derivative (35) , purified by TLC, silica - methylene chloride, 90% yield, lower R_F product.

Infra-red spectrum, ν max (liq.film) 1740, 1235, 1030 cm^{-1}.

P.m.r. spectrum (35)

(i) τ 5·5 1H multiplet

(ii) τ 6·05, 2H multiplet

(iii) τ 7·3 - 9·5, 9H envelope

(iv) τ 7·94, 7·98, 6H singlets.

GLC, as experiment 29(a); see discussion.

35. Reduction of the hydroxy-esters (20,27)

The hydroxy ester (27) (526 mgs, MW = 170) was added to a slurry of LAH (260 mgs MW = 38, excess) in ether (40 mls). The mixture was refluxed for 2 hours and excess reagent destroyed with saturated sodium sulphate solution. The ether was decanted and evaporated to yield the diol (488 mgs) which was acetylated, experiment 12.

The diacetate was purified by TLC - silica - methylene chloride.

Physical data, (see (35) expt. 34)

In a similar manner, the hydroxy ester (20) (1·6g) yielded the diol (810 mgs) which was acetylated and purified by TLC above.

Physical data, (see (31) experiment 31.)

36. Preparation of the bromodiol (53)

Norbornenol (9ab, 3·5g) was treated with NBS (6·5g) in aqueous acetone as described in experiment 14. The crystalline product was recrystallised from nitromethane. Yield 1·8g.

MPt. 163°C.

Analysis Found C = 40·34%, H = 5·27%

$C_7H_{11}BrO_2$ requires C = 40·6%, H = 5·36%.

P.m.r. spectrum ;

(i) τ 4·68, 2H broad, exchanges D_2O.

(ii) τ 5·47, 1H multiplet, proton adjacent to bromine

(iii) τ 6·2, 2H multiplet, methine carbinol protons

(iv) τ 7·3 - 8·6, 6H envelope.

Diacetate derivative (54) (procedure as in experiment 12)

Infra-red spectrum,

ν max. liquid film 1730, 1240 cm^{-1}

P.m.r. spectrum ;

(i) τ 5·3, 2H multiplet.

(ii) τ 5·75, 1H broad signal.

(iii) τ 7·2 - 8·5, 6H envelope.

(iv) τ 7·95, 6H singlet.

Bis - tetrahydropyranyl ether (56)

The bromodiol (1·5g) was stirred with dihydropyran (6 mls) and a drop of concentrated hydrochloric acid added. The mixture was warmed on a steam bath for 30 minutes, cooled and stirred with excess anhydrous potassium carbonate. After filtration, the excess dihydropyran was removed under reduced pressure to yield the bis - ether (1·2 g)

Dicarbonate ester (55)

Procedure as for the diacetate derivative.

Reagents,

Bromo diol (50 mgs)

Ethyl chloroformate (100 mgs)

Pyridine (100 mgs)

Yield 63 mgs.

M+ (calc) 352·034579, (observed) 352·032295

Infra-red spectrum,

ν max (liq.film) 1735, 1280, 1020 cm^{-1}

P.m.r. spectrum,

(i) τ 4·9 - 5·7, 3H multiplet

(ii) τ 5·47, 4H quartet, J = 7 Hz.

(iii) τ 6·7 - 8·9, 6H envelope

(iv) τ 8·4, 6H triplet, J = 7 Hz.

37. General procedure for lithium-ammonia reductions. (53,54,55).

The compound (ca 800 mgs) was added, as a solid or an ethereal solution to a ten fold excess of lithium in anhydrous liquid ammonia. The blue solution was stirred for 2 hours, and excess solid ammonium chloride added. The ammonia was allowed to evaporate, expelling the last traces by gentle heating on a steam bath, and the solid residue extracted with ether. The ethereal solution was washed with dilute acid, dried (Na_2SO_4) and evaporated under reduced pressure.

In a typical procedure,

bromodiol (920 mgs) reduced with lithium (100 mgs) in ammonia (60 mls) yields the diol (57) (290 mgs)

Diol (57)

MPt 177-181°C

Analysis found C = 65·8%, H = 9·0%

$C_7H_{12}O_2$ requires C = 65·7%, H = 9·3%

Diacetate (58) (experiment 12)

P.m.r. spectrum,

(i) τ 5·37, 2H, quadruplet, $W_{\frac{1}{2}}$ = 15 Hz

(ii) τ 7·6, 2H, bridgehead protons

(iii) τ 7·98, 6H, singlet,

(iv) τ 8·4, 6H multiplet.

38. Dione (59)

Procedure as experiment 18.

Diol (57) 80 mgs, yields the dione (59), 63 mgs, purified by vacuum sublimation, MPt 142°C.

TLC silica-chloroform - 1 spot.

(M+ calc = 124·052621, M+ found 124·052456)

Infra-red spectrum,

ν max (CCl_4) 1766 (shoulder 1735 cm^{-1}), 1410, 960 cm^{-1}.

39. Reaction of the dione (59) with sodium methoxide.

The dione (20 mgs) was stirred for 16 hrs with a solution of sodium methoxide (from sodium 5 mgs) in methanol 3 mls. The solution was acidified (conc HCl) and evaporated. The residue was extracted with ether, dried (Na_2SO_4) and evaporated to yield the starting material, as shown by TLC; infra-red, p.m.r. spectra.

40. Attempted Grignard preparations.

General procedure as cited in reference (10). see discussion.

a) The bis ether (56), 1·08g, was added to magnesium (1·5g) in ether, which had been activated by the reaction with a few drops of ethylene dibromide. The mixture was refluxed for 1 hour, and carbon dioxide passed through for 30 mins. Dilute hydrochloric acid was added, and the mixture shaken. The ethereal layer was dried, and evaporated to yield starting material (56) 860 mgs. (Repeated - adding solid cardice.)

b) Methyl magnesium iodide was prepared from methyl iodide (1g) and excess magnesium (1g) in ether (25 mls). The bis - ether (800 mgs) was added and the solution refluxed for 1 hour. Carbon dioxide was passed in for 30 minutes. Dilute hydrochloric acid was added dropwise to destroy excess reagent. The ethereal layer was dried (sodium sulphate) and evaporated to yield the bis ether. (Repeated - adding solid cardice.)

c) (b) was repeated using tetrahydrofuran as solvent.

41. Reaction of the bromodiol (53) with base.

The bromodiol (1 equivalent) was stirred for 16 hrs with 1 equivalent of base. The mixture was acidified with dilute hydrochloric acid and extracted with ether. The ether was dried (sodium sulphate) and evaporated under reduced pressure.

(i) Potassium hydroxide - butanol; - bromodiol (53) recovered

(ii) 3N sodium hydroxide - several products.

42. a) Reaction of the bromhydrin (42) with silver perchlorate/sodium methoxide in methanol.

The bromhydrin (560 mgs) was treated with a solution of silver perchlorate (600 mgs) in sodium methoxide (from 20 mgs sodium) in methanol (20 mls). The mixture was stirred for 48 hours, acidified with conc HCl, filtered, and the filtrate evaporated under reduced pressure. The residue was extracted with ether, dried ($MgSO_4$) and evaporated to yield the product (412 mgs), which was treated with ethereal diazomethane to esterify any acids produced.

b) Reaction of the bromhydrin (42) with silver acetate-acetic acid[11].

The bromhydrin (105 mgs) was treated with silver acetate (200 mgs) in glacial acetic acid (1·5 ml) as described in the reference cited. A 92% yield of starting material was obtained.

Preparation of the epoxides (65 a,b).

Treatment of 2- norbornene - 5 - acetate (8 ab) with m - chloroperbenzoic acid as described in experiment 28 gave the epoxides (65 a b). (ca 90%)

P.m.r. spectrum :-

(i) τ 4·9, 5·35, 1H

(ii) τ 6·5 - 9·3, 8H envelope.

(iii) τ 7·95 , 3H.

Reduction and acetylation of the epoxides (65 a,b)

Procedure as in experiment 29.
Epoxides (150 mgs) yield after acetylation the diacetates (65 c d e f). (53 mgs).

P.m.r. spectrum,

(i) τ 4·8 - 5·5, 2H

(ii) τ 7·2 - 9·3, 8H envelope.

(iii) τ 7·95, 6H singlet

Experimental procedure used for the attempted Denney conversion.

The hydroxy acid (29) 234 mgs, was stirred at room temperature for 16 hrs with acetic anhydride (350 mgs)

and pyridine (500 mgs). Ether was added, and the ether washed with dilute hydrochloric acid, dried (sodium sulphate). The ether and excess acetic anhydride, acetic acid were removed under reduced pressure to leave the acetate (243 mgs)

The acid acetate was heated at 50°C with excess thionyl chloride (700 mgs) and excess reagent removed under reduced pressure to leave the acid chloride (66) 220 mgs.

The acid chloride was treated with m - chloroperbenzoic acid as described by Denney[12]; after saponification with alkali, the residue was acetylated to give crude product in low yield (21 mgs).

Experimental procedure for attempted oxidation of the ketone (67)

The hydroxy acid (29), 1·24g in ether (10 mls) was treated at 0°C with three equivalents of methyl lithium. The solution was stirred for 2 hours and excess reagent destroyed with aqueous ammonium chloride. The ethereal layer was washed with sodium bicarbonate solution, dried (sodium sulphate) and evaporated under reduced pressure to give the crude product (880 mgs)

Preparative TLC, silica - chloroform/25% ethyl acetate. gave the hydroxy methyl ketone (13%) which was acetylated (67). Hydroxy methyl ketone, infra-red, max. 1710,3350 cm^{-1}. P.m.r. τ 6.23,1H;7.5-9.1,10H;7.95(7.92),3H,singlet.

The ketone (30 mgs) was treated with pertrifluoro acetic acid (1 equivalent) in methylene chloride (5 mls) containing sodium hydrogen phosphate (50 mgs) [13].

The solution was stirred 1 hour, washed with aqueous sodium metabisulphite, sodium carbonate, dried (sodium sulphate) and evaporated. Yield 26 mgs.

TLC silica - methylene chloride.

The residue was reduced and oxidised as described in experiments 10, 18.

TLC silica - chloroform.

The keto acid (68)

The hydroxy acid (29), 706 mgs, in acetone (15 mls) was oxidised with Jones reagent. The reaction was stirred for 2 hours and excess reagent destroyed by adding a few drops of methanol. The solvent was removed under reduced pressure and the residue extracted with ether. The ether was dried (sodium sulphate) and evaporated to give the product (430 mgs).

Reduction of the keto acid (68)

The keto acid (400 mgs) was dissolved in methanol (3 mls) containing sodium hydroxide (100 mgs). Sodium borohydride (100 mgs) was added slowly. After initial effervescence had

ceased the solution was heated on a water bath for 5 hours. The solvent was removed under reduced pressure and the residue treated with 4N sulphuric acid (4 mls). The aqueous phase was extracted with ether (6 x 10 mls) with salting out. The ether was dried (sodium sulphate), and evaporated to yield the product.

Preparation of 7 - t-Butoxy norbornadiene (75)

prepared as described [17] by Story.

BPt 70-72°C (14mm)

Attempted preparation of 7 - alkyl norbornadienes.

The procedure used was that described by Story[17], Cobalt bromide was dried at 110°C for 2 weeks prior to use and was present in 2 molar excess, based on concentration of Grignard.

Tetra hydro furan replaced diethyl ether in the procedure where necessary.

7 - Phenyl norbornadiene [17] (77)

Product isolated by preparative TLC, silica-benzene

P.m.r. spectrum

(i) τ 2·3 - 3·2, 7H, envelope.

(ii) τ 3·5, 2H, multiplet.

(iii) τ 4·3, 3H, multiplet.

7 - heptyl norbornadiene (78)

Procedure as described [17]

Heptyl bromide (900 mgs)

Magnesium (200 mgs)

7-t-butoxy norbornadiene (410 mgs)

Preparative TLC, silica - 85% 40/60 petrol / 15% benzene

yields the product ca 40%,

P.m.r. spectrum,

(i) τ 3·15, 3·4 ; 4H

(ii) τ 4·7 ; 3H

Reaction of 7 - t - butoxy norbornadiene with the vinyl alane (86)

Di-isobutyl aluminium hydride (3·4 mls of a 2·43 M solution in toluene) was added to 1-heptyne (790 mgs) under Argon to yield the vinyl alane as described[20]. 7-t-butoxy norbornadiene (665 mgs, 0·5 equiv) was added and the solution refluxed for 2 days. Excess reagent was carefully destroyed with ice cold 20% sulphuric acid, and the organic layer dried (sodium sulphate.). The toluene was distilled from the reaction mixture. Most of the starting material was recovered.

Preparation of 1 - heptenyl - 1 - bromide

The procedure was as cited in the references[18]

BPt 165 - 70°C (760 mm)

Preparation of 1 - heptenyl - 1 - iodide

Procedure as described in the references cited

BPt 70 - 5 (30 mm), decomposition.

Reaction of norbornadiene with paraformaldehyde - formic acid.

Norbornadiene (2·7g) was stirred with paraformaldehyde (5·4g) in 98/100% formic acid (80 mls) for 16 hrs. Ether (250 mls) was added and the ethereal solution washed with water (X 10), and with aqueous sodium carbonate. The ether was dried (sodium sulphate) and evaporated under reduced pressure to yield the crude formates (1·8g).

The formates (540 mgs) were shaken with 10% sodium carbonate for 12 hours and the mixture extracted with ether. The ether was dried (sodium sulphate) and evaporated under reduced pressure. The alcohols (210 mgs) were acetylated. (Expt. 12).

Preparative TLC yields the two products,

silica - 1:2, chloroform : methylene chloride.

crude acetates (120 mgs) give

Nortricyclyl acetate (15 mgs)

M+ (calc.) 152·083728, (observed) 152·083526.

P.m.r. spectrum,

(i) τ 5·35, 1H

(ii) τ 7·95, 3H.

(iii) τ 8·0 - 9·0, 8H envelope.

Diacetate (70 mgs)

M+ (calc) 224·104856, (observed) 224·103314

P.m.r. spectrum,

(i) τ 5·3, 1H

(ii) τ 6·0, 2H, 'triplet'

(iii) τ 7·95, 6H singlet

(iv) τ 7·7 - 9·0, 7H envelope.

Keto acid

The alcohols (1·4g) in acetone (20 mls) were oxidised with Jones reagent, the solution was stirred for 2 hours and excess reagent destroyed with a few drops of methanol. The solvent was evaporated under reduced pressure and the residue extracted with ether. The ether was dried (sodium sulphate) and evaporated to give a crystalline residue.

Recrystallised (benzene - 40/60 petrol)

Analysis found C = 62·9%, H = 5·2%

$C_8H_8O_3$ requires C = 63·1%, H = 5·3%.

Reaction of norbornenyl acetate with paraformaldehyde - formic acid.

Norbornenyl acetate (3·1g) was stirred with paraformaldehyde (3g) in 98/100% formic acid (40 mls). Ether was added, the

ethereal solution was washed with water (X 10), aqueous sodium carbonate, dried (sodium sulphate). The ether was evaporated to give the diformates (1·2g).

The diformates (1·2g) were treated '880' ammonia (2 equivalents) in methanol (5 mls) at 0°C for 2 hours. The methanol was evaporated and the residue extracted with ether. The ether was dried (sodium sulphate) and evaporated to yield the alcohols (750 mgs).

The alcohols (750 mgs) were oxidised with Jones reagent in acetone as described above for the keto acid. The ethereal solution was extracted with sodium bicarbonate, which was re-acidified, extracted with ether.

The ethereal solutions were dried (sodium sulphate) to yield a neutral fraction (100 mgs) and an acid fraction (110 mgs).

The neutral fraction was warmed with 2N. sodium hydroxide, acidified (conc. HCl) and ether extracted. The ether was dried (sodium sulphate), and evaporated to yield an acidic product (42 mgs).

Reaction of norbornadiene with hexanal

Norbornadiene (2·8g), hexanal (4·8g), 98/100% formic acid (20 mls) were shaken at room temperature for 2 days.

Excess solvent was distilled off at reduced pressure (ca. 20 mm) and ether (250 mls) added. The ether was washed with water, aqueous sodium carbonate, and dried (sodium sulphate). The ether was evaporated to give the crude product (5.8g).

Preparative TLC silica - 20% ethyl acetate - chloroform gives the product.

Infra-red spectrum,

ν max (liq film) 1725 cm^{-1}

P.m.r. spectrum,

(i) τ 2·0, 1H

(ii) τ 5·3, 1H

(iii) τ 7·5 - 9·5, 11H

The product (200 mgs) was shaken with aqueous sodium carbonate (10 ml) for 6 hours. The product was ether extracted, dried (sodium sulphate) and evaporated to yield the starting material (112 mgs) identified by its spectral data.

Reaction of norbornadiene with chloral - formic acid.

Norbornadiene (4g), chloral (distilled from conc. sulphuric acid) (8g) 98/100% formic acid were shaken for 2 days.

Excess chloral and formic acid were distilled off (0·1mm). The residue was treated with ether (250 mls), and the ethereal solution washed with water, aqueous sodium carbonate, dried (sodium sulphate) and evaporated to yield the crude product, 9·1g.

Infra-red ν max. (liq.film) 1725 cm^{-1}

Preparative TLC,

450 mgs crude product yield,

Nortricyclyl formate (103 mgs)

P.m.r. spectrum,

(i) τ 2·0, 1H

(ii) τ 5·3, 1H

(iii) τ 7·5 - 9·0, 8H

Major product (277 mgs)

P.m.r. spectrum,

(i) τ 2·0, 1H

(ii) τ 4·8 - 5·3, 1H

(iii) τ 7·2 - 9·4, 5H.

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