Synthetic and Rearrangement Studies in the Terpenoid Field.

THESIS

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by

Roy W. Mills

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ProQuest LLC.
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106 – 1346

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S U M M A R Y.

Section A.

Synthesis of (±)-trans-Chrysanthemic Acid and some Analogues.

(+)-trans-Chrysanthemic acid is the major acidic hydrolysis product of the pyrethrins, a group of six naturally occurring esters which exhibit important insecticidal properties. Its structure contains a cyclopropane ring bearing a gem-dimethyl grouping and a carboxylic acid function which is trans to an isobutenyl side-chain. Synthetic pyrethrins, often with improved insecticidal properties, are obtained by esterifying the appropriate alcohol with (+)-trans-chrysanthemic acid or a suitable analogue. A flexible and potentially commercial synthesis of this racemic acid is herein described, in which both isoprenoid "halves" of the monoterpenoid skeleton are essentially derived from the same starting material, 2-methylbut-3-yn-2-ol. Since this alcohol is effectively obtained by reaction of acetylene with acetone, this versatile synthesis is based upon inexpensive starting materials.

Treatment of readily derived 3-chloro-3-methylbut-1-yne with strong base in the presence of 3,3-dimethylallyl alcohol, afforded dimethylallenecarbene, which

reacted *in situ* with the double bond of the allylic alcohol to give 2-(2'-methylpropenylidene)-3,3-dimethylcyclopropanemethanol. This allenic cyclopropane contains the essential structural elements of the chrysanthemic acid skeleton, with however an additional double bond, and a primary hydroxyl group where a carboxylic acid function is required. Regioselective and stereoselective reduction of the cyclopropyl double bond was effected with sodium in liquid ammonia, producing a high yield of racemic chrysanthemyl alcohol of which over 75% was the required *trans* isomer. A variety of oxidizing conditions was investigated during attempts to convert chrysanthemyl alcohol to the acid, but many proved unsuccessful due to the sensitivity of the chrysanthemyl molecule to acidic conditions. The desired oxidation was, however, effected using chromium trioxide in pyridine, racemic chrysanthemic acid being obtained without loss of stereochemical integrity.

The synthesis was adapted for the production of chrysanthemic acid analogues. The use of 1-ethynylcyclohexyl chloride and 1-ethynylcyclopentyl chloride led to the expected acids, while oxidation of the intermediate allenic alcohols provided the first available synthesis of allenic derivatives.

Attempts to effect the carbene addition reaction on

3,3-dimethylacrylic acid and related compounds proved unsuccessful.

Section B.

Acid-catalysed Rearrangement of a Diterpenoid Epoxide.

Treatment of erythroxylol A epoxide, a naturally occurring tetracyclic diterpenoid of the beyerane series, with 95% formic acid, led to the formation of at least seventeen products. It was shown that these resulted from two distinct concentration dependent rearrangement pathways, one of which was analogous to the previously established hibaene epoxide rearrangement which produces compounds of the kaurane series. This route accounted for four of the identified products whose structures were elucidated both spectroscopically and chemically. Their interconvertibility was demonstrated by hydrolysis and dehydration experiments.

At higher concentrations of the epoxide in formic acid, the major product was an enediol monoformate which was shown spectroscopically and chemically to contain an allylic secondary alcohol grouping, probably in ring C. It was readily oxidized to a conjugated cyclohexenone, while reduction experiments demonstrated its close structural relationship to dihydroerythroxylol A, the fully-saturated parent compound of the starting epoxide.

A possible mechanism for its formation is suggested which could conceivably account for the remaining rearrangement products, some of which were isolated and assigned tentative structures.

Synthetic and Rearrangement Studies in the Terpenoid Field.

S E C T I O N A.

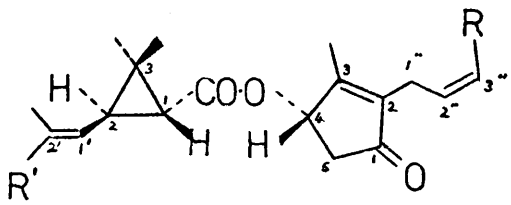
Synthesis of

(±)-*trans*-Chrysanthemic Acid.

Chemistry of the Pyrethrins.

Introduction. The flowers of Chrysanthemum cinerariaefolium, a herbaceous perennial belonging to the Compositae family, have been valued for their insecticidal properties since the early nineteenth century when their activity first became known in Eastern Europe[1,2]. They have since found considerable application in the control of insects affecting man[3,4], and interest in them has been revived recently due to restrictions on the use of chlorinated hydrocarbon insecticides. Commercial supplies were originally obtained from Dalmatia and Japan[5], but more recently Kenya has become the principal world source. Harvesting entails a considerable amount of hard labour[5], since maximum yields are obtained by gathering the flower when five rows of disc florets are open. After artificial drying and baling, the product is known commercially as "pyrethrum". The active insecticidal principles, the pyrethrins, occur mostly in the achenes of C. cinerariaefolium[6,7,8], and have the advantage of low mammalian toxicity and rapid "knock-down" properties which are valuable in dealing with flying insects[5]. So far, insects have been unable to develop resistance towards them.

The early investigation of the pyrethrins, much of it carried out by Japanese workers[9-12], was reviewed in 1923[13], and although it was shown that the active principles were esters, many of the other conclusions have since proved

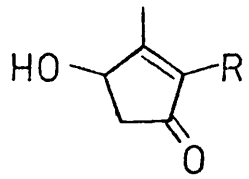


1	R= $-CH=CH_2$,	R'= $-CH_3$
2	R= $-CH=CH_2$,	R'= $-CO_2CH_3$
3	R=R' = $-CH_3$	
4	R= $-CH_3$,	R'= $-CO_2CH_3$
5	R= $-CH_2CH_3$,	R'= $-CH_3$
6	R= $-CH_2CH_3$,	R'= $-CO_2CH_3$

to be erroneous. The basic form of the structures was first elucidated by Staudinger and Ruzicka[14], whose extensive investigations were carried out between 1910 and 1916 but were not published until 1924. Since then, the subject has been reviewed by Harper in 1948[15], and again by Crombie and Elliott in 1961[5].

The pyrethrins have now been shown to comprise six active principles. Two of them, pyrethrin I (1) and pyrethrin II (2), were isolated and formulated, with later structural revision, during the early work of Staudinger and Ruzicka[14], while two more esters, cinerin I (3) and cinerin II (4), were discovered by La Forge and Barthell[16,17] some thirty years later. The remaining two pyrethroids, jasmolin I (5) and jasmolin II (6) remained undetected until the advent of a gas-liquid chromatographical method[18] for detection and identification of small quantities of pyrethroids. In 1966, Godin[19] found that the jasmolins were present as small percentages of total pyrethrins, (jasmolin I < 0·01%, jasmolin II < 4%), and assigned their structures on the basis of spectroscopic evidence. In spite of several claims[20, 21] for the isolation of other pyrethroids, these six are now considered to be the only active principles.

Pyrethrin I, cinerin I and jasmolin I, with a double bond and a cyclopropane ring capable of showing geometric

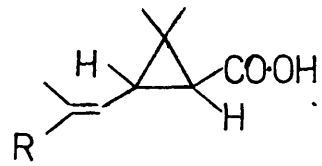


17

7 R= $-CH_2CH{=}^{c}CHCH{=}CH_2$

8 R= $-CH_2CH{=}^{c}CHCH_3$

9 R= $-CH_2CH{=}^{c}CHCH_2CH_3$



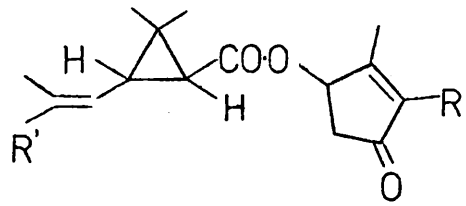
10 R= $-CH_3$ 11 R= $-CO_2H$

12 R= $-CO_2CH_3$

isomerism[5], are all one of sixteen possible stereoisomers. In pyrethrin II, cinerin II and jasmolin II, the presence of yet another double bond capable of geometric isomerism means that each natural ester is one of 32 possible stereoisomers.

Hydrolysis of the natural pyrethrins yields a mixture of ketols, pyrethrolone (7), cinerolone (8) and jasmololone (9), the last isolated as its O-methyl 2,4-dinitrophenyl hydrazone[19], and two acids, chrysanthemic acid (10) and chrysanthemum dicarboxylic acid (11). By mild hydrolysis, pyrethric acid (12) can be isolated.

A considerable amount of research has been directed towards devising viable commercial syntheses of natural pyrethrins, and from this work has stemmed the preparation of several synthetic analogues, some of which exhibit high insecticidal activity. Of these, allethrin (13)[24,25], furethrin (14)[26] and cyclethrin (15)[27] were among the first to be developed, the former having achieved the status of commercial production. Harper[28] synthesized the chrysanthemic esters of the cyclohexenone analogues of cinerone and pyrethrone, but the products did not show insecticidal properties. Replacement of the natural alcohol portions by furanyl derivatives[29], and variation of the alkenyl side-chain attached to the cyclopropane ring[30], resulted in chrysanthemates of varying activity.



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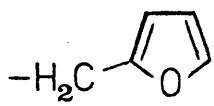
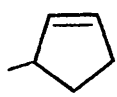
13 R= $-CH_2CH=CH_2$, R'= $-CH_3$

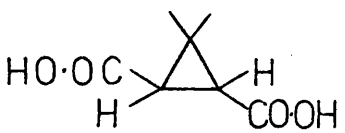
14 R=  R'= $-CH_3$

15 R=  R'= $-CH_3$

Nomenclature.

A system of nomenclature for dealing with pyrethrins, their hydrolysis products and their synthetic counterparts has been devised by Harper[22]. The stem (16 minus R and R') is denoted by "-rethrin", and individual compounds named by prefixing the alkyl or alkenyl side-chain R, and suffixing 1 if R' is CH_3 and 11 if R' is $COOCH_3$. Thus the systematic name for cinerin I (3) is but-2'-enylrethrin 1 and that for pyrethrin II (2) penta-2',4'-dienylrethrin 11. The alcohol portion of the ester (17) is termed "-rethrolone", the individual ketols being distinguished from one another by prefixing the radical R.

The system can be expanded to involve the names of the acid portions and to express stereochemistry. Thus jasmolin I (5), made from esterifying (±)-penta-cis-2'-enylrethrolone with (+)-trans-chrysanthemic acid becomes (±)-penta-cis-2'-enylrethrolone (+)-trans-chrysanthemate. In rethrins-II, where pyrethric acid is esterified, the two geometric centres to be described in the acid component can be differentiated by using "cis_o" or "$trans_o$" for the olefinic and "cis_c" or "$trans_c$" for the cyclic source of isomerism[5]. Since the absolute configuration in the natural rethrins is now known, the (R) and (S) system of Cahn, Ingold and Prelog[23] can be used, thus eliminating the need for describing the geometric arrangement about the cyclopropane ring. Under



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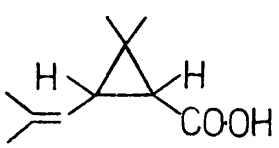

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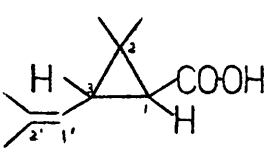
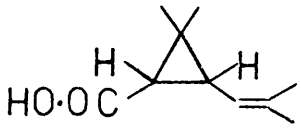


20

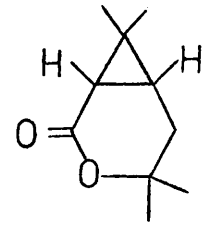
this convention, pyrethrin II is called penta-cis-2',4'-dienyl-4-(S)-rethronyl-1 (R), 2(R)-trans-pyrethrate, the last "trans-" designation referring to the cyclopropane trans- olefinic side-chain.

Structures and Properties of Chrysanthemic and Pyrethric Acids.

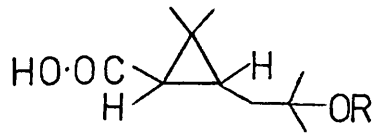
From the hydrolysis of natural pyrethrins, Staudinger and Ruzicka[14] isolated two monoterpene acids, namely (+)-chrysanthemic acid (10) and (+)-chrysanthemum dicarboxylic acid (11). On separation by steam distillation, they were found to have m.p. 17-21°, $[\alpha]_D$ +14·6 (in ethanol)[31], and m.p. 164°, $[\alpha]_D^{17}$ +72·8 (in methanol)[14] respectively. (+)-Chrysanthemic acid absorbed bromine, while catalytic reduction resulted in the formation of a dihydro derivative in which the cyclopropane ring had remained intact[14,32]. The survival of the latter, which would be expected to be susceptible to hydrogenolytic cleavage, may be due[5] to hindrance of the substituents at the catalyst surface. Ozonolysis of (+)-chrysanthemic acid produced acetone and (-)-trans-caronic acid (18), thus establishing structure 10 with the exception of its absolute configuration. Both (±)-cis- and (±)-trans-chrysanthemic acids have been resolved and characterized[33], the melting points of the (+)-cis- (19) and (+)-trans- (20) isomers being 40-42° and



$\overset{H^+}{\rightleftharpoons}$

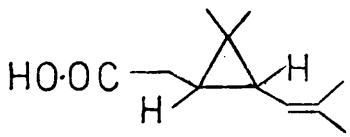


21 22

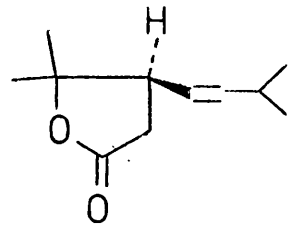


23 R= H

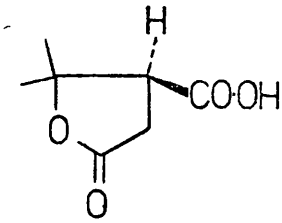
24 R= CH_3



$\xrightarrow{H^+}$



$\xrightarrow{O_3}$



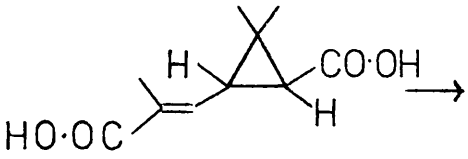
25 26 27

17-21° respectively.

The geometry of the cis-acids was verified by their conversion on refluxing with hot acid into an equilibrium mixture of 21 and 22, while the trans-acids were hydrated to compounds of type 23[34,35]. As is to be anticipated, a carbonium ion is readily formed at position 2' in acid solution, leading to formation of methyl esters of ether-acids of the type 24[36] on treatment with methanolic sulphuric acid. For this reason, esterification is best carried out using diazomethane.

The geometry of natural (+)-trans-chrysanthemic acid (20) is such that the 1-centre must have the (R) configuration, but direct determination of absolute configuration has been achieved by Arndt-Eistert homologation to the homoacid 25. On refluxing with mineral acid this lactonized to 26, and on ozonolysis the lactone yielded isobutyraldehyde and (-)-terebic acid (27). The lactonization preserves the 1-centre intact, showing that the absolute configuration is (R) as in 20[5,37].

Staudinger and Ruzicka[14] also elucidated the structure of (+)-chrysanthemum dicarboxylic acid, demonstrating that it could be thermally decarboxylated to 28, and that ozonolysis gave trans-caronic acid (29) and pyruvic acid. Its structure and absolute configuration are thus as in 30, [1(R), 2(R)], the trans orientation of the side-chain



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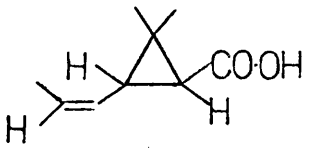

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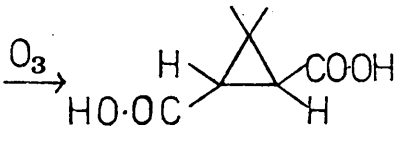

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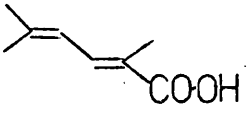


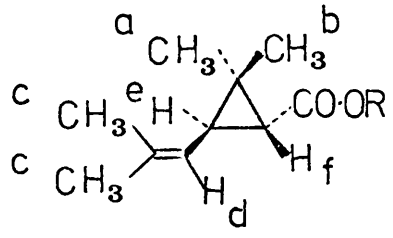
31

following from its synthesis from trans-2-α,δ-dimethyl-sorbic acid (31)[38], and from its NMR spectrum[37].

In the natural rethrins II, chrysanthemum dicarboxylic acid is esterified at one carboxyl with methanol and at the other with a rethrolone, the orientation of the esters following from the fact that pyrethrins II semicarbazone concentrate gives, on mild hydrolysis, pyrethric acid (12), $[\alpha]_D^{18}$+103·9 (in carbon tetrachloride). The latter on ozonolysis gives (-)-trans-caronic acid and methyl pyruvate.

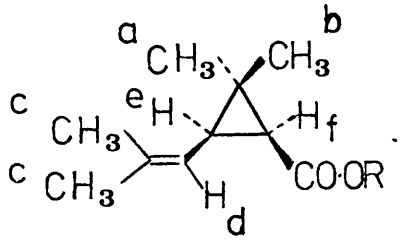
During the last ten years, the structures established by chemical means have been confirmed by spectroscopic techniques, particularly NMR, (table 1), which has also been used for conformational studies[39]. The NMR spectrum of chrysanthemic acid was published in 1962 by Hutton and Schaefer[40], and again in 1969 as a result of more extensive studies by Crombie and coworkers[41].

The cyclopropane ring protons ^{e}H, ^{f}H, and the olefinic proton ^{d}H in both isomers constitute ABX-type systems, which approximate to the AMX case with $J_{AX} \sim 0$Hz[41]. Hutton and Schaefer have calculated J 5·4 (trans) and J 8·7 (cis) Hz for the cyclopropane ring proton ($J^{e}H-^{f}H$) couplings in the two isomers, which agree with calculations based on the Karplus equation[42]. The NMR data for cis- and trans-chrysanthemic acids and their methyl esters in deuteriochloroform solution are summarized in table I,



32 R= H

33 R= CH_3



34 R= H

35 R= CH_3

TABLE I

Cmpd.	$^{a}CH_3$	$^{b}CH_3$	$^{c}CH_3$ d(J~1·5)	^{d}H dm (J~8)	^{e}H dd(J5·5 and 8)	^{f}H d (J~5·5)*	-OH or OCH_3
32	8·7	8·85	8·30	5·1	7·9	8·62	-1·64
33	8·75	8·89	8·31	5·09	7·9	8·63	6·33
34	8·74	8·79	8·23, 8·29	4·63	8·02	8·36	-
35	8·77	8·80	8·26, 8·32	4·62	8·12	8·40	6·38

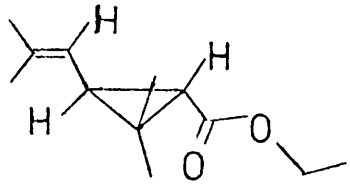
*applies to trans- isomers only.

as published by Bramwell and coworkers[41]. In both isomers the olefinic protons (^{d}H) resonate as doublets (J~8Hz) of partially resolved multiplets, the complex multiplicity of each component resulting from coupling (J~1·5Hz) to the adjacent gem-dimethyl protons[41]. The signal for the olefinic protons (^{d}H) in the cis- isomers (34,35) appears at lower field (~τ 4·62) than in the case of the trans- isomers (32,33; ~τ 5·1). This feature is a result of the relative orientation of these protons with respect to the neighbouring carboxy function in the two isomers, and is useful in assessing percentage compositions in mixtures of chrysanthemic acid isomers[43]. The ^{e}H-protons in the

trans- compounds are also deshielded relative to those in the cis- (τ~8·02-8·12), by the adjacent carboxy function, and resonate at lower field (τ 7·9)[41]. Significantly, the ^{f}H-protons in the trans- isomers appear at higher field than the corresponding protons in the cis-, showing that the neighbouring isobutenyl group adopts a conformation in which the double bond shields these protons in the trans- compounds.

The saturated methyl protons ($^{a}CH_3$:$^{b}CH_3$) resonate at different chemical shifts in both chrysanthemyl isomers; these differences are more pronounced in the trans- (32,33; τ 8·75, 8·89) than in the cis- compounds (34, 35; τ 8·77, 8·8) and are associated with the position of these protons relative to the carboxy and isobutenyl functions. It seems probable that the methyl protons ($^{a}CH_3$) which resonate at lowest field in the trans- isomers are cis to the neighbouring carboxy groups[41]. The saturated methyl protons in the cis- compounds resonate at approximately the same field, this apparently being due to the deshielding effect of the carboxy function being partially counteracted by the shielding effect of the isobutenyl group[41].

The isobutenyl methyl protons ($^{c}CH_3$) resonate as doublets (J ~ 1·5Hz) in both isomers. Although these protons have the same chemical shift in the trans- compounds, (32,33; τ 8·30), one of the methyl groups in the cis- is



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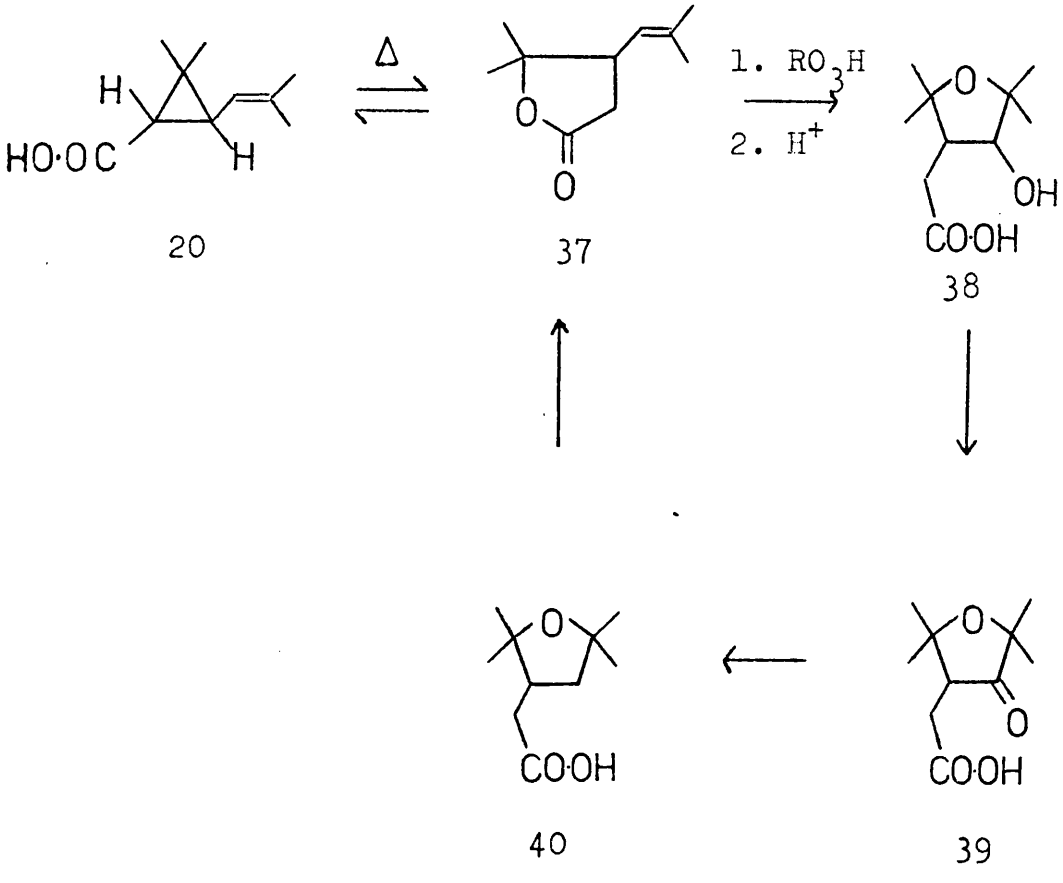


20 37 38 39 40

SCHEME 1

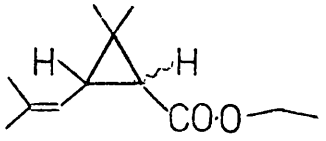
deshielded relative to the other, by virtue of its proximity to the adjacent carboxy group, so that two signals are observed (τ 8·23, 8·29).

Pierre and coworkers have demonstrated by means of NMR that the preferred conformation for ethyl chrysanthemate is that shown in 36, this being favoured on both steric and electronic grounds.[39]

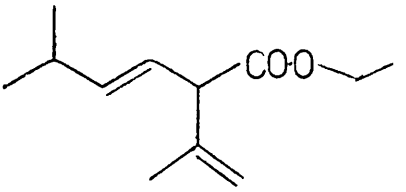
The mass spectra of pyrethroids have been studied by King and Paisley[44], who showed that the primary fragmentations of cis- and trans-chrysanthemic acids are those due to peripheral losses from the molecular ion of a methyl radical or the carboxy group, the latter process leading to the base peak of the spectrum ($^{m}/e$ 123). Subsequent fission of the cyclopropane ring leads to elimination of butene or propene molecules to give fragment ions at $^{m}/e$ 81 and $^{m}/e$ 67.

Chemistry of Chrysanthemic Acid and Related Compounds.

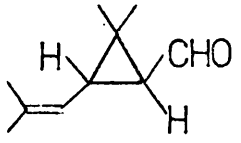
Much of the chemistry carried out on chrysanthemic acid has been of a pyrolytic nature. While pyrolysis of (±)-cis- and (±)-trans-chrysanthemic acid gives rise to the same lactone, (±)-pyrocin, the (+)-trans- acid gives (-)-pyrocin. Such lactones[45] were originally thought to be as in 22[46], but Crombie and Harper[34, 47] have since shown that they arise from cyclopropane ring rupture,



$\xrightarrow{\Delta}$

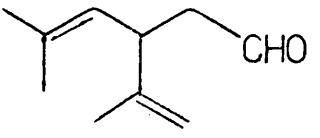


41



42a

$\xrightarrow{\Delta}$



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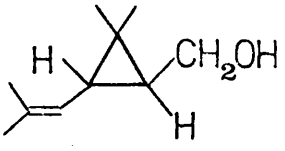
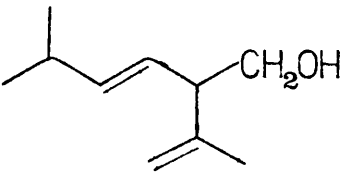


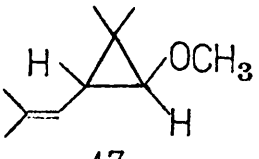
43

$\xrightarrow{\Delta}$



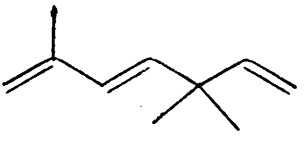
44

$\xrightarrow{\text{PTSA}}$



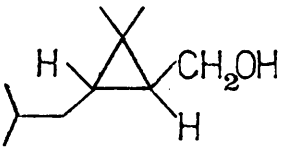
47

$\xrightarrow{\text{PTSA}}$

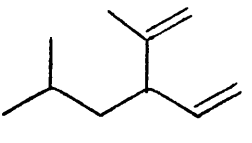


48

$\xrightarrow{SOCl_2}$



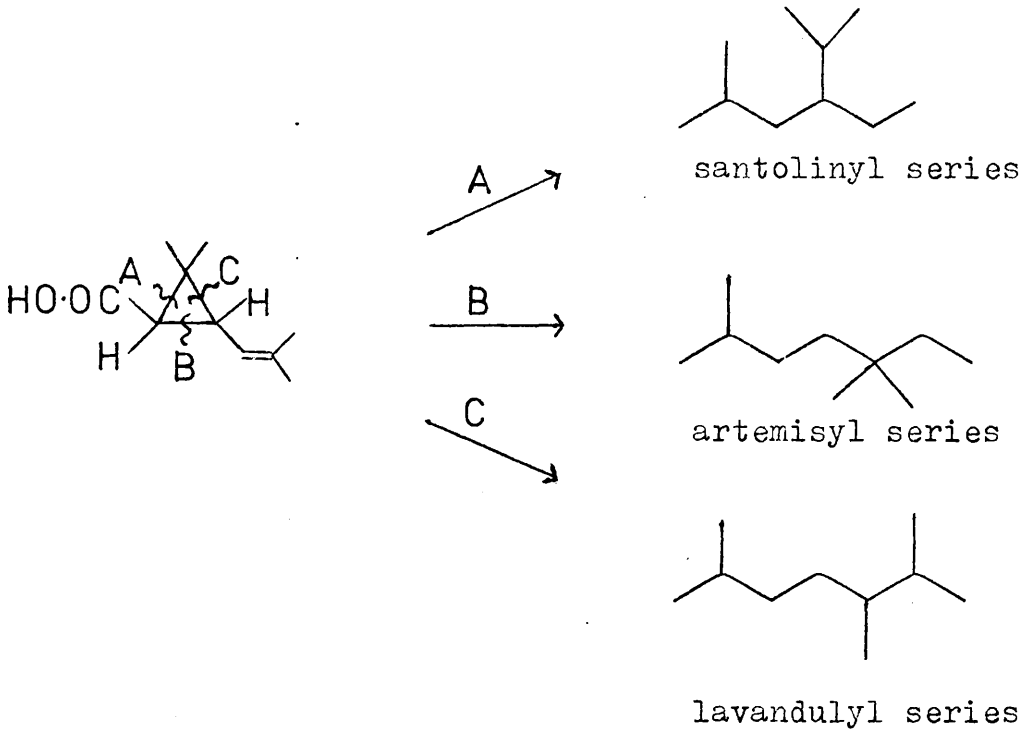
45



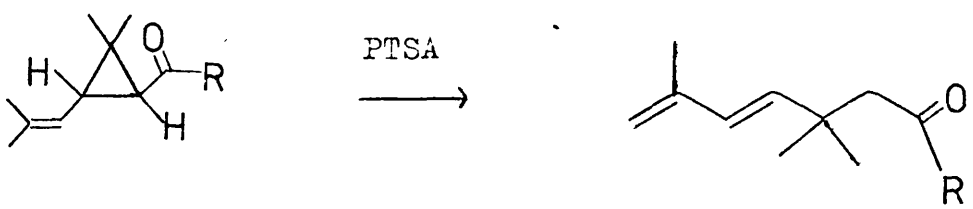
46

as in 37, and have deduced from (-)-pyrocin the absolute configuration of natural (+)-trans-chrysanthemic acid.

Julia and coworkers[48] have demonstrated the possibility of converting pyrocin to the trans- acid[49] by refluxing in benzene with thionyl chloride; this interconvertibility led Ueda and Matsui[50] to suggest the use of such an approach for the derivation of racemic trans-chrysanthemic acid from the optical antipode, a technique which could have important synthetic applications, (scheme 1). The (+)-trans- acid, when refluxed for five hours under nitrogen, gave a 46% yield of (-)-pyrocin, which upon peracid oxidation and subsequent acid treatment gave the (-)-hydroxy compound (38). Jones oxidation of 38 afforded the (-)-keto acid (39), which, after boiling in alkaline solution, gave the racemic analogue. The latter was reduced to the acid (40), which on heating under reflux with acetyl chloride and zinc chloride produced (±)-pyrocin in good yield. The combination of these reactions allows racemic trans-chrysanthemic acid to be obtained from the optically active one. It was found[51] that thermal equilibration of the two geometric isomers of methyl chrysanthemate could be readily attained in the temperature range 240-260°. Above 260°, however, structural isomerization leading to cyclopropane ring opening becomes gradually ascendant over geometric isomerization[52].



SCHEME 2

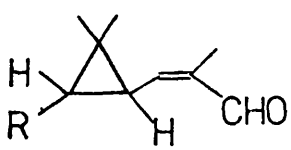


42a, R= H

49, R= CH_3

50, R= H

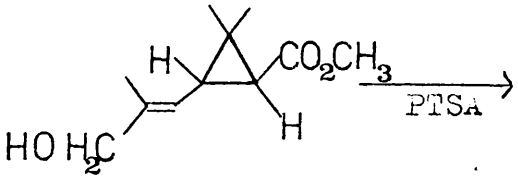
51, R= CH_3



52

On heating a mixture of cis- and trans- ethyl chrysanthemates at 500°, the lavandulyl ester (41) was obtained, while the dihydro analogue of the former appears to be stable under these conditions[52,53]. The main product from pyrolysis of chrysanthemaldehyde was the acyclic aldehyde (42). Under analogous conditions, chrysanthemyl alcohol (43)[54] gave rise to lavandulol (44)[52].

Although dihydro analogues appear to be stable on heating, (+trans-dihydrochrysanthemyl alcohol (45) remains unchanged even in the presence of toluene-p-sulphonic acid)[53], treatment of 45 with thionyl chloride at 0° leads to the isolation of santolinadiene (46) in 40% yield from a mixture of five products. The presence of unsaturation in the chrysanthemyl side-chain, however, considerably affects the course of the reaction, due to a drastic alteration[53] in the energy of the transition state leading to rupture A (scheme 2), which is predominant in the dihydro series. The conjugated homoallylic system of the chrysanthemic molecule renders route B (scheme 2) more favourable than in the dihydro case, and causes the formation of compounds of the artemesia series. Both cis- and trans-chrysanthemyl alcohol (43) and the methyl ether (47) gave trans-artemisiatriene (48) in 55% yield when heated with a small quantity of toluene-p-sulphonic acid (PTSA) in benzene. The same product was obtained in



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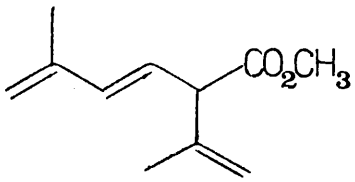

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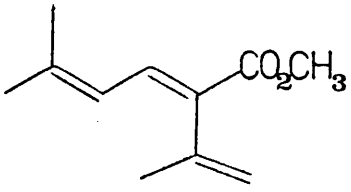

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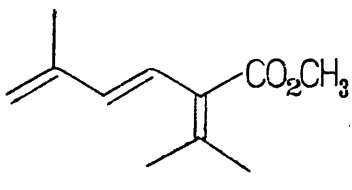

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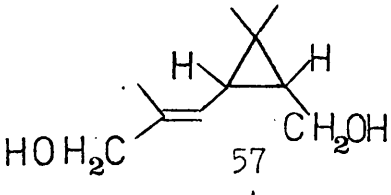
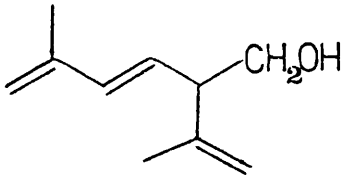


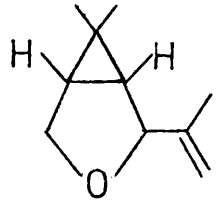
57

PTSA



58

+

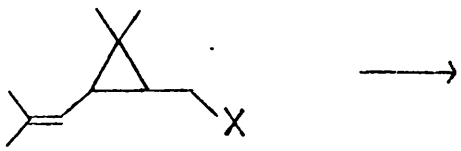


59

varying yields when 43 was treated with PTSA in pyridine, thionyl chloride or phosphorus tribromide in pyridine. Functionalised trans- products from this type of artemisia cleavage were formed when the aldehyde (42a)[55] or the ketone (49)[56] were refluxed with PTSA in benzene, the products being 50 and 51 respectively. However, compounds of type 52 ($R=CH_2OH$ and CHO), were resistant to ring cleavage with PTSA under normal conditions, indicating the destabilisation of the homoallylic carbonium ion system by the electron-withdrawing aldehyde group[53].

A third type of ring cleavage (C, scheme 2) occurs under carbonium ion conditions to give lavandulyl derivatives when the isobutenyl side-chains are suitably functionalised. Thus the alcohol (53), on heating with PTSA, gave the trans-triene ester (54)[57], which on standing as a petrol solution over alumina partially isomerized to 55 and 56. A further example of the lavandulyl type of cleavage is observed when the diol (57) is heated with PTSA in benzene. Here, cleavages of all three types, A, B and C are possible, and while five components have been detected[53] among the reaction products, the major compound is 58. A second substantial product [53] is reported to be 59, derived by internal trapping of the intermediate carbonium ion.

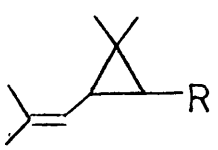
Thus, under various circumstances, chrysanthemic acid



60, X= +

61, X= tosylate

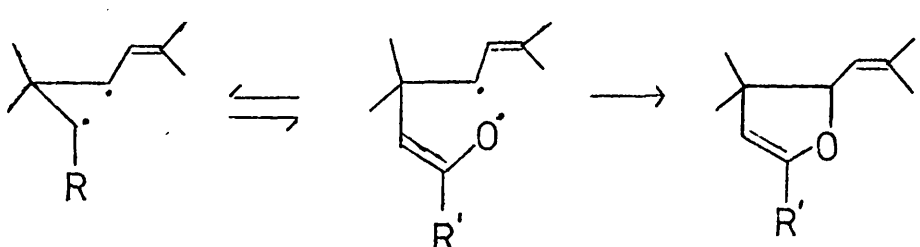
48



63, R= $-CO_2H$

64, R= $-CO_2C_2H_5$

65, R= $-CONH_2$



63a, R'= $-OH$

64a, R'= $-OC_2H_5$

65a, R'= $-NH_2$

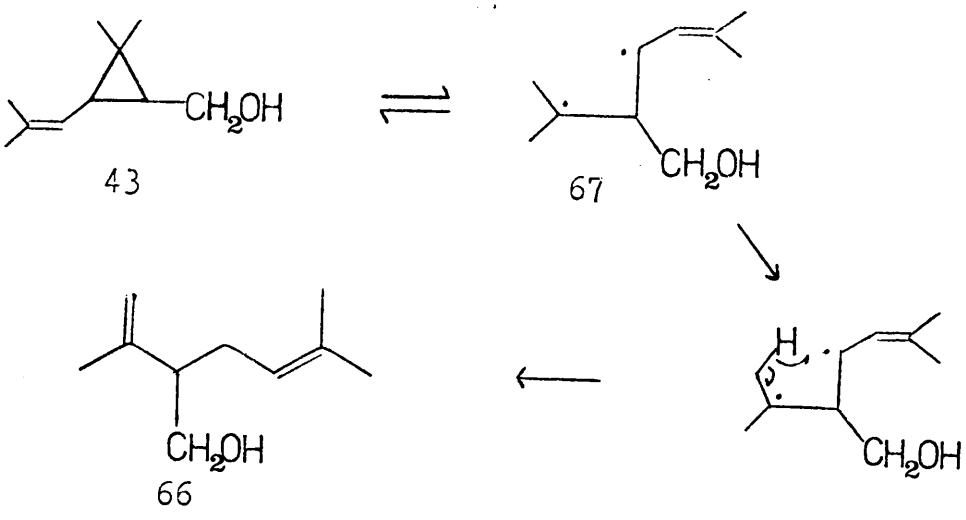
62

SCHEME 3

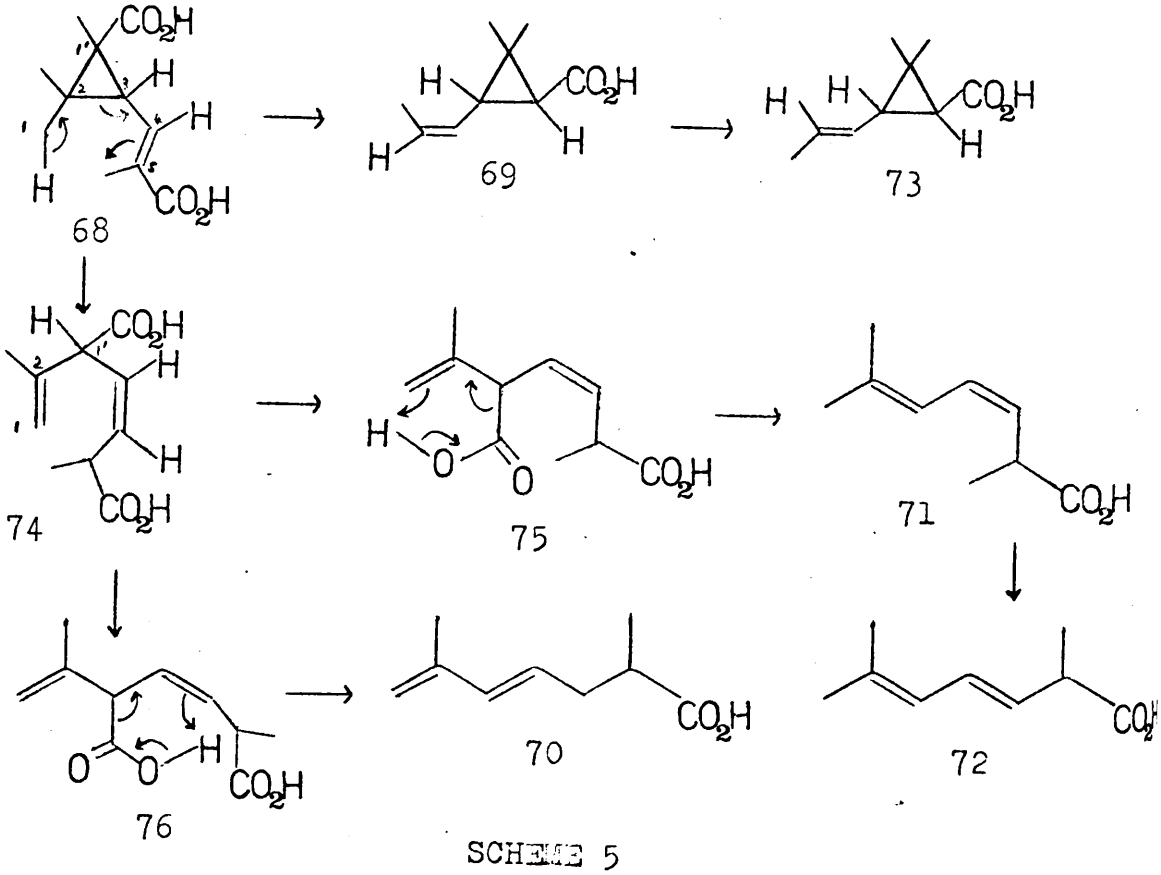
derivatives are capable of rearranging to monoterpene types of the santolinyl, artemisyl and lavandulyl series, a fact that has led to speculation concerning possible biogenetic analogies[58, 59], especially since the co-occurrence of such compounds has been confirmed in Santolina chamaecyparissus[60,61]. Stimulated by the proposal that chrysanthemyl pyrophosphate may be the precursor of naturally occurring compounds of the artemisyl series, Bates and Feld[62] confirmed the observation of Crombie and coworkers[53] that, during in vitro experiments, the carbonium ion (60), generated via the tosylate (61), opened and lost a proton to give trans-artemisiatriene (48). The formation of artemisyl species from the thermal decomposition of chrysanthemyl oxalate and from the de-amination of chrysanthemylamine has also been reported[63].

Largely because of their insecticidal applications, the photochemistry of chrysanthemic acid derivatives has been extensively studied. Ueda and Matsui have succeeded in promoting cis-trans isomerisation of the acid by photochemical means[64], while sensitized racemization of both acid and ester has been accomplished[64].

The photolytically induced rearrangement of chrysanthemic acid and some related compounds has been reported by Sasaki[65], who found that the lactone (62) was formed as a recyclization product resulting from cyclopropane ring



SCHEME 4

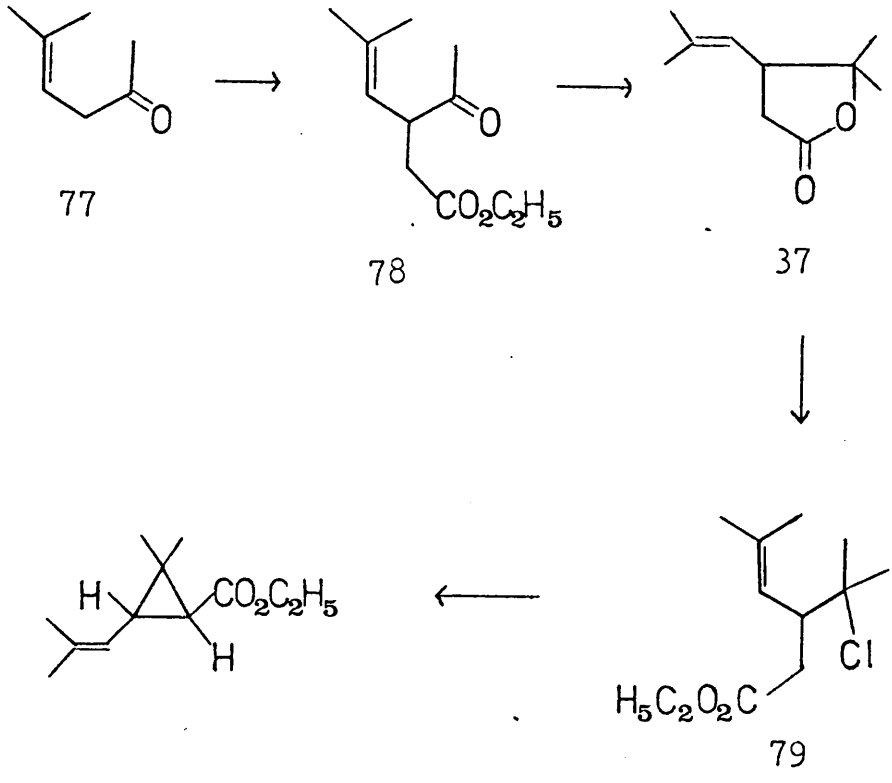


SCHEME 5

cleavage of chrysanthemic acid (63), ethyl chrysanthemate (64) and chrysanthemamide (65) (scheme 3). Fragmentation products, ethyl 3,3-dimethylacrylate and 3,3-dimethylallyl alcohol were produced from 64 and 43 respectively in considerable yield, while the latter (43, scheme 4) was found to give lavandulol (66), presumably via a 1,4-hydrogen migration in the initially formed diradical intermediate (67). Sasaki[65] suggests that the cleavage positions of the cyclopropane ring can be rationalized in terms of a stabilizing effect of the substituent on the intermediate diradicals.

The acidic thermal decomposition products of natural chrysanthemum dicarboxylic acid (68) have been examined by Crombie and coworkers[66]. At 260-320° under nitrogen, 68 produced a liquid distillate comprising 50% acidic components and 20% neutral, with concomitant liberation of approximately 0·7 mol. equivalents of carbon dioxide. Esterification of the acid fraction followed by GLC analysis indicated six products, identified as the methyl esters of the acids 69, which had been isolated by Staudinger and Ruzicka[14] under similar conditions, 70, 71, 72 and 73, along with a minor component whose structure could not be unambiguously assigned.

The formation of the ring cleavage products (70) and (71) can be rationalized in terms of an initial homo-

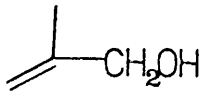


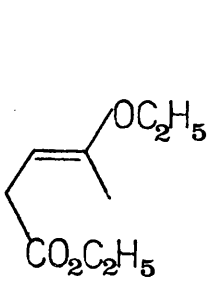
77 78 37 79

(1,5)-sigmatropic shift to produce the 1,4-diene (74), followed by loss of carbon dioxide from the doubly-unsaturated carboxy group at C-1' in the two senses indicated (scheme 5). Elimination of carbon dioxide from 74 via 75 (leading to 71 and 72) rather than via 76 is sterically more favourable, and accounts for the fact that there are approximately ten times more of compounds 71 and 72 present in the pyrolysis product than there is of 70. Experiments with ^{14}C-labelled chrysanthemum dicarboxylic acid (68)[66,67] have shown that 63% of the liberated carbon dioxide comes from the cyclopropane ring carboxy group, an observation which supports the proposed mechanism of the formation of the ring-cleaved pyrolysis products.

Synthesis of Chrysanthemic Acid and Related Compounds.

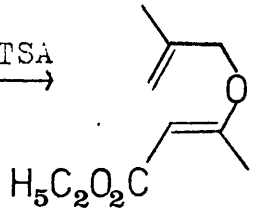
The first synthesis of chrysanthemic acid was achieved by Staudinger and Ruzicka[14] who added ethyl diazoacetate to 2,5-dimethylhexa-2,4-diene and obtained, after hydrolysis, (±)-*cis*-chrysanthemic acid in poor yield. This approach was greatly improved by Campbell and Harper[31, 68], who obtained a 2:1 mixture of (±)-*trans*- and (±)-*cis*- acids, the main modification of the previous method being in the preparation of the diene. The two racemates are separable by crystallization from ethyl acetate, and resolution of both may be accomplished using quinine and (-) or (+)



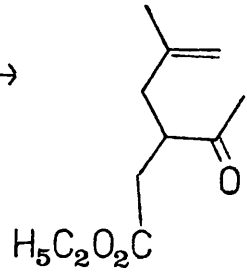


80

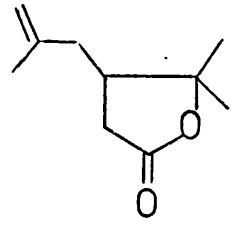
PTSA



Δ



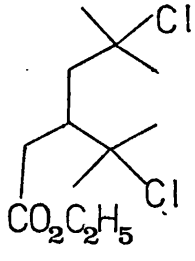
81



82

SOCl$_2$

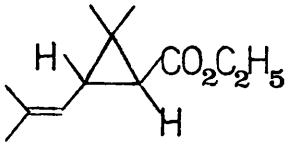
HCl/EtOH



83

NaH

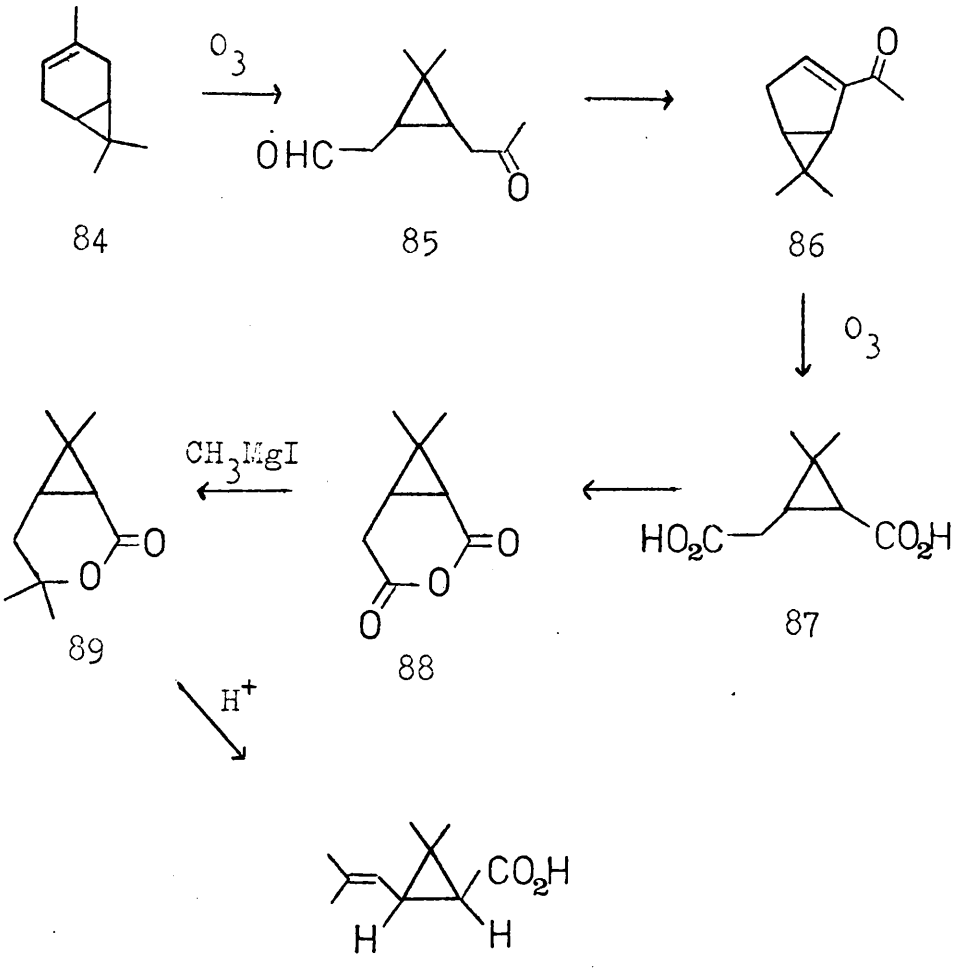
DMF



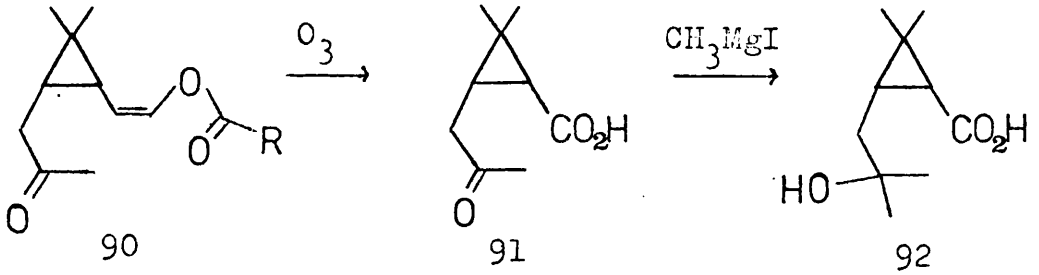
-α-phenylethylamine[5]. The use of t-butyl diazoacetate in this synthesis has been reported to result in the stereoselective formation of trans-chrysanthemic acid[69], the geometry being confirmed by the absence in the NMR spectrum of the olefinic proton doublet associated with the cis- isomer. Apparently the steric course of the reaction is controlled by the bulkiness of the t-butyl group.

An alternative synthesis of the racemic trans- acid was first reported by Julia and coworkers[70]. The ketone (77) was α-substituted via the pyrrolidine enamine using ethyl bromoacetate. Treatment of the resulting keto-ester (78) with methyl magnesium bromide yielded (±)-pyrocin (37), which, on reaction with thionyl chloride in benzene followed by treatment with ethanolic hydrogen chloride gave the chloro-ester (79). The latter cyclized under the influence of sodium t-amylate to give ethyl (±)-trans-chrysanthemate. The racemic dihydro- acid has been similarly synthesized[71].

In a similar synthesis[72], the enol ether of ethyl levulate (80) was reacted with 2-methylallyl alcohol in the presence of PTSA and the product pyrolysed to give (81), which on treatment with methyl magnesium iodide, was converted to 82, an isomer of pyrocin. Reaction of 82 with thionyl chloride and ethanolic hydrogen chloride


O3
OHC
O
84
85
86
O3
CH3MgI
HO2C
CO2H
87
88
89
H+
CO2H
H
H

SCHEME 6

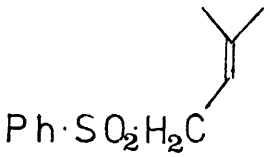

O3
O
O
R
O
90
CO2H
91
CH3MgI
CO2H
HO
92

produced the dichloro-ester (83) which, with sodium hydride in dimethylformamide was converted to ethyl chrysanthemate in a yield of 56% (based on 82).

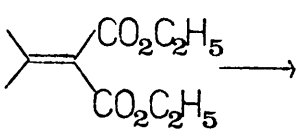
(±)-trans-Chrysanthemic acid has also been made by adding diazoacetonitrile to tetramethylbutadiene[73]. The product was a 73:27 mixture of (±)-trans- and (±)-cis-nitriles, but on hydrolysis the cis- compound was epimerized to yield almost pure racemic trans- acid.

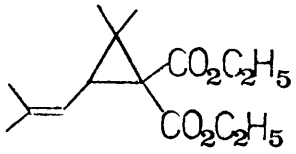
Another approach has been established by Matsui and coworkers[74] (scheme 6), starting from (+)-Δ^3-carene (84). Ozonolysis of 84 gave the keto-aldehyde (85), which on aldol condensation produced the α,β-unsaturated ketone (86). 86, on treatment with ozone, gave (+)-cis-homocaronic acid (87). Reaction of the derived anhydride with methyl magnesium iodide resulted in a 50% yield of δ-lactone (89), which was converted to (-)-cis-chrysanthemic acid with dilute sulphuric acid. The route was modified to synthesize (-)-trans-chrysanthemic acid, and was also adapted by Sasaki in the synthesis of cis-homocaronic acid and its derivatives[75].

Optically pure dihydrochrysanthemolactone (89) can also be obtained by modifying the method thus[76]: 85 is converted into the enol ester (90) which is then subjected to ozonolysis to give the acid (91). Treatment with methyl magnesium iodide produces the hydroxy acid (92) which



93





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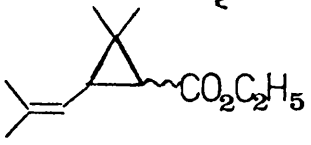

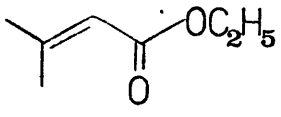

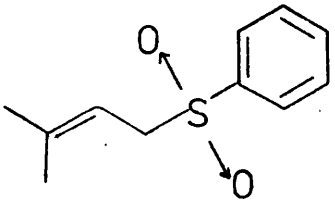

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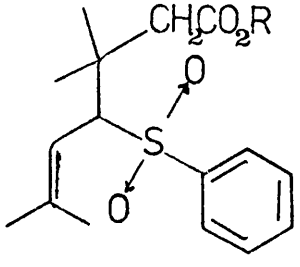
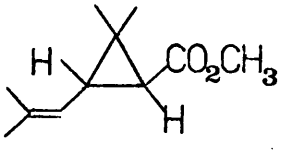


96, R= H

97, R= CH_3



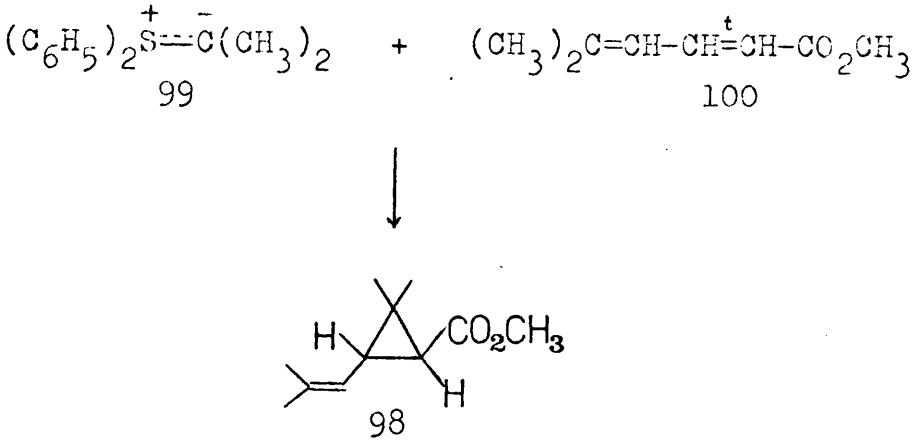
98

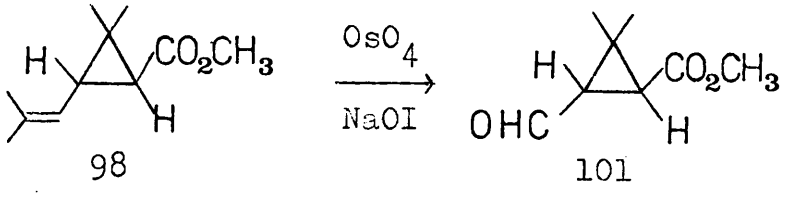
SCHEME 7

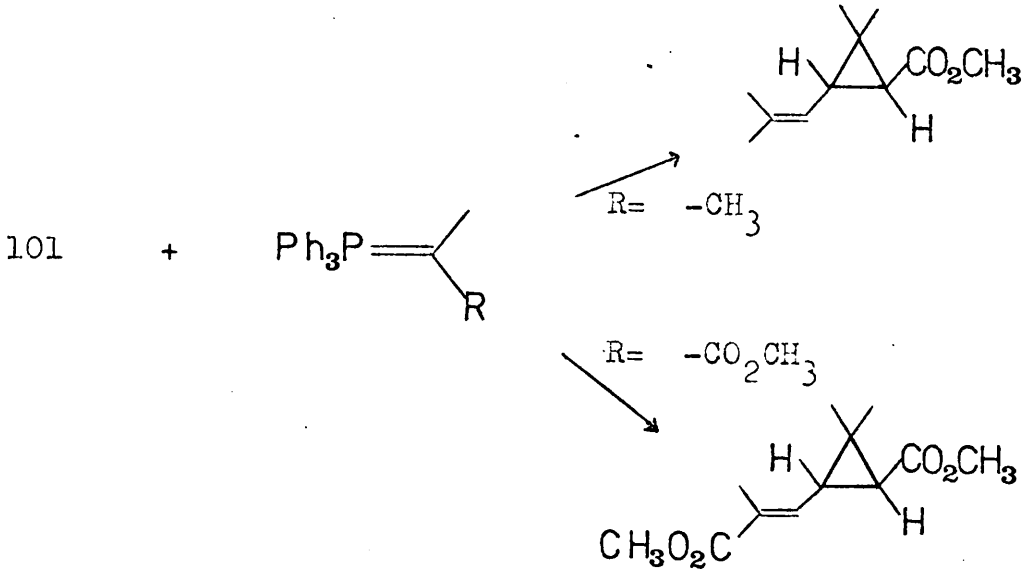
readily lactonizes to 89.

A recently developed synthesis with considerable commercial application[77] involves the intermediacy of novel aryl sulphones. The method was first reported by Julia and Guy-Roualt[78], who prepared the sulphone (93) and condensed it with diethyl isopropylidenemalonate in the presence of cuprous chloride. A mixture of two isomers in roughly equal proportions was obtained, the first of which was identified as the diester (94), while the second led to a diacid. Partial saponification and decarboxylation in quinoline containing powdered copper produced a mixture of cis- and trans- ethyl chrysanthemates. Equilibration and hydrolysis yielded crystalline trans-chrysanthemic acid.

A variation of this method has been successfully adapted for the production of chrysanthemic acid and synthetic analogues, some of which give rise to pyrethrins of considerable insecticidal activity[79,80]. The starting material for the preparation of chrysanthemic acid itself is phenyl 3-methyl-2-butenyl sulphone (95), made by reacting benzenesulphinic acid (from action of zinc powder on benzenesulphonyl chloride) with 3-methyl-2-butenyl bromide under basic conditions. 95 (scheme 7) is then added to a solution of potassium t-butoxide in THF, cooled to 0°, and treated with one equivalent of ethyl senecioate. Acidification and ether extraction produces the acid (96),


(C6H5)2S+—C−(CH3)2
99
+
(CH3)2C=CH-CH=CH-CO2CH3
100
H
CO2CH3
H
98


H
CO2CH3
H
98
OsO4
NaOI
H
CO2CH3
OHC
H
101

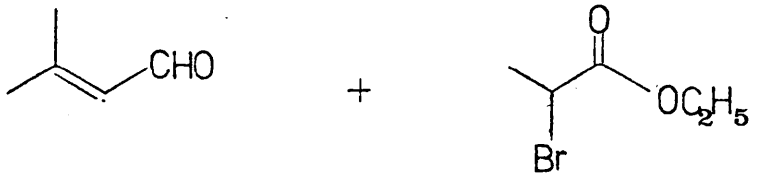

101
+
Ph3P
R
R= -CH3
R= -CO2CH3
H
CO2CH3
H
H
CO2CH3
H
CH3O2C

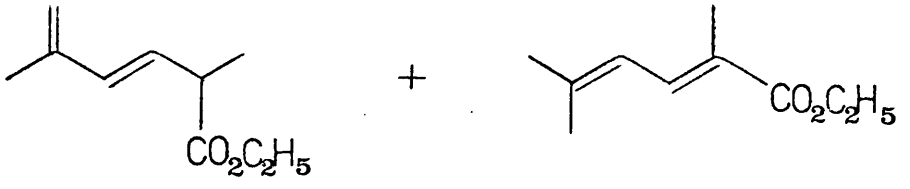
which is treated with diazomethane to give the methyl ester (97). After prolonged stirring in a benzene solution of sodium t-amylate under a nitrogen atmosphere, 97 is converted to methyl (±)-trans-chrysanthemate (98).

A particularly simple yet stereospecific synthesis of (±)-trans-chrysanthemic acid was devised by Corey[81]. Reaction of the highly sensitive sulphur ylide diphenylsulphonium isopropylide (99) with methyl 5-methyl-trans-2,4-hexadienoate (100), produced methyl (±)-trans-chrysanthemate in good yield. 100 is readily available from the reaction of methallyl chloride, acetylene and methanol in the presence of nickel carbonyl[82]. It is interesting to note that synthesis of the desired acid has now been achieved using all three possible methods of cyclopropane ring formation.

Syntheses of ^{14}C-labelled (+)-trans-chrysanthemum mono- and dicarboxylic acids for use in biosynthetic and toxicological work have been devised[67]. Methyl trans-chrysanthemate, on osmium tetroxide-sodium periodate oxidation, gave a high yield of the aldehyde (101), which was then condensed under Wittig conditions with the appropriate ^{14}C-labelled phosphorane to generate the mono- or di- chrysanthemic ester.

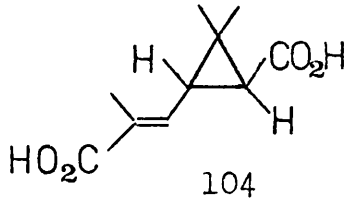
The recent advances in synthetic techniques for the production of chrysanthemic acid, yet another of





102 103

1. $N_2CH_2CO_2R$
2. OH^-

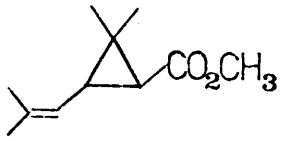


104

which constitutes a major part of this thesis and is discussed elsewhere[83], have been accompanied by developments designed to facilitate resolution of the optical isomers. A recently reported method[84] involves heating the trans- racemate with L-lysine in methanol, and treating the precipitated salt with hydrochloric acid to obtain a 25% yield of (+)-trans-chrysanthemic acid. A similar technique employs D-(-)-threo 1-p-nitrophenyl 2-dimethylaminopropane 1,3,-diol as the resolving agent[85].

Separation of cis- and trans-chrysanthemic acids has been effected by GLC, a technique which complements NMR as a means of assessing the relative amounts of the two geometric isomers. The optimum conditions reported by Myamoto and coworkers[86] are those in which a 2·1m. glass column with 3mm. inner diameter and packed with 10% polypropyleneglycol sebacate coated on 60-80 mesh of acid-washed Chromosorb W, is kept at a temperature of 160°. Experiments show the cis- compound to be slightly the less polar isomer.

Synthesis of chrysanthemum dicarboxylic acid has been effected by Harper and coworkers[38,87]. Reformatski reaction between β-methylcrotonaldehyde and ethyl α-bromopropionate gave a mixture of the esters (102) and (103). After isomerising the former to the latter with phosphorus oxychloride, treatment with diazoacetic



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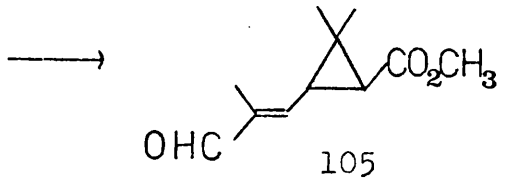

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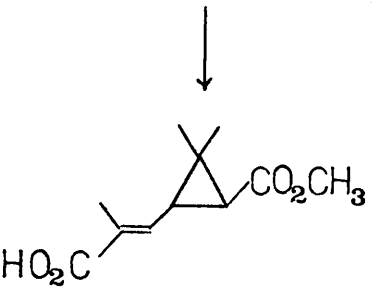

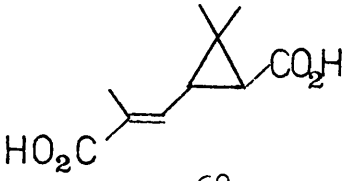

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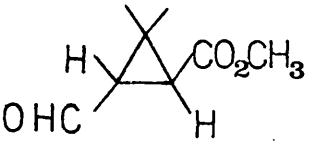

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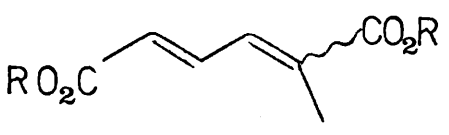

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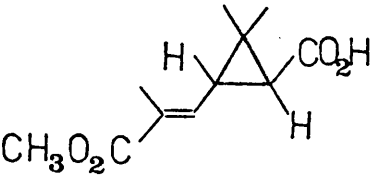
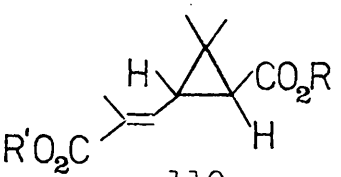


108

ester and subsequent hydrolysis yielded (±)-$\underline{cis}_c$- and (±)-$\underline{trans}_c$-chrysanthemum dicarboxylic acids (104). Resolution of the trans- racemate with (-)-α-phenylethylamine gave the (+)- acid, m.p. 162-164°, $[\alpha]_D^{11}$ +70·9 (in ethanol), identical with the natural acid[88,89]. The ester (103) was shown to have the $\underline{trans}_o$-2-configuration since the corresponding acid could not be lactonized[38]. The synthetic cis- and trans- racemates were therefore considered to have trans- olefinic side-chains as in 104, and in the case of the trans- racemate this has been confirmed by NMR[5].

In another route to the di-acid (104), (±)-methyl chrysanthemate was oxidized to the aldehyde (105), which after further oxidation with silver oxide, was hydrolised to racemic chrysanthemum dicarboxylic acid[90]. Matsui and coworkers[90] have converted the aldehyde (106) into the di-acid by Perkin reaction using potassium propionate and propionic anhydride. Inouye[91] approached the matter by adding dimethyldiazomethane to trans-2, trans-4 and cis-2, trans-4-α-methylmuconic esters (107) and pyrolysing the pyrazolines thus formed. In the first case (±)-trans-chrysanthemum dicarboxylic acid with a trans- olefinic side-chain was obtained, while the latter was reported to give the same compound with a cis- side-chain[92].

trans-Pyrethric acid (108), isolated from mild hydrolysis



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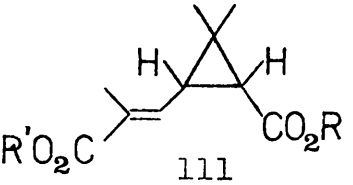

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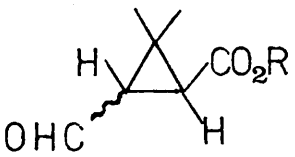

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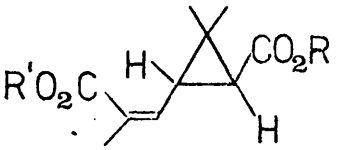
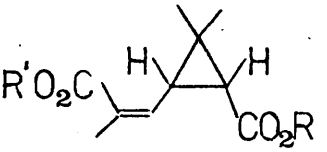


112

R= $-C(CH_3)_3$

R'= $-CH_3$



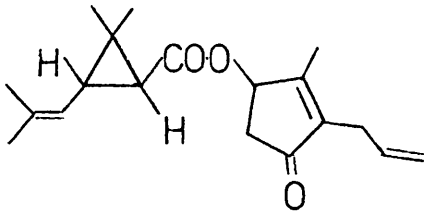
113

of rethrins II, was synthesized by complete esterification of (+)-trans-chrysanthemum dicarboxylic acid followed by half-hydrolysis of the dimethyl ester[38]. It has also been synthesized utilizing selenium dioxide oxidation of t-butyl (±)-trans-chrysanthemate as the key step[93]. Formation of the four geometric isomers of (±)-pyrethric acid has been effected by Ueda and Matsui[94] using a method rather similar to that adopted by Crombie for obtaining ^{14}C-labelled chrysanthemum mono- and dicarboxylic acids[67]. The aldoester (109, cis or trans) was prepared by ozonolysis of the corresponding chrysanthemate, and then treated with the appropriate Wittig reagent to give the t-butyl esters (110, 111, 112 and 113). Removal of the t-butyl groups to give the corresponding pyrethric acids was effected with PTSA.

Structure and Chemistry of Rethrolones and Related Pyrethroids.

Since this thesis is not directly concerned with rethrolones and pyrethrins, they are accorded a brief discussion only; their chemistry and physical properties have been reported elsewhere, (see references 5,. 14 and 95-99).

Pyrethrolone (17, R= $-CH_2-\overset{cis}{CH=CH}-CH=CH_2$) was isolated and characterized (with later structural revision)



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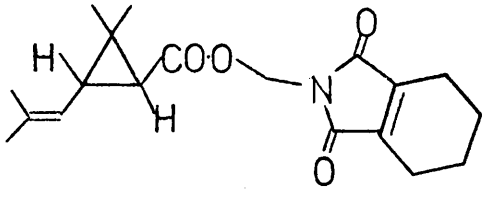

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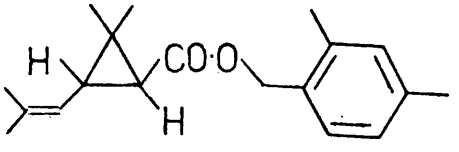


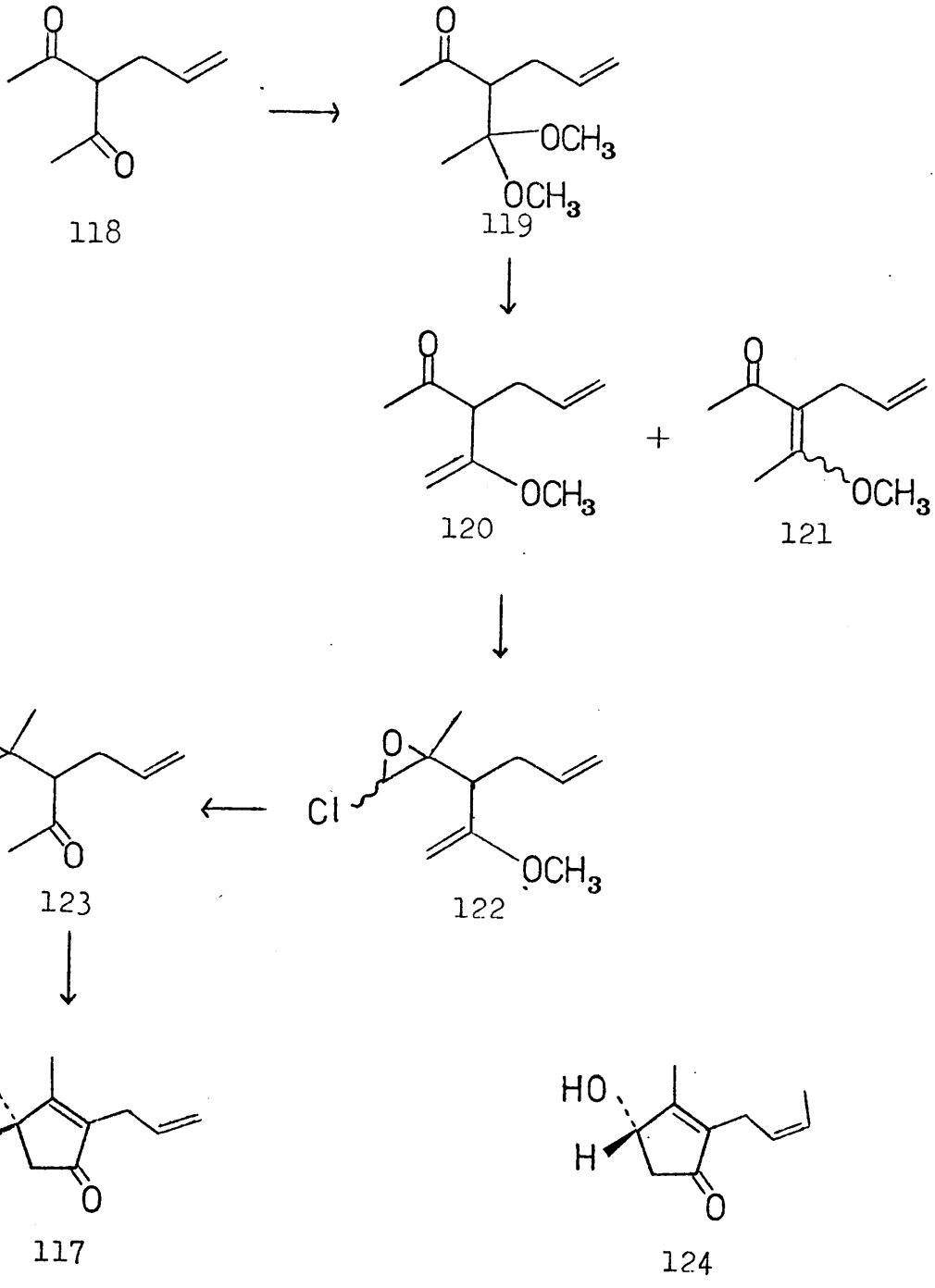
116

during the early investigations of Staudinger and Ruzicka[14], while cinerolone (17, R= $-CH_2-\overset{cis}{CH=CH}-CH_3$), whose occurrence was not recognized until some years later, was initially investigated by La Forge and Barthel[100,101]. The absolute stereochemistry of pyrethrolone has been established by Inouye[102,103].

The NMR spectra of natural rethrolones and pyrethrins have been extensively discussed in the literature[41], those of the latter being almost a direct summation of the alcohol and acid from which the ester is derived.

In the mass spectra of pyrethroids[44], the most significant feature is that the primary fragments result from fission at the internal ester function, subsequent fragmentation being very similar to that observed for chrysanthemic acid (10) and the associated rethrolone.

In view of their insecticidal applications, some of the most significant properties of pyrethroids are of a photochemical nature. It has been shown[104] that pyrethrin I (1), allethrin (13), phthalthrin (115) and dimethrin (116) readily decompose when irradiated by a sun-lamp in air. The reactions involved in photochemical attack of the alcohol portion are unknown, but photochemical changes in the acid moiety involve stepwise oxidation of a methyl group of the isobutenyl side-chain to the hydroxymethyl, the aldehydic and finally the acidic



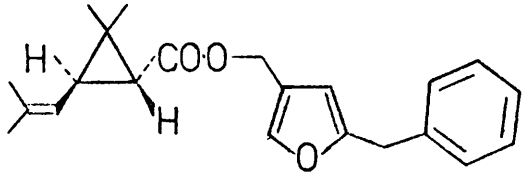
SCHEME 8

compound. The isobutenyl double bond is oxidized to a keto derivative, after which bond rupture produces esters of trans-caronic acid (18).

Synthesis of Rethrolones and Related Pyrethrins.

Although it is outwith the scope of this thesis to discuss all the rethrolone syntheses which have been published, (see references 5,14 and 105-112), particular mention should be made of the very efficient route to allethrolone (117) recently developed by Büchi[113] (scheme 8). Ketal exchange between 2,2-dimethoxypropane and allyl-acetylacetone (118) gave a high yield of the monoketal (119), which on distillation over a catalytic amount of PTSA produced a mixture of the vinyl ether (120, 64%) and the stereoisomeric β-methoxy-α,β-unsaturated ketones (121). Condensation of the ketone (120) with dichloro-methyllithium gave a chloroepoxide (122) which was hydrolysed to ketone (123). Cyclization of 123 with 0·1M aqueous methanolic barium hydroxide at room temperature gave allethrolone (117; 72% based on 120). (±)-cis-Cinerolone (124) was prepared by the same method.

Natural rethrins are readily formed by esterification of the appropriate rethrolones with (+)-trans-chrysanthemic or pyrethric acids[14,114-116]. This is usually accomplished by reaction of the ketol with the acid chloride in the



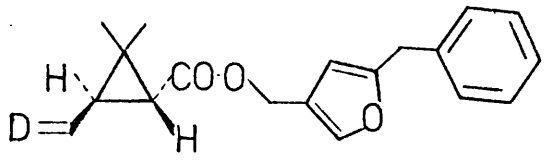
125

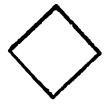
presence of pyridine.

Synthetic Analogues of Pyrethrins.

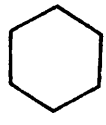
The methods developed for making natural pyrethrins and their components have been used to synthesize a large number of compounds resembling the natural esters in structure. Several of these synthetic analogues have proved to be insecticidally active. Among the first to be prepared were allethrin (13)[24,25,117], furethrin[118] (14) and cyclethrin (15)[119]. The former, which is produced commercially, was developed by Schechter and coworkers[108], who prepared (±)-allylrethrolone (allethrolone, 117) and esterified it with chrysanthemic acid. The commercial product is a mixture of (±)-allylrethronyl (±)-cis- and (±)-trans-chrysanthemates.[120]

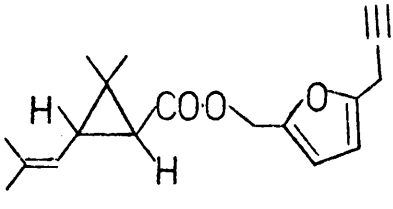
Experiments in which the alkadienyl side-chain of pyrethrin I (1) is varied, have shown that replacement by an allyl[108] or benzyl[121] group results in no great loss of insecticidal activity, while with the benzyl side-chain toxicity is greatly enhanced by substituting the 3-furylmethyl nucleus for the methyloxocyclopentenyl ring[122,123], to give 5-benzyl-3-furylmethyl chrysanthemate (125). Elliott has shown[124] by synthesis of nor-rethrins[22], that the methyl group on the oxocyclopentenyl ring of the natural esters is probably not essential for



126 D= 

127 D= 

128 D= 



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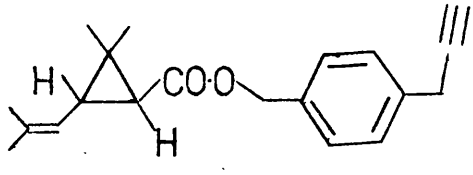


130

insecticidal activity.

With the advent of flexible syntheses of chrysanthemic acid, it has become possible to vary the acid portion of synthetic pyrethrins[79,80]. It has been shown[67] that variation of the substituents on position 3 of the cyclopropane ring (1) leads to esters of lower activity than the natural pyrethrins. However, alteration of the substituents at position 2' of the alkene chain has demonstrated that the activity of the ester decreases as the size of the substituent increases. Replacement of the geminal methyl groups at 2' (1) by a cyclic structure also enhances the activity of the compound, and comparison of esters 126, 127 and 128 has shown that 127, 5-benzyl-3-furylmethyl (+)-trans-ethanochrysanthemate, is the most active of the three[125,126].

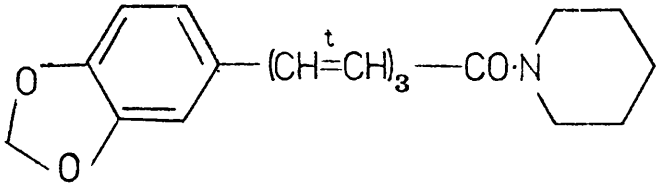
Katsuda and coworkers[127] have found that chrysanthemic esters containing a propargyl function as an integral part of the alcohol component are highly toxic against common house-fly and are far more active than their allyl analogues. Thus 5-propargylfurfuryl chrysanthemate (prothrin, 129) is 11·6 to 29·0 times as toxic in knock-down as allethrin, and exhibits low toxicity to mammals, while p-propargylbenzyl chrysanthemate (130) displays similar properties. Esters containing the 3-butynyl, 4-pentynyl and ethynyl functions have also been found

to be strongly active.[128]

Insecticidal Action of Rethrins.

As has already been indicated, steric factors play an important role in the insecticidal activity of rethrins. Thus esters made from (+)-trans-chrysanthemic acid are more toxic than those from the (+)-cis-, while both (+)-acids give rethrins 40-50 times more potent than their (-)-counterparts[5]. The esters from (+)-cinerolone and (+)-allethrolone are at least five times as toxic as those from the (-)- alcohols[5].

The absolute and relative toxicity of the rethrins varies with the insect species, with the age, sex and storage environment before and after treatment, and also with the medium and method by which the insecticide is applied[5, 129]. In comparing two compounds, the method of application must be such that each insect receives the same dose, and this is best achieved by treating individual insects with measured volumes of insecticide dissolved in a suitable solvent. On the basis of the weight required to affect a given weight of insect species, the natural pyrethrins compare well with many other insecticides such as DDT, aldrin, dieldrin and parathion[130, 131]. Because they are unstable in air, few films of diminishing potency exist for any significant length



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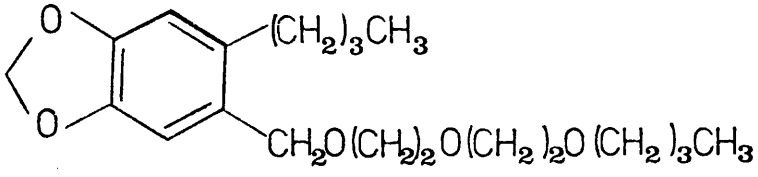

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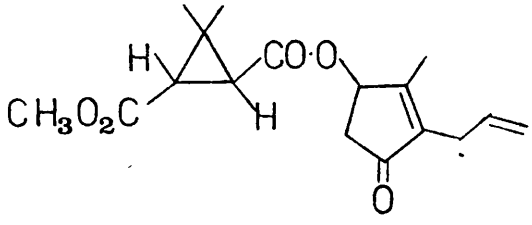

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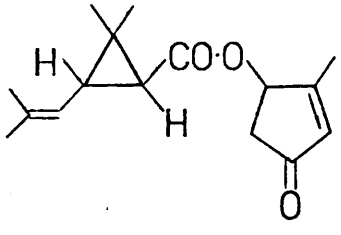


134

of time after application, a factor which may have hindered insects from aquiring resistance[5].

Although there is no evidence of synergistic or antagonistic activity towards the pyrethrins by other compounds in the pyrethrum extract[132], certain compounds have been found to greatly enhance the insecticidal effectiveness of the natural pyrethrins and cinerins[5]. Most of the synergists contain a methylenedioxyphenyl group and/or an amide linkage[133]. Among those of natural origin are piperettine (131)[134] and various lignans including hibbalactone[135] and sesamolin[136,137]. The amide N-isobutylundecylenamide has long been used as a synthetic synergist, while piperonyl butoxide (132) has also been used with success[138]. The effectiveness of synergists is illustrated by the fact that an 8:1 mixture of sesamolin and natural pyrethrins is 31 times as effective towards house-flies as natural pyrethrins alone[139]. A pyrethrins preparation giving an 18·4% kill gave, when synergized with (+)-sesamin, a kill of 82·3%.

The toxicity level of the rethrins is very sensitive to structural and stereochemical alterations[140,141]. Thus (±)-allylrethronyl methyl-(±)-trans-caronate (133)[142] and (±)-H-rethronyl (±)-trans-chrysanthemate (134) are not toxic to Mustard Beetles[5], showing that the side-chains in both acid and alcohol portions are essential

for activity. For highest potency, these side-chains should be unsaturated, since when the double bond in both cis- and trans-chrysanthemic acids is hydrogenated, the resultant dihydroesters are less toxic[5]. Similarly, rethrins from rethrolones with saturated side-chains exhibit reduced activity[5].

A considerable number of synthetic rethrins have now been tested and found to be active in varying degrees with respect to both knock-down and mortality effects. Thus Ogami and coworkers[143] have shown that prothrin (129), on comparison with pyrethrin and allethrin, displays the most potent activity against house-flies and mosquitoes. The acute toxicity of 129 to mice, rats and carp is low, its oral LD50 being 5900 and 10000mg/kg in male mice and rats respectively.

TABLE II

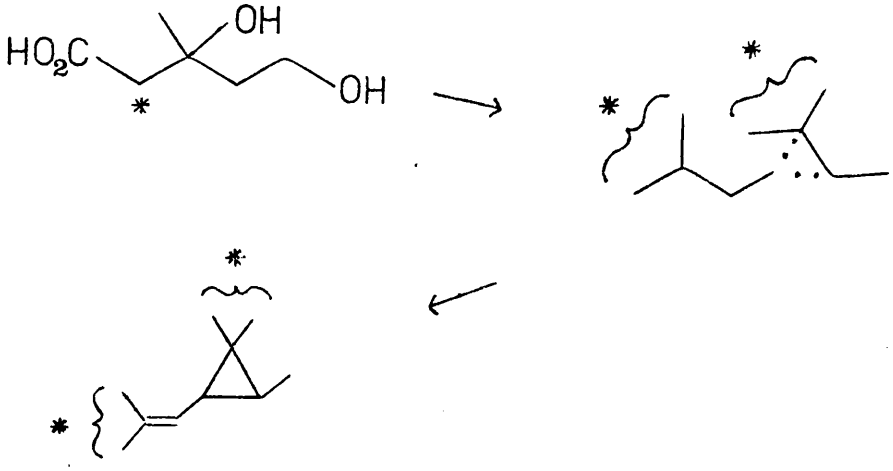
Pyrethroid + PPB x 8	KD%, 62mg/l. conc. after 5min.	after 10min.	LD50 mg/l.
127	2·5	27·0	13·8
135	42·0	56·0	125
136	1·5	27·5	160
137	11·6	42·2	18·5
natural pyrethrins	46·2	67·6	104·7

Table II[125] compares the effect of several synthetic rethrins and natural pyrethrins on Musca domestica using piperonyl butoxide (132, PPB) as a synergist. The results show the extreme toxicity of 127 compared with natural pyrethrins.

The mode of application is such that the exact quantity of insecticide applied per insect is known[125]; consequently, one can calculate the dose which is lethal to 50% of the insects (LD50). This can be expressed in 10^{-3} µg per fly, so that for 127, the lethal quantity is 3·15±1 for the male fly and 5·25±1·5 for the female.

The testing of natural and synthetic pyrethroids as water-based pressurized formulations in closed barns has shown that the synthetic compounds tend to be less irritating to the nasal passages than natural preparations[144].

The main advantage of pyrethrins over other insecticides is their low toxicity to mammals, a fact which is probably due to their susceptibility to oxidative metabolism[145]. Experiments directed at determining the exact nature of the physiological action of pyrethrins in insects[146] have shown that allethrin is metabolized in living house-flies and in the house-fly mixed-function oxidase system by attack at the trans- (major site) and cis- (minor site) methyl groups of the isobutenyl side-

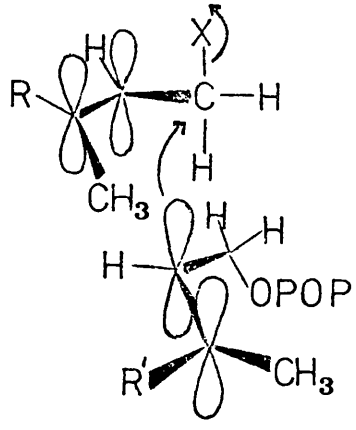


SCHEME 9

chain, forming in succession the hydroxymethyl, aldehyde and acid compounds. No hydrolysis or attack at the alcohol part of the ester has been detected, although there are trace amounts of unidentified metabolites. Piperonyl butoxide inhibits hydroxylation of the methyl groups, presumably exposing the insect to the toxic effects of the pyrethrins for a longer time. Living house-flies excrete the hydroxymethyl compounds, probably as glycosides. Pyrethrin I (1), phthalthrin (115) and dimethrin (116) are similarly metabolized both in vivo and in vitro. Information and speculation regarding the precise mode of insecticidal action of pyrethrins is available in references 147-151.

Biosynthesis of Pyrethroids.

Chrysanthemic acid and chrysanthemum dicarboxylic acid are formally derived from two isoprene units linked in a "meso to tail" fashion[5] (scheme 9). Thain and coworkers[152] have shown that (±)-2-^{14}C-mevalonic acid is incorporated into the two chrysanthemic acids when fed to the achenes of pyrethrum flowers, a fact which supports isoprenoid derivation. The mechanism involved in the biogenesis may be very similar to that proposed for presqualene[153] (scheme 10). Initially, a new σ-bond is formed through interaction of two allylic pyrophosphate



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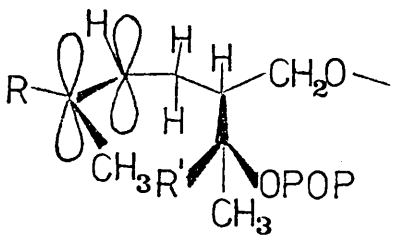

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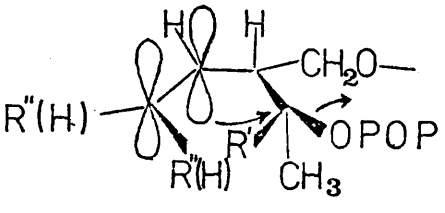

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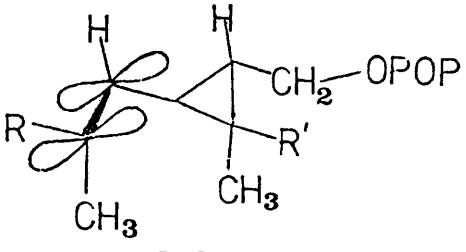

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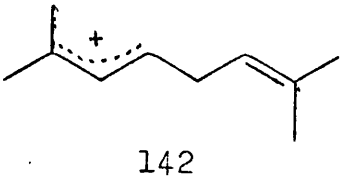
SCHEME 10



142

units, involving S_N2 displacement by the π-bond in one centre of the pyrophosphate anion in the second (138). Once formed, 139 is subjected to the action of an isomerase which produces the disubstituted olefin (140). The resulting homoallylic system is subject to cyclopropane ring closure accompanied by proton elimination to establish a trans- trisubstituted olefinic bond at the original site prior to isomerase action. It has been suggested[154] that the transformation of the chrysanthemyl skeleton to a carbonium ion of type 142 represents the monoterpene equivalent of the presqualene alcohol to squalene interconversion.

The recently observed transformation[154] of an artemisyl skeleton into chrysanthemyl and santolinyl systems contradicts the proposal[53,58] that the chrysanthemyl skeleton is the precursor of the artemisyl and santolinyl series of monoterpenes.

There is no evidence that (±)-2-^{14}C-mevalonic acid is directly involved in the formation of ketols which constitute the alcohol portions of natural pyrethrins. These do not seem to be built up on a partial isoprenoid basis; however, there is evidence[152] that they are derived at least in part from acetate.

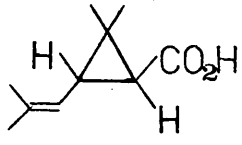
Labelling studies[155] have suggested that pyrethrins II are derived from pyrethrins I in Nature, probably via

an enzymic hydroxylation-oxidation process at the trans-methyl groups of the isobutenyl side-chains, followed[156] by "esterification" with the S-methyl group of L-methionine. This mode of oxidation is similar to that established in the biological oxidation of pyrethrins in house-flies[146c] and also in their photochemical decomposition[104].

A Novel Synthecis of (±)-*trans*-Chrysanthemic Acid.

The following abbreviations have been made in the presentation of NMR data:

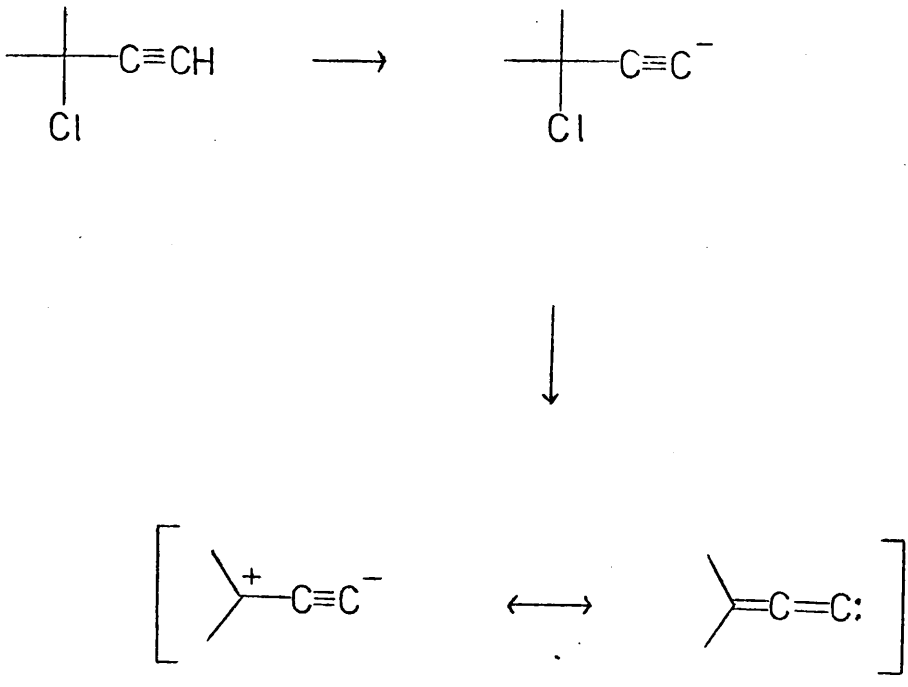
bd	broad doublet
bm	broad multiplet
ct	complex triplet
d	doublet
dd	doublet of doublets
m	multiplet
q	quartet
s	singlet
t	triplet



10

The high insecticidal activity and low mammalian toxicity[5,111] of the pyrethrins have encouraged the development of synthetic routes to chrysanthemic acid (10). It has been found that the four isomers do not give rise to insecticidal esters of equal potency, and that generally the trans- acids produce more toxic esters than the cis- acids; the latter, however, usually give rise to esters with better knock-down properties. Since the most toxic esters are normally derived from (+)-trans-chrysanthemic acid, it is important that any viable synthesis of the acid and its analogues should be stereoselective, allowing the trans- isomer to be produced predominantly.

The original commercial synthesis of chrysanthemic acid involving the reaction of ethyl diazoacetate with 2,5-dimethylhexa-2,4-diene in the presence of a copper catalyst[31], is dangerous, and only produces about 65-70% ethyl chrysanthemate in the trans- form. It was therefore the object of this thesis to devise an alternate, stereoselective synthesis. From a commercial viewpoint, it was desirable that such a synthesis should involve inexpensive and readily available starting materials and should proceed in reasonably high yield. It was also required that the synthesis should be adaptable, and allow scope for the variation of functional groupings on the

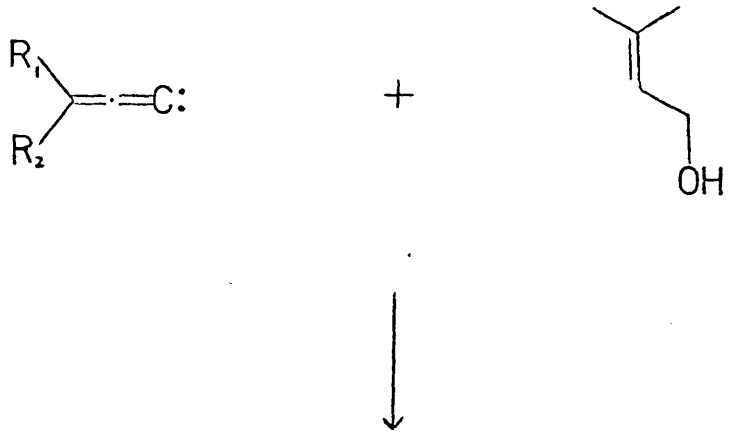


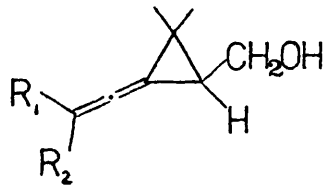
SCHEME 11

acid molecule.

The dominant feature of the chrysanthemic acid structure is the cyclopropane ring, facile formation of which must form the basis of the chosen synthetic route. The manner of cyclopropane ring formation employed in the present synthesis was inspired by the work of Hartzler[157], who found that treatment of 3-chloro-3-methylbut-1-yne with base produced dimethylvinylidene carbene[171] (scheme 11), which reacted with olefins to yield alkenylidenecyclopropanes. This work has been substantiated recently by Leandri and Santelli-Rouvier[158], while other workers[159] have reported the formation of dimethylvinylidene carbene from various starting materials, including 1-halogenoallenes. By suitable choice of olefin to trap the allene carbene, it was proposed to use the above method to synthesize (±)-trans-chrysanthemic acid, starting with 3-chloro-3-methylbut-1-yne.Ideally, it was desirable that such an olefin should be 3,3-dimethyl-acrylic acid or a corresponding ester. However, it was found that carbene addition did not proceed in such circumstances, presumably because of the conjugative effect of the carbonyl function. Attempts to overcome this problem will be discussed later.

The synthesis of racemic trans-chrysanthemic acid was successfully achieved starting with 3,3-dimethyl-





143

a) $R_1 = R_2 = -CH_3$

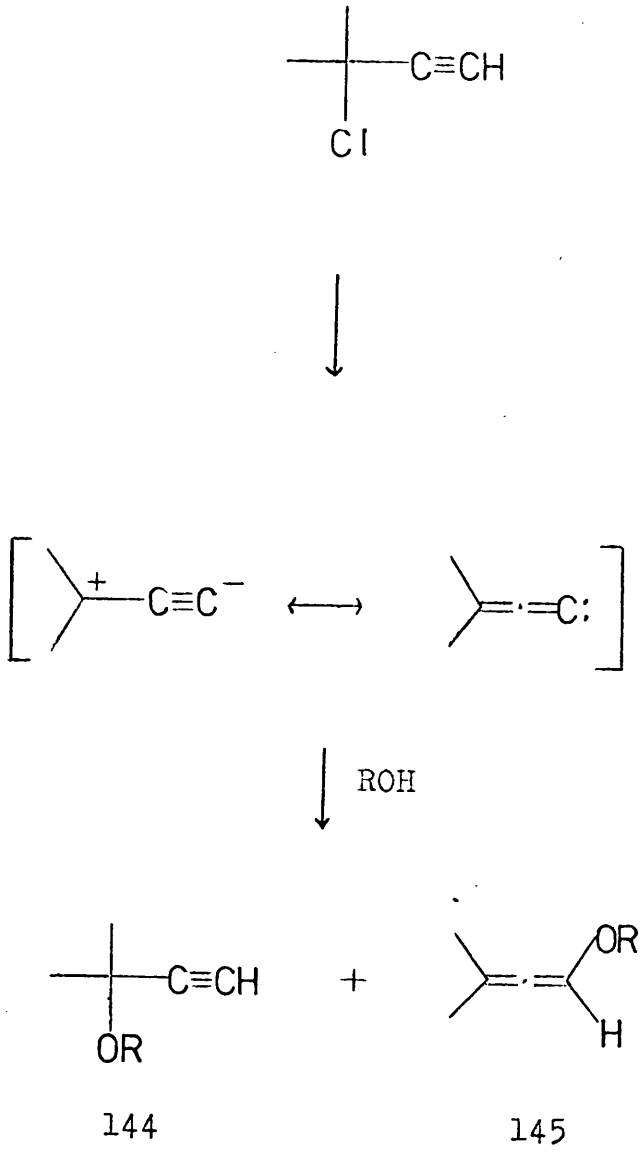
b) $R_1, R_2 = -(CH_2)_5-$

c) $R_1, R_2 = -(CH_2)_4-$

SCHEME 12

allyl alcohol, so that both isoprenoid "halves" of the carbon skeleton were essentially derived from the same starting material, 2-methylbut-3-yn-2-ol. The tertiary halide, 3-chloro-3-methylbut-1-yne and the other halides used in the synthesis of chrysanthemic analogues, can all be readily prepared from the corresponding carbinols according to the methods of Hennion[160], while 3,3-dimethyl-allyl alcohol was prepared cleanly in high yield by reduction of 3,3-dimethylacrylic acid with lithium aluminium hydride. The NMR spectrum shows resonances at τ 8·30 and 8·25 (each 3H, s; vinylic methyl), 5·90 (2H, d, J 7Hz) and 4·60 (1H, ct, J 7Hz; vinylic hydrogen).

3-Chloro-3-methylbut-1-yne reacted with potassium t-butoxide below 0° under a nitrogen atmosphere, to produce dimethylvinylidene carbene, which reacted <u>in situ</u> with 3,3-dimethylallyl alcohol to give 2-(2'-methyl-propenylidene)-3,3-dimethylcyclopropanemethanol (143a) in 45% yield, based on chloride (scheme 12). Initial experiments were carried out using 3,3-dimethylallyl alcohol (4M excess) both as solvent and substrate; it was later found, however, that a 1:1:1 molar ratio of reactants could be used in n-pentane, although the yield of allene (143a) was reduced. Potassium or sodium hydroxide may be used satisfactorily as bases in the reaction. The structure of the allenic alcohol (143a) was established



144 145

SCHEME 13

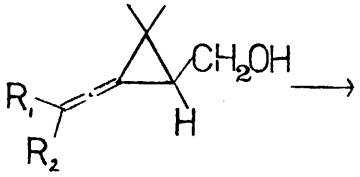
spectroscopically, the NMR spectrum showing resonances at τ8·73 and 8·72 (each 3H, s; geminal tertiary methyl), 8·25 (6H, s; allenic methyl), 8·15 (1H, t, J 7Hz) and 6·24 (2H, dd, J 7 and 2 Hz); the coupling of the methylene protons and the adjacent cyclopropane proton was confirmed by double resonance. Further support for the structure is provided by the mass spectrum which has a molecular ion peak at m/e 152, and the IR spectrum which shows bands at ν_{max} 3620 (free primary -OH), 3320 (bonded -OH) and 2000 (allene) cm^{-1}, while further characterization was obtained by formation of the p-nitrobenzoate.

Since the yield for the carbene addition is comparable to that reported by Hartzler using non-functionalized olefins, it appears that the presence of the allylic hydroxy group does not adversely affect the course of the desired reaction. There are, however, several by-products, which, although not specifically examined, may be rationalized on the basis of previous observations. TLC (ethyl acetate:light petroleum 85:15) of the crude reaction mixture showed the main impurity to be a very non-polar compound. This may be accounted for by the formation of unrearranged acetylenic ethers (144)[157,158] as a result of reaction of t-butanol or 3,3-dimethylallyl alcohol on the zwitterion formed from the acetylenic halide. It is also possible for dimethylvinylidene carbene

to insert into the oxygen-hydrogen bond of carbinols[161] (145, scheme 13), but absence of an allenic band in the IR spectrum suggests that this is of little significance in the present case.

The only other significant impurity was a compound (or compounds) which was only slightly less polar than the allenic alcohol. The high instability of this compound precluded its isolation in a pure state, hence rendering spectroscopic evidence unreliable, apart from establishing its alcoholic nature. It may have resulted from carbene insertion into the C-H bond of the carbon atom bearing the hydroxyl group, such reactions having been previously observed[162]. Compounds resulting from vinylidene carbene insertion have also been found to be highly unstable[163]. Although the yield of the compound was small (5%) in the absence of an additional solvent, it increased considerably when n-pentane was used, while on performing the reaction with 1-ethynylcyclopentyl chloride, a compound of identical polarity was formed in greater yield than the desired allene. This by-product decomposed rapidly however during column chromatography, thus facilitating its separation from the allenic alcohol.

An additional complication in the carbene addition reaction was the possibility of insertion into the allene once the latter had formed[164], although this was not



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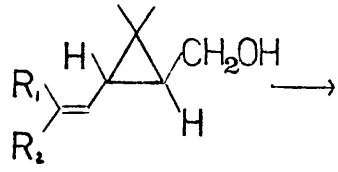

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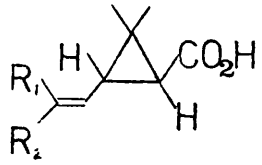
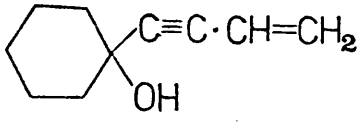


147

a) $R_1 = R_2 = -CH_3$

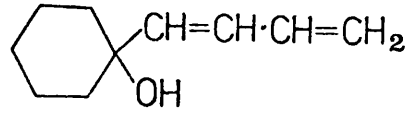
b) $R_1, R_2 = -(CH_2)_5-$

c) $R_1, R_2 = -(CH_2)_4-$



148

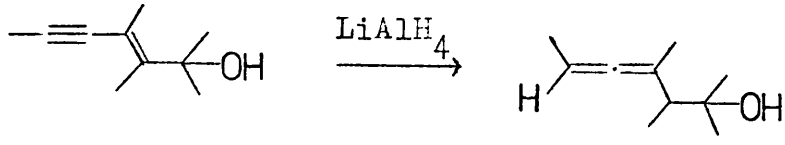
$\xrightarrow{LiAlH_4}$



149

thought to be serious in the present case. Slow, dropwise addition of the halide to the stirring reaction reduced the formation of by-products to a limited degree.

The next stage in the synthesis of (±)-trans-chrysanthemic acid was the regioselective and stereoselective reduction of the allenic alcohol (143a) to (±)-trans-chrysanthemyl alcohol (146a). Catalytic hydrogenation was inapplicable, since cyclopropyl allenes[157] in such conditions undergo simultaneous hydrogenation of both double bonds and of the cyclopropane ring. Initial experiments were directed towards achieving the desired reduction by means of controlled hydride delivery using lithium aluminium hydride, a technique which had been successfully applied to allylic systems[165]. It was hoped that the lithium aluminium complex of the carbinol would be sterically suited to internal hydride transfer to the cyclopropyl double bond. However, experiments carried out under a variety of conditions produced only the unreacted allene. The failure of this approach is not altogether surprising in view of the results of Bates[166], who found that treatment of the acetylenic alcohol (148) with lithium aluminium hydride results in the corresponding diene-alcohol (149), the bond which is reduced occupying a position in the molecule which is analogous to that of the cyclopropane ring in the allenic alcohol (143a).



150 151

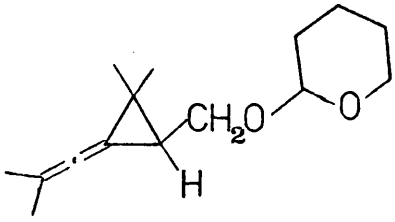
This suggests that the hydroxyl group in 143a is one carbon atom too distant from the cyclopropyl double bond to allow sterically controlled hydride delivery in the desired manner to take place. Further evidence for the infeasibility of the above method is provided by the work of Santelli[167], who showed that the acetylenic alcohol (150) is reduced with lithium aluminium hydride to the allenic alcohol (151), a product so closely related to 143a as to suggest that the latter would be completely unreactive under the same conditions.

Since partial reduction of acyclic allenes by alkali metals in liquid ammonia leads to non-stereospecific addition of hydrogen, mainly at the most hindered double bond[168], it was considered probable that the cyclopropyl double bond in allene 143a, being the more strained, would be selectively reduced in these conditions, although in some instances treatment with sodium or lithium in ammonia has led to reductive cleavage of cyclopropanes[169]. Treatment of the allenic alcohol (143a) with sodium in liquid ammonia proceeded in a regioselective and stereoselective manner to give a high yield of (±)-chrysanthemyl alcohol (146a) in a trans:cis ratio of not less than 3:1, as shown by NMR and GLC. The alcohol, obtained from the reaction without further purification, was identified by comparison with an

authentic sample. The NMR spectrum of the trans- alcohol (146a) shows resonances at τ8·92 and 8·84 (each 3H, s; geminal tertiary methyl), 8·29 (6H, s; vinylic methyl), 6·34 (2H, AB of ABX, J ~11Hz), 5·10 (1H, bd, J 8Hz; vinylic hydrogen) and ~9 (1H, X of ABX, obscured; 1H dd, obscured) the presence of the cis- isomer being detected by the resonance of the vinyl proton at τ5·04 (1H, bd, J 7Hz). The main difference between the spectra of the cis- and trans- alcohols is the ABX system resulting from the non-equivalence of the methylene protons in the trans- isomer, the corresponding protons in the cis- compound being equivalent and resonating as a doublet at τ6·35 (2H, d, J 7Hz). These values are in agreement with those published for chrysanthemyl alcohol[41], while the structure is also verified by the mass spectrum which shows a molecular ion peak at m/e 154, and the IR spectrum which indicates the presence of a primary hydroxyl group (ν_{max} 3620cm^{-1}).

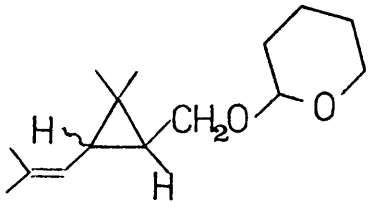
The compound was further characterized by formation of the 3,5-dinitrobenzoate, from which the trans- isomer was preferentially crystallized and found to be identical with a genuine sample.

The mechanism of the reduction is not clear, although the stereoselectivity would appear to result from protonation of an intermediate cyclopropyl carbanion[170]



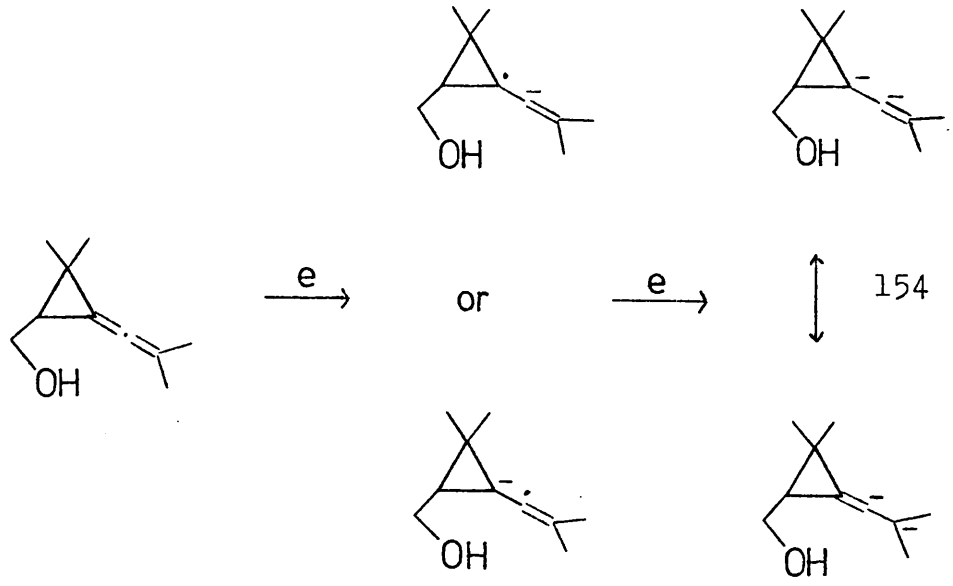
152

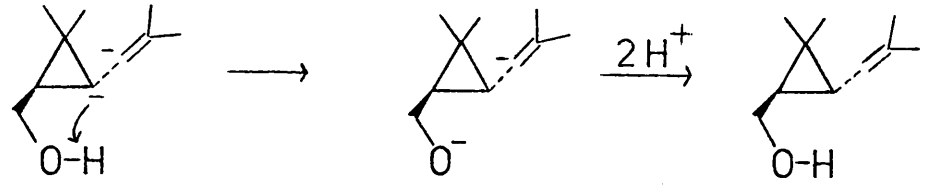
Na/NH3



153

by intramolecular delivery from the pendant hydroxyl group. Evidence for this theory is provided by experiments using the tetrahydropyranyl ether (152) of the allenic alcohol (143a), which was readily formed by the usual method. The NMR spectrum shows resonances at τ8·72 (6H, s; geminal tertiary methyl), 8·25 (6H, s; allenic methyl), 6·32 (2H, d, J 7Hz, obscured) and 5·37 (1H, bm), while the structure was verified by the mass spectrum which shows a molecular ion peak at m/e 236, and the IR spectrum, ν_{max} 2000cm^{-1} (allene) . The tetrahydropyranyl ether (152) was treated with sodium in liquid ammonia, regioselective reduction of the cyclopropyl double bond again occurring, as shown by NMR and IR. Hydrolysis of the ether produced (±)-chrysanthemyl alcohol, which was shown by NMR and GLC to consist of a 1:1 mixture of the cis- and trans- isomers. This result suggests that in the absence of the directing influence of the hydroxyl group, the reduction occurs non-stereoselectively. Reduction using allene (143a) with a deuterated hydroxyl group or neutralizing the reduction with D_2O produced no change in the NMR spectrum, allowing no further elucidation of the mechanism to be achieved. By analogy with the previously proposed mechanism for the sodium/ammonia reduction of acyclic allenes[172], it may be presumed that the reaction proceeds

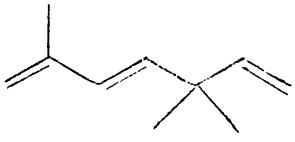




SCHEME 14

by addition of one electron to give radical anions, followed by subsequent addition of a further electron to produce an allylic dianion (154, scheme 14) which can exist in resonance forms. The more stable resonance form might be expected to be that in which the double bond is in the least strained position, i.e. away from the ring, and where the negative charge is on the cyclopropane ring, thus accounting for the regio-selectivity of the reduction. It is known that in the case of cyclopropyl carbanions, inversion is slower than the rate of proton capture[173], so that it would seem that the dianion, once formed, preferentially adopts a trans-configuration prior to internal delivery of a proton from the hydroxyl group to the cyclopropyl anion. Transfer of the hydroxyl proton would be facilitated by the hydrogen bonding between it and the bonds in the cyclopropane ring[174], a phenomenon which, in the case of cyclopropyl carbinol, hinders rotation and allows only one rotational isomer to be detected.

The final stage in the synthesis was the oxidation of (±)-trans-chrysanthemyl alcohol to the acid. The step presented a considerable amount of difficulty, largely because of the inherent instability of the chrysanthemyl system towards acidic media. While cyclopropanes are known to undergo ring-opening in acid[175], both cis- and trans-



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chrysanthemyl alcohols are converted to artemisia triene (155) on heating with PTSA in benzene[53]. Consequently, attempted Jones-type oxidations of chrysanthemyl alcohol resulted in a mixture of acidic compounds, from which the desired product could not be isolated in acceptable yield. Of the oxidations attempted in basic media, only hydrogen peroxide in sodium hydroxide solution appeared promising. This method, however, suffered from irreproducibility, and apparently caused equilibration into a 3:2 cis:trans mixture. Of all the oxidative methods tried, only that carried out using chromium trioxide/pyridine proceeded in a satisfactory yield to the desired acid. Treatment of (±)-trans-chrysanthemyl alcohol with chromium trioxide in pyridine under anhydrous conditions for twelve hours at room temperature led to facile formation of (±)-trans-chrysanthemyl aldehyde, which could be isolated in high yield. The NMR spectrum shows resonances at τ 8·81 and 8·67 (each 3H, s; geminal tertiary methyl), 8·28 (6H, s; vinylic methyl), 5·06 (4·59 for cis- isomer) (1H, bd, J 8Hz; vinylic hydrogen) and 0·58 (1H, d, J 5·5Hz), while the IR spectrum exhibits bands associated with the aldehyde function, ν_{max} 2730 and 1700cm^{-1}. In the synthesis of chrysanthemic acid, the aldehyde was not isolated but, after the addition of a few drops of water,

the reaction was allowed to continue for a further four days. Since the use of dilute hydrochloric acid in the work-up led to very low yields, the pyridine was removed with sodium bisulphate to give, after work-up, racemic chrysanthemic acid (147a) along with a little aldehyde. After preparative TLC, (ethyl acetate:light petroleum 40:60), the acid was identified by comparison with an authentic sample, and shown (NMR) to contain not less than 75% of the trans- isomer. The NMR spectrum shows resonances at τ8·85 and 8·70 (each 3H, s; geminal tertiary methyl), 8·30 (6H, s; vinylic methyl), 5·10 (1H, bd, J 8Hz; vinylic hydrogen), 8·63 (1H, d, J 5·5Hz) and 7·92 (1H, dd, J 5 and 8Hz). In the cis- isomer, the vinylic proton resonates at τ4·67, and comparison of the integration associated with this proton with that of the corresponding proton in the trans- isomer, allows a fairly accurate estimate of the cis:trans ratio to be made. These values are in agreement with those published for (±)-trans-chrysanthemic acid[41], while the mass spectrum (M^+ 168) and IR spectrum are identical to those of a genuine sample.

Having established a route to (±)-trans-chrysanthemic acid, it was necessary to extend the synthesis to the preparation of analogues, since a considerable number of these have been synthesized by alternate routes and

found to be active. The first analogue which was synthesized by the present route was (±)-trans-2-cyclohexylidene-methyl-3,3-dimethylcyclopropanecarboxylic acid (147b). 1-Ethynylcyclohexyl chloride was prepared from the corresponding carbinol and reacted with 3,3-dimethylallyl alcohol in the presence of potassium t-butoxide to yield 2-cyclohexylidenemethylene-3,3-dimethylcyclopropane-methanol (143b). As in the chrysanthemic case, the use of n-pentane as solvent caused an increase in the amount of by-products at the expense of the desired allene. The NMR spectrum shows resonances at τ8·75 and 8·73 (each 3H, s; geminal tertiary methyl), 8·28 (1H, t, J 7Hz), 6·28 (2H, dd, J 7 and 2Hz), 7·84 (4H, bm) and 8·45 (6H, bm), while further verification of the structure is provided by the mass spectrum which shows a molecular ion peak at m/e 192, and the IR spectrum which exhibits bands at ν_{max} 3620cm^{-1} (primary -OH) and 2000cm^{-1} (allene). The compound was further characterized as the 3,5-dinitro-benzoate, in which, it was noted, the non-equivalence of the methylene protons in the NMR spectrum was enhanced, so that they and the adjacent cyclopropane proton formed an ABX system. The allene (143b) was reduced with sodium in liquid ammonia to (±)-2-cyclohexylidenemethyl-3,3-dimethylcyclopropanemethanol (146b) which was shown by NMR and GLC to comprise predominantly the trans- isomer,

(<75%). The NMR spectrum shows resonances at τ8·96 and 8·89 (each 3H, s; geminal tertiary methyl), 7·92 (4H, bm), 8·50 (6H, bm), 5·28 (1H, bd, J 7Hz; vinylic hydrogen) and 6·43 (2H, AB of ABX, J ~12Hz), while the IR spectrum indicates the presence of the primary hydroxyl group ν_{max} 3620cm^{-1}, and the mass spectrum confirms the molecular weight as 194. The compound was further characterized as the 3,5-dinitrobenzoate.

Oxidation of the alcohol (146b) to the corresponding acid (147b) was achieved using the same conditions as in the chrysanthemic case. The structure of 147b was established spectroscopically, the NMR spectrum showing resonances at τ8·82 and 8·70 (each 3H, s; geminal tertiary methyl), 7·9 (4H, bm), 8·44 (6H, bm) and 5·12 (2H, bd, J 7Hz; vinylic hydrogen), a further small vinylic signal at τ4·70 (2H, bd, J 7Hz) indicating the presence of the cis- isomer. The mass spectrum shows a molecular ion peak at m/e 208, while the IR spectrum exhibits a carbonyl band at ν_{max} 1700cm^{-1}.

The acid (147b) has previously been synthesized and used in the preparation of synthetic pyrethrins which, however, do not exhibit the same degree of insecticidal activity as the natural esters. The cyclopentyl analogue (147c) on the other hand, gives rise to esters of considerably increased toxicity, so the synthesis of

(±)-trans-2-cyclopentylidenemethyl-3,3-dimethylcyclopropanecarboxylic acid (147c, ethanochrysanthemic acid) was attempted by the present route.

A considerable set-back to the viability of this approach as a commercial synthesis of 147c, is the high cost of the starting material, 1-ethynylcyclopentanol, the preparation of which from cyclopentanone and acetylene proved to be very laborious[197]. The carbinol was converted to the chloride by the same method used for the cyclohexyl analogue[160], although considerable difficulty was encountered due to the high instability of 1-ethynylcyclopentyl chloride. As the latter has never been reported in the literature, it was desirable to characterize it spectroscopically; however, it was found impossible to obtain a diagnostic NMR spectrum before a significant amount of decomposition had occurred, and the best evidence which could be obtained for the authenticity of the compound was an IR spectrum (liquid film) run immediately after preparation and distillation. This showed the presence of the acetylenic function and the absence of the hydroxyl group.

Freshly prepared 1-ethynylcyclopentyl chloride was reacted with potassium t-butoxide in the presence of 3,3-dimethylallyl alcohol to produce 2-cyclopentylidenemethylene-3,3-dimethylcyclopropanemethanol (143c), in

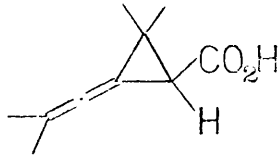
much poorer yield than was obtained in the two previous carbene addition reactions. The NMR spectrum of the compound shows resonances at τ 8·68 and 8·71 (each 3H, s; geminal tertiary methyl), 7·65 (4H, bm), 8·30 (4H, bm) and 6·25 (2H, AB of ABX), while the mass spectrum shows the expected molecular ion peak at m/e 178, and the IR spectrum indicates the presence of the primary hydroxyl and allenic functions with bands at ν_{max} 3630 and 2000cm^{-1} respectively. The compound was further characterized as the 3,5-dinitrobenzoate, the NMR spectrum of which shows more distinctly than in the parent compound, the ABX system formed by the methylene protons and the adjacent cyclopropane proton.

The poor yield of the allene (143c) was largely due to the formation of a by-product which was only slightly less polar than 143c and which, on TLC (ethyl acetate: light petroleum 85:15), ran as a negatively-staining spot (iodine) just above that due to the desired compound. Although this by-product or an analogue had always been observed in previous carbene addition reactions, in experiments involving 1-ethynylcyclopentyl chloride it was produced in much greater quantities, regardless of whether n-pentane was used as a solvent or not; its yield, in fact, somewhat exceeded that of 143c. Since it was highly unstable and decomposed on column chromatography,

this by-product did not present any separation difficulties.

The allenic alcohol (143c) was cleanly reduced with sodium in liquid ammonia to racemic 2-cyclopentylidene-methyl-3,3-dimethylcyclopropanemethanol (146c), which was shown by NMR and GLC to comprise 75% of the trans- isomer. The NMR spectrum shows resonances at τ 9·0 and 8·94 (each 3H, s; geminal tertiary methyl), 7·8 (4H,bm), 8·4 (4H, bm), 6·45 (2H, AB of ABX) and 5·10 (1H, bd, J 7Hz; vinylic hydrogen), a further vinylic signal at 5·0 indicating the presence of the cis- isomer. The molecular weight of 180 is confirmed by the mass spectrum, while a band at ν_{max} 3630cm^{-1} in the IR spectrum verifies the presence of the primary hydroxyl group, which as always, gives rise to an additional band at ν_{max} 3320cm^{-1} indicative of hydrogen bonding. The compound was further characterized as the 3,5-dinitrobenzoate.

Oxidation of the alcohol (146c) was achieved using chromium trioxide and pyridine as before, although a longer reaction time was required, by-products were formed, and a proportionately lower yield of the acid (147c) was obtained along with a substantial amount of the corresponding aldehyde. It is notable that aldehydes of the chrysanthemic series are unusually resistant to oxidation to the corresponding acid, since in all the primary alcohol oxidation steps attempted, a considerable



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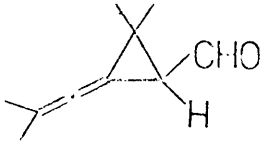
amount of aldehyde (usually about 20%) was obtained along with the acid even after seven or eight days.

The structure of 147c, isolated from the oxidation, is confirmed by its mass spectrum, which is identical to that of a genuine sample; its NMR spectrum shows resonances at τ 8·84 and 8·68 (each 3H, s; geminal tertiary methyl), 8·6 (1H, d, J 5·5Hz; resonance obscured), 7·7 (4H, bm), 8·3 (4H, bm) and 4·96 (1H, bd, J 7Hz; vinylic hydrogen), a further vinylic signal at 4·50 (1H, bd, J 7Hz) indicating the presence of the cis-isomer. The IR spectrum shows a carbonyl peak at ν_{max} 1700cm^{-1} and a broad band typical of a carboxylic acid function. Although the present synthesis provides a route to the very much desired acid (147c), the overall yield is unacceptably low; it is not, therefore, under the present conditions, a viable commercial proposition.

While the acids 147b and 147c are attainable from other routes, the present synthesis provides the only method so far available for preparing allenic analogues of chrysanthemic acid. The simplest analogue, 2-(2'-methylpropenylidene)-3,3-dimethylcyclopropanecarboxylic acid (156), was obtained from chromium trioxide/pyridine oxidation of the allenic alcohol (143a). Although the time required was somewhat longer than for the oxidation of chrysanthemyl alcohol, the reaction was fairly clean



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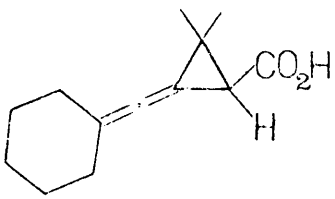
and yielded the acid (156) along with some of the corresponding aldehyde. Spectroscopic confirmation for the structure (156) is provided by the NMR spectrum which shows resonances at τ8·66 and 8·50 (each 3H, s; geminal tertiary methyl) and 8·20 (6H, s; allenic methyl), the mass spectrum which shows a molecular ion peak at m/e 166 and the IR spectrum which exhibits bands corresponding to the acid carbonyl and allenic functions at ν_{max} 1715 and 2025cm^{-1} respectively.

As in the oxidation of chrysanthemyl alcohol, the aldehyde could be isolated in high yield by stopping the reaction after twelve hours. The allenic aldehyde (157) was identified from the NMR spectrum which shows resonances at τ8·64 and 8·50 (each 3H, s; geminal tertiary methyl), 8·17 (6H, s; allenic methyl), 7·57 (1H, d, J 7Hz) and 0·85 (1H, d, J 7Hz; aldehyde proton), the mass spectrum which shows a molecular ion peak at m/e 150, and the IR spectrum which has characteristic bands at ν_{max} 2720 (aldehyde), 1700 (carbonyl) and 2000 (allene) cm^{-1}.

Although rather slow, the above reaction provides a mild method for the oxidation of allenic derivatives without attack at the allenic double bonds. Many other oxidative procedures would be unsuitable, since alkenylidenecyclopropanes have been shown to rearrange under acidic conditions[176]. By the same means, the allenic



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alcohol (143b) was oxidized to 2-cyclohexylidene-methylene-3,3-dimethylcyclopropanecarboxylic acid (158), the structure of the latter being confirmed by the NMR spectrum, which shows resonances at τ8·65 and 8·58 (each 3H, s; geminal tertiary methyl), 7·84 (4H,m) and 8·44 (6H, m), the mass spectrum which shows a molecular ion peak at m/e 206, and the IR spectrum which shows bands at ν_{max} 1700 (carbonyl) and 2015 (allene) cm^{-1} in addition to the usual strong band associated with carboxylic acids.

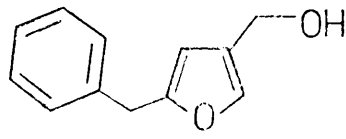
All the reactions involved in the syntheses of chrysanthemic acid and its analogues were of course followed by analytical TLC. The various primary alcohols were conveniently studied using a solvent system of ethyl acetate:light petroleum, 15:85, in which they all had an R_f of about 0·3. Iodine vapour was found to be the best developing agent, since both the allenic and olefinic alcohols exhibited an easily identifiable negative stain on its application. Ceric sulphate solution was only used once the plate had been developed with iodine. The acids were studied in a solvent system of ethyl acetate:light petroleum, 40:60, in which they exhibited R_f values of between 0·2 and 0·5. Again, iodine was used for developing.

It was noted that all the carbene addition reactions,

regardless of whether the desired compound was detected or not, were accompanied by the generation of a deep red-brown colour, a phenomenon which appeared to be indicative of the production of the allene carbene in the reaction medium.

It had been presupposed that the allene compounds involved in the synthesis would be structurally unstable. It was found, however, that under normal conditions, they appeared to be even more stable than their reduced analogues. During the long periods involved in the oxidation reactions, the small amount of by-products which was invariably formed was observed to be more prevalent in the case of the olefinic cyclopropane derivatives. The allenic compounds were perfectly stable under all the chromatographic conditions encountered, while the allenic alcohol (143a), during an attempt to reduce it with lithium aluminium hydride, was recovered unaltered after several hours refluxing in pyridine. Crystalline derivatives could be obtained analytically pure, although difficulty was encountered in subliming allenic oils to analytical purity.

Although the NMR spectra of cis- and trans-chrysanthemyl alcohol have been discussed in the literature[41], the difference in magnetic environment of the methylene protons attached to the carbon atom



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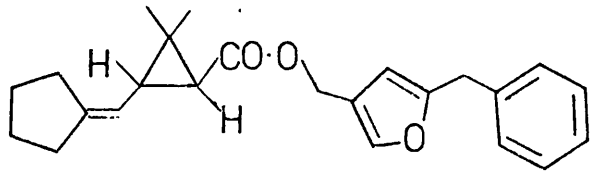
bearing the hydroxyl group in each isomer was not explicitly mentioned. In the cis-isomer, these protons are equivalent and resonate as a doublet at τ6·35 (J 7Hz), while in the trans- isomer they appear at the same chemical shift as the AB portion of an ABX system formed with the adjacent cyclopropane proton. In the allenic analogue (143a), the methylene protons exhibit a much smaller degree of non-equivalence, resonating as a double doublet (τ6·24, J 7 and 2Hz) in which the small second-order splitting is not identical in each half of the first-order doublet. The signal collapses to a singlet on irradiation at τ8·15, the chemical shift of the triplet due to the adjacent cyclopropane proton. These variations in magnetic environment are undoubtedly a consequence of the assumed or enforced conformation of the unsaturated side-chain[177].

In the NMR spectra of some of the compounds discussed above, the resonances of the cyclopropane protons were obscured, and their chemical shifts have not therefore been cited.

In recent years it has been found that synthetic pyrethrins having as their alcohol component, 5-benzyl-3-furylmethanol (159)[122], exhibit an insecticidal activity greater than that of naturally occurring pyrethrins. Consequently, synthetic chrysanthemic acid



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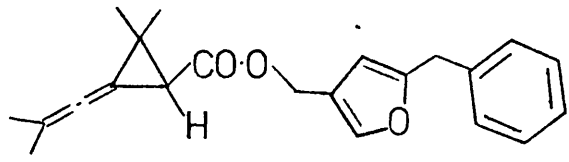

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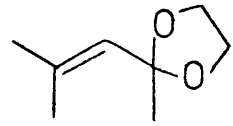
analogues have been esterified with this alcohol and biologically tested, 5-benzyl-3-furylmethyl (+)-trans-ethanochrysanthemate (137)[126] having been found to possess the greatest toxicity. Esterification of the allenic acid (156) in this way produced a compound (160) whose knock-down properties were somewhat less than 0·1 times as good as the corresponding (±)-trans-chrysanthemate, (LD50 0·13 compared with 0·01). The ester (160) was identified from its NMR spectrum, which shows resonances at τ8·68 (6H, s; geminal tertiary methyl), 8·24 (6H, s; allenic methyl), 8·6 (1H, s; resonance obscured), 5·07 (2H, s), 2·65 (1H, s), 3·95 (1H, s), 6·08 (2H, s) and 2·72 (5H, s); the mass spectrum shows a molecular ion peak at m/e 336 while the IR spectrum exhibits bands at ν_{max} 2020 (allene) and 1730 (carbonyl) cm^{-1}.

Since the first step of the described synthesis involves the reduction of 3,3-dimethylacrylic acid to the primary alcohol, while the final step is re-oxidation at the same carbon atom, the approach would benefit greatly if the carbene addition could be carried out on either 3,3-dimethylacrylic acid itself or a suitable derivative. Many attempts were made to effect the condensation on both the acid and the methyl ester under a variety of conditions, but in all cases the



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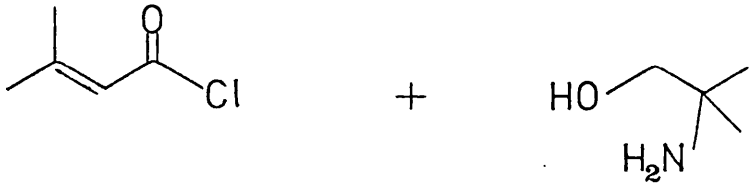

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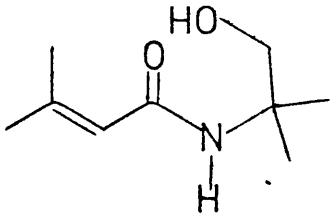

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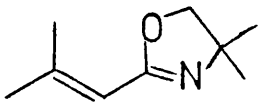

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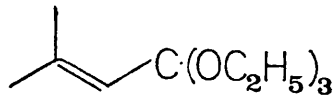
only products were the very non-polar compounds which occurred as by-products in successful carbene additions, these presumably being ethers (scheme 13) or the results of self-addition of dimethylvinylidene carbene. These products appeared to be formed in all attempted allene carbene additions regardless of whether the desired compound was observed or not; in the latter instance, unreacted olefin was recovered.

The inertness of the acid and ester to carbene insertion being presumably due to the conjugative effect of the carbonyl group, attempts were made to prepare derivatives which took the form of "protected" 3,3-dimethylacrylic acid and which would undergo carbene insertion prior to generation of the carboxylic acid function. Consequently, the ethylene glycol ketal of mesityl oxide (161) was treated with 3-chloro-3-methylbut-1-yne in the presence of potassium t-butoxide at both low and elevated temperatures, but in all cases only the non-polar compounds were formed and the ketal was recovered unchanged.

Another derivative, the oxazoline (165)[194], was prepared by reacting 3,3-dimethylacrylyl chloride with 2-amino-2-methylpropan-1-ol (163). The intermediate amide (164) was characterized by its NMR spectrum, which shows resonances at τ8·70 (6H, s; geminal tertiary

methyl), 8·16 and 7·89 (each 3H, d, J 1Hz; vinylic methyl), 4·40 (1H, bm) and 6·40 (2H,s), while the presence of the hydroxyl and amide functions is verified by the IR spectrum. The amide (164) was converted to the oxazoline (165) by refluxing in freshly purified thionyl chloride, the product again being identified by its NMR spectrum, which shows resonances at τ8·70 (6H, s; geminal tertiary methyl), 8·12 and 7·90 (each 3H, d, J 1Hz; vinylic methyl), 4·25 (1H, bm) and 6·06 (2H, s). The spectra of the amide and oxazoline are very similar, the diagnostic difference, and proof of ring formation, being a broad signal in the spectrum of the amide at τ4·80, which, however, disappears on treatment of the sample with D_2O. The structure of 165 is confirmed by its mass spectrum, which shows a molecular ion peak at m/e 153.

The oxazoline (165) was treated with 3-chloro-3-methylbut-1-yne in the presence of potassium t-butoxide at low and elevated temperatures both with and without solvent (benzene), but although the reaction assumed the red-brown colour which always accompanied carbene addition reactions, the oxazoline was recovered unchanged, the only major product being the omnipresent non-polar compound. Although as always with the unsuccessful carbene addition experiments, the reaction mixture was



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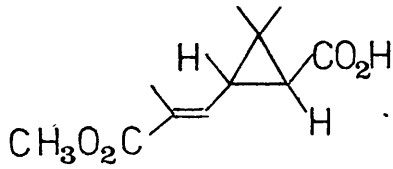

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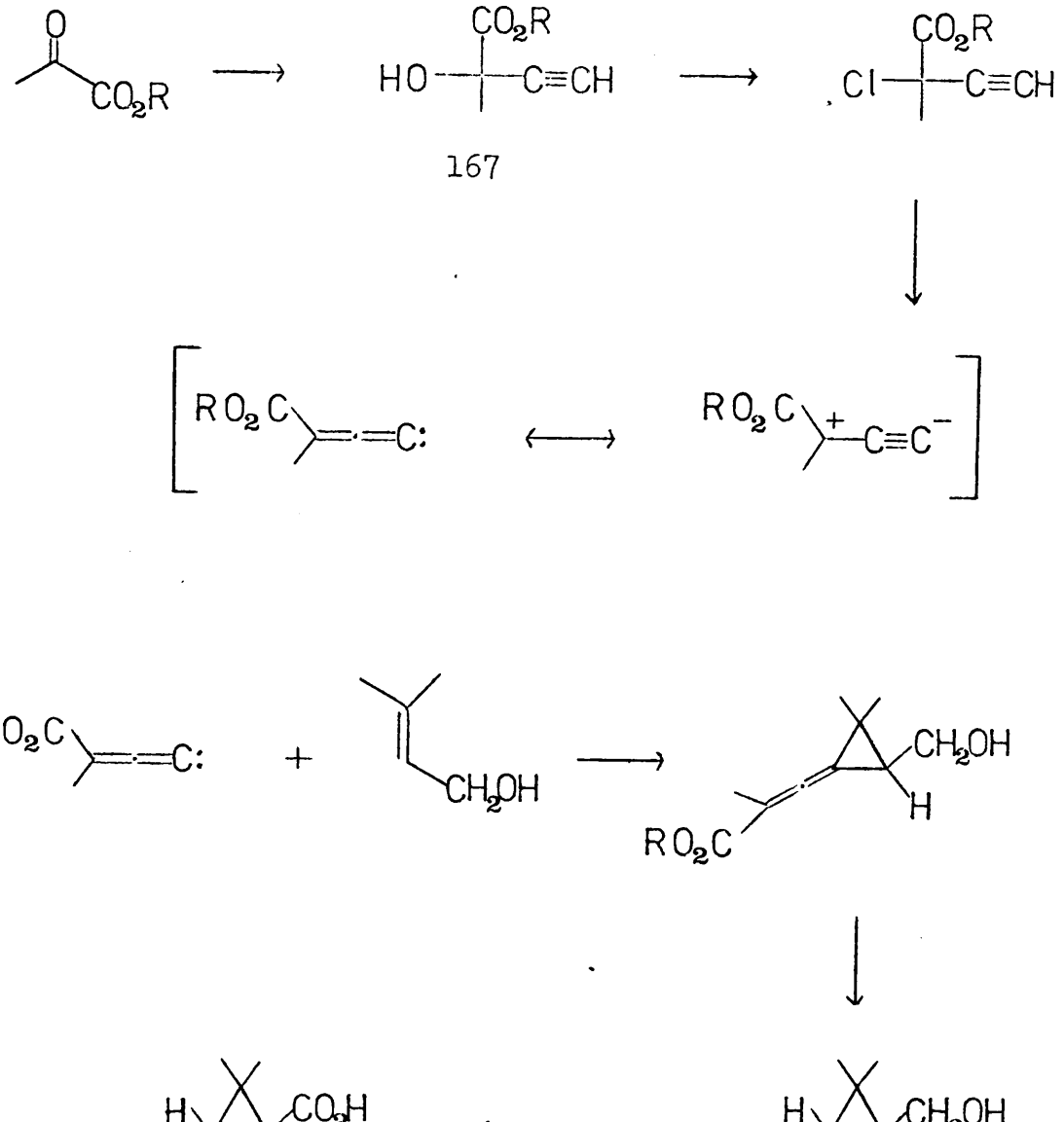
carefully examined by preparative TLC (ethyl acetate: light petroleum 40:60), no material was found which gave rise to a characteristic allenic band in the IR spectrum, indicating the inertness of the oxazoline to carbene insertion.

It was hoped that carbene insertion might proceed on the triethyl ortho-ester[178] of 3,3-dimethylacrylic acid (162), to which end 3-methylcrotononitrile was prepared by condensation of cyanoacetic acid with acetone followed by decarboxylation[196]. The nitrile was identified from its NMR spectrum, which shows resonances at τ 8·07 (3H, d, J 1Hz), 7·93 (3H, s) and 4·87 (1H, m), and its IR spectrum (liquid film) which shows bands at ν_{max} 1630 (alkene) and 2230 (nitrile) cm^{-1}. Attempts to convert the nitrile to the required ortho-ester by treatment with hydrochloric acid and ethanol[178] proved fruitless, while 3-methylcrotononitrile itself was inert to carbene insertion.

Throughout this work, the vinylidene carbene has been generated by elimination of the elements of hydrogen chloride from the appropriate acetylenic chloride. In order to investigate the possibilities of an alternate leaving group to chloride, attempts were made to prepare 3-tosyl-3-methylbut-1-yne. Although the IR spectrum of the product showed the presence of acidic material,



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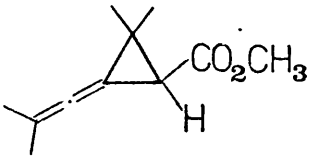
SCHEME 15

its melting point was much lower than that of PTSA, so it was assumed that a significant amount of the desired tosylate was present; the material was therefore treated with potassium t-butoxide in the presence of 3,3-dimethylallyl alcohol. The red-brown colour which has been taken to be indicative of carbene generation was not produced, and the reaction mixture, which did not give rise to a characteristic allene band in the IR spectrum, was found to contain unreacted 3,3-dimethyl-allyl alcohol and some non-polar material.

The other acidic component of the naturally occurring pyrethrins is pyrethric acid (166), and it was hoped that the route to chrysanthemic acid described above might be adapted to its synthesis according to scheme 15. Numerous attempts were made to convert either pyruvic acid or ethyl pyruvate into the required acetylenic carbinol using either acetylene and lithium aluminium hydride or lithium acetylide-ethylenediamine complex[192,193]. The best result which could be achieved, however, was from the treatment of ethyl pyruvate with lithium acetylide, (generated by reacting lithium aluminium hydride with acetylene in refluxing tetrahydrofuran for two days), which afforded a 5% yield of a compound which could be tentatively assigned the structure of the required acetylenic carbinol (167, R= $-CH_2CH_3$) on



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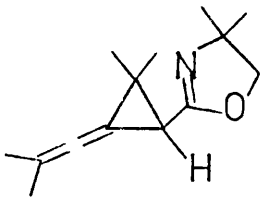
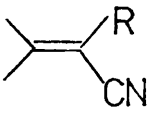
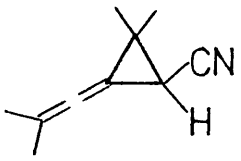


169



170 R= H

171 R= CO_2H



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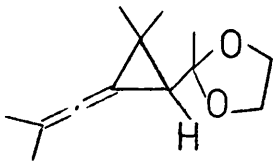

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the basis of its spectral properties. The NMR spectrum shows resonances at τ8·30 (3H, s; tertiary methyl), 7·45 (1H, s), 5·69 (2H, q, J 7Hz and 7Hz; methylene hydrogen) and 8·66 (3H, t, J 7Hz; primary methyl), while the IR spectrum shows bands at ν_{max} 3550 (tertiary hydroxyl), 3320 (acetylene) and 1750 (carbonyl) cm^{-1}. Although the yield of 167 (R= $-CH_2CH_3$) by this method was very low, its preparation from ethyl pyruvate and ethynylmagnesium bromide, followed by conversion to the corresponding chloride, has been reported[198], so that the suggested synthesis of pyrethric acid (scheme 15) may yet prove feasible.

I am grateful to Professor L. Crombie for providing samples of (±)-trans-chrysanthemic acid and (±)-cis- and (±)-trans-chrysanthemyl alcohols. I am also indebted to Dr. M. Elliott and Dr. N.F. Janes for the biological assay of the allenic ester (160), and for providing a sample of the ethylene glycol ketal of mesityl oxide along with spectra of (±)-trans-ethanochrysanthemic acid.

EXPERIMENTAL

Melting points were determined on a Reichert hot-stage apparatus. Unless otherwise stated, IR spectra were recorded in carbon tetrachloride solutions (0·1mm cell) using Perkin-Elmer 257 and Unicam SP 100 Mark II spectrophotometers. NMR spectra were recorded on a Varian T-60 spectrometer using deuterochloroform solutions (unless otherwise stated), and tetramethylsilane as internal standard. Mass spectra were recorded with a AEI-GEC MS 12 mass spectrometer. Where not otherwise stated, analytical TLC was carried out using ethyl acetate :light petroleum, 15:85. TLC plates were developed with iodine, sprayed with a solution of ceric ammonium sulphate (10g) in dilute sulphuric acid (330ml) and water (660ml), and then warmed at 160° for approximately 3 minutes. Light petroleum refers to the fraction b.p. 60-80°. Kieselgel G (Merck) was used for analytical TLC (0·25mm) and Kieselgel HF_{254} (Merck) for preparative TLC (1mm). Analytical GLC separations were performed on a Pye-Argon chromatograph using a 5% carbowax column at 100° unless otherwise stated. Solutions were dried over anhydrous magnesium sulphate.

Separation of allenic alcohols from carbene addition reactions was achieved by column chromatography, using a 40:1 ratio of silica to crude product. A gradient elution technique was employed, elution being commenced

with light petroleum, into a reservoir of which was added dropwise ethyl acetate-light petroleum, 8:92, until the first fraction was obtained. Elution was then continued with ethyl acetate-light petroleum, 15:85 for the remainder of the column, 250ml fractions being collected.

Reactions with chrysanthemyl alcohol and its analogues prepared by reduction of the corresponding allenes, were performed on the racemic compounds without prior removal of the cis- component.

Reduction of 3,3-Dimethylacrylic Acid.

Prior to use, commercial 3,3-dimethylacrylic acid was dissolved in benzene, filtered and azeotroped dry twice. A solution of the purified acid (55g, 0·55mol.) in dry ether (500ml) was heated overnight under reflux with an excess of lithium aluminium hydride (18g, 0·46mol.). Work-up afforded 3,3-dimethylallyl alcohol (40g, 83%) which was used without further purification.

Esterification of 3,3-Dimethylacrylic Acid.

Purified 3,3-dimethylacrylic acid (73g) was refluxed overnight in methanol (220ml) in the presence of a catalytic amount of concentrated sulphuric acid. Work-up yielded methyl 3,3-dimethylacrylate (50g, 60%).

3-Chloro-3-methylbut-1-yne.

2-Methyl-3-butyn-2-ol (100g, 1·2mol.) was shaken

intermittently at room temperature for 45 minutes with anhydrous calcium chloride (130g, 1·2mol.), hydroquinone (1g) and concentrated hydrochloric acid (500ml). The product (60g, 50%) was separated directly and dried over anhydrous potassium carbonate. Distillation at normal pressure afforded three fractions in the boiling ranges 62-70°, (15g), 70-76°, (23g) and 76-81°, (22g). The structure of the product was verified by the IR spectrum.

1-Ethynylcyclohexyl Chloride.

1-Ethynylcyclohexanol (50g, 0·4mol.) was added to a solution of freshly prepared cuprous chloride (8g, 0·1 mol.) in concentrated hydrochloric acid (175ml). After one hour of intermittent shaking, the upper layer was washed with concentrated hydrochloric acid(2x80ml), shaken with anhydrous potassium carbonate and dried overnight over a fresh layer of potassium carbonate. Distillation gave 1-ethynylcyclohexyl chloride (40g, 70%), b.p. 57-60° (10mm).

1-Ethynylcyclopentyl Chloride.

1-Ethynylcyclopentanol (25g, 0·23mol.) was reacted as above with cuprous chloride (4·5g, 0·045mol.) and concentrated hydrochloric acid (100ml). After drying over potassium carbonate, the product was immediately distilled from fresh potassium carbonate to yield 1-ethynylcyclopentyl chloride (15g, 55%), b.p. 42-50°(15mm).

1-Ethynylcyclopentanol[197].

Powdered potassium hydroxide (300g) was added to dry ether (2lit.) contained in a 5 litre 3-necked flask fitted with stirrer and dropping-funnel. After bubbling acetylene (passed successively through conc. sulphuric acid and silica gel)into the slurry for two hours, a solution of freshly distilled cyclopentanone (80g) in ether (250ml) was added dropwise for eight hours, the passage of acetylene being continued throughout. When the addition was complete, acetylene was passed into the reaction mixture for a further hour and the latter allowed to stand overnight. The mixture was decomposed with ice/water and extracted with ether. After drying and removal of solvent, the product was distilled to yield 24g (23%) of 1-ethynylcyclopentanol, b.p. 54° (15mm).

2-(2'-methylpropenylidene)-3,3-Dimethylcyclopropane-methanol (143a).

a) A flask containing 3,3-dimethylallyl alcohol (15g, 0·175mol.) was flushed with dry nitrogen for thirty minutes and potassium t-butoxide (5·06g, 0·045mol.) added. The slurry was stirred and cooled to -10°. 3-Chloro-3-methylbut-1-yne (4·64g, 0·045mol.) was added over a thirty minute period with the temperature maintained at -10 to 0°. Stirring was continued for three hours, during which time the temperature was

allowed to rise slowly to room temperature. n-Pentane (50ml) was added to the residue, which was then filtered. The solid was washed with n-pentane (3 x 20ml), and the solvent removed from the combined filtrates under reduced pressure (20mm). Excess 3,3-dimethylallyl alcohol was recovered at the oil-pump (30°/0·1mm). The allene (143a; 3·1g, 45%) was isolated as a mobile oil from the residue (8g) by column chromatography over silica (300g). The compound (143a), which distilled at 40° at 0·02mm, was characterized as the p-nitrobenzoate, m.p. 98-99° (from ether-light petroleum) (Found: C,67·6; H, 6·2; N, 4·6. $C_{17}H_{19}NO_4$ requires C, 67·8; H, 6·4; N, 4·65%).

b) A flask containing a solution of 3,3-dimethylallyl alcohol (4·1g, 0·047mol.) in n-pentane (30ml) was flushed with dry nitrogen for thirty minutes and potassium t-butoxide (5·3g, 0·047mol.) added. The slurry was stirred and cooled to -10°. 3-Chloro-3-methylbut-1-yne (4·72g, 0·047mol.) in n-pentane (10ml) was added dropwise over a thirty minute period with the temperature maintained at -10 to 0°. Stirring was continued for three hours, during which time the temperature was allowed to rise slowly to room temperature. The reaction mixture was filtered and the solid washed with n-pentane (3 x 20ml). The allene (143a) (1·4g, 20%) was isolated as above.

Variations of the above reaction were carried out

using different solvents and bases; the results of these experiments are summarized below.

Base	Solvent	Yield of 143a
$KOBu^t$	benzene	20%
$KOBu^t$	THF	20%
$KOBu^t$	MeOH	no reaction
KOH	3,3-dimethyl-allyl alcohol	35%
KOH	MeOH	trace
NaOH	3,3-dimethyl-allyl alcohol	35%
K t-amylate	benzene	20%
NaOEt	EtOH	trace
NaOMe	MeOH	trace

2-Cyclohexylidenemethylene-3,3-dimethylcyclopropane-methanol (143b).

a) Using the same reaction conditions and work-up procedure as in preparation (a) of (143a) above, 3,3-dimethylallyl alcohol (10g, 0·12mol.) was treated with potassium t-butoxide (3·38g, 0·03mol.) and 1-ethynyl-cyclohexyl chloride (4·32g, 0·03mol.) to yield the allenic alcohol, (143b; 1·16g, 20%), m.p. 45-46°. The product was characterized as the 3,5-dinitrobenzoate, m.p. 82-84° (needles from ether-light petroleum)

(Found: C, 62·0; H, 5·95; N, 6·90. $C_{20}H_{22}N_2O_6$ requires C, 62·2; H, 5·7; N, 7·25%).

b) Using the same reaction conditions and work-up procedure as in preparation (b) of 143a above, 3,3-dimethylallyl alcohol (5·16g, 0·06mol.) was treated with potassium t-butoxide (6·66g, 0·06mol.) and 1-ethynylcyclohexyl chloride (8·56g, 0·06mol.) in n-pentane (50ml) to yield the allenic alcohol, (143b; 1·04g, 10%).

2-Cyclopentylidenemethylene-3,3-dimethylcyclopropane-methanol (143c).

a) Using the same reaction conditions and work-up procedure as in preparation (a) of 143a, 3,3-dimethyl-allyl alcohol (4·0g, 0·05mol.) was treated with potassium t-butoxide (2·6g, 0·023mol.) and 1-ethynylcyclopentyl chloride (3·0g, 0·023mol.) to yield the allenic alcohol, (143c; 0·415g, 10%), a mobile oil which was characterized as the 3,5-dinitrobenzoate, m.p. 151-152° (needles from ether-light petroleum) (Found: C, 61·1; H, 5·45; N, 7·5. $C_{19}H_{20}N_2O_6$ requires C, 61·3; H, 5·4; N, 7·5%).

b) Using the same reaction conditions and work-up procedure as in preparation (b) of 143a, 3,3-dimethyl-allyl alcohol (4·63g, 0·058mol.) was treated with potassium t-butoxide (5·96g, 0·053mol.) and 1-ethynyl-cyclopentyl chloride (6·94g, 0·053mol.) in n-pentane (50ml)

to yield the allenic alcohol, (143c; 0·20g, 2%).

Attempted Preparation of Methyl 2-(2'-methylpropenyl-idene)-3,3-Dimethylcyclopropanecarboxylate (168).

a) Using the same reaction conditions as in preparation (a) of 143a, 3-chloro-3-methylbut-1-yne (1·76g, 0·02mol.) was added dropwise to a stirring slurry of potassium t-butoxide (2·0g, 0·02mol.) and methyl 3,3-dimethylacrylate (7·0g, 0·06mol.). The reaction was found to yield a considerable number of products, (TLC), none of which corresponded to the required compound, (IR).

b) A flask containing methyl 3,3-dimethylacrylate (2·0g, 0·02mol.) was flushed with dry nitrogen for thirty minutes and potassium t-butoxide (4·0g, 0·04mol.) added. The slurry was stirred and a solution of 3-chloro-3-methyl-1-butyne (1·8g, 0·02mol.) in benzene (10ml) added dropwise while the temperature of the reaction was slowly raised until refluxing started. After three hours stirring under gentle reflux, the reaction mixture was cooled. A number of products were observed (TLC), none of which corresponded to the required compound. The reaction mixture was treated with dilute hydrochloric acid to acidify any carboxylic salts which had formed from ester hydrolysis during the reaction. After conventional work-up, TLC showed no unique spot.

Attempted Preparation of 2-(2'-methylpropenylidene)-3,3-Dimethylcyclopropanecarboxylic Acid (156).

A flask containing a stirred slurry of azeotropically dried 3,3-dimethylacrylic acid (2·21g, 0·022mol.) in cyclohexane (30ml) was flushed with nitrogen for thirty minutes. Potassium t-butoxide (5·45g, 0·05mol.) was added, followed by dropwise addition of 3-chloro-3-methylbut-1-yne (2·56g, 0·025mol.) at room temperature. After three hours, the reaction mixture was acidified, poured into water and extracted with ether. After washing and drying in the usual manner, the product was found to comprise a large number of compounds (TLC), none of which proved to be the required allene. A considerable quantity of starting material was recovered.

2-(2'-methylpropenylidene)-3,3-Dimethylcyclopropane-methyl Tetrahydropyranyl Ether (152).

The allenic alcohol, (143a), (224mg, 1·5m.mol.), and freshly distilled dihydropyran (148mg, 1·7m.mol.) were stirred in dry benzene (4ml) at 0° in the presence of a catalytic amount of phosphoryl chloride for ninety minutes. The solution was then poured into ether (10ml) and washed successively with 10ml portions of dilute sodium hydroxide, water and brine. After drying and removal of solvent, 152 was obtained in good yield, (310mg, 90%).

(±)-Chrysanthemyl alcohol (146a).

Sodium (100mg, 4·3m.mol.) was dissolved in liquid ammonia (10ml) contained in a flask fitted with an acetone/solid CO_2 condenser. A solution of the allene (143a; 300mg, 2·0m.mol.) in dry ether (3ml) was added dropwise with stirring. After one hour's further stirring, excess sodium was destroyed with ammonium chloride and the ammonia distilled off by gentle heating. Water (2ml) was added to the reaction flask followed by extraction with ether to yield, after conventional work-up, racemic chrysanthemyl alcohol, (146a; 270mg, 90%; trans:cis = 3:1), identical in every respect (TLC, IR, NMR and MS) with a genuine sample. Crystallization of the derived 3,5-dinitrobenzoate preferentially afforded the derivative, m.p. 97-105°, of the trans- isomer, the melting point of which was not depressed by admixture with a genuine sample; (needles from ether-light petroleum) (Found: C, 58·6; H, 5·7; N, 8·1. $C_{17}H_{20}N_2O_6$ requires C, 58·6; H, 5·8; N, 8·1%).

(±)-2-Cyclohexylidenemethyl-3,3-dimethylcyclopropane-methanol (146b).

Using the same reaction conditions and work-up procedure as for 146a above, the allene (143b; 195mg, 1·0m.mol.) in dry ether (4ml) was added to a solution of sodium (50mg, 2·2m.mol.) in liquid ammonia (10ml)

to produce, as a mobile oil, the racemic alcohol (146b; 177mg, 90%; trans:cis =3:1). Crystallization of the derived 3,5-dinitrobenzoate preferentially afforded the trans- isomer, m.p. 110-112°, (needles from ether-light petroleum) (Found: C, 61·8; H, 6·0; N, 7·0. $C_{20}H_{24}N_2O_6$ requires C, 61·9; H, 6·2; N, 7·2%).

(±)-2-Cyclopentylidenemethyl-3,3-dimethylcyclopropanemethanol (146c).

Using the same reaction conditions and work-up procedure as for 146a, the allene (143c; 240mg, 1·35 m.mol.) in dry ether (4ml) was added to a solution of sodium (70mg, 3·0m.mol.) in liquid ammonia (10ml) to produce, as a mobile oil, the racemic alcohol (146c; 195mg, 80%; trans:cis =3:1). Crystallization of the derived 3,5-dinitrobenzoate preferentially afforded the trans- isomer, m.p. 106-108°, (prisms from ether-light petroleum) (Found: C, 61·0; H, 6·0; N, 7·4. $C_{19}H_{22}N_2O_6$ requires C, 60·95; H, 5·9; N, 7·5%).

2-Isobut-1'-enyl-3,3-dimethylcyclopropanemethyl Tetrahydropyranyl Ether (153).

Using the same reaction conditions and work-up procedure as for 146a, the allene (152; 127mg, 0·55m.mol.) in dry ether (4ml) was added to a solution of sodium (40mg, 1·7m.mol.) in liquid ammonia (5ml) to produce the olefinic tetrahydropyranyl ether (153; 118mg, 92%).

Cleavage of the Tetrahydropyranyl Ether (153).

The tetrahydropyranyl ether (153; 110mg) was refluxed in ethanol (4ml) for two hours in the presence of a catalytic amount of PTSA. After cooling, the solvent was removed under reduced pressure and water (3ml) added. Neutralization with sodium bicarbonate was followed by extraction with ether and conventional work-up. The resultant chrysanthemyl alcohol (64mg, 90%) was present in a cis:trans ratio of 1:1, as was shown by NMR and GLC.

Attempted Reduction of the Allene (143a) to Chrysanthemyl Alcohol with Lithium Aluminium Hydride.

a) The allene (143a) (27mg, 0·18m.mol.) was refluxed overnight in ether with lithium aluminium hydride (7mg, 0·18m.mol.). Subsequent work-up led to quantitative recovery of starting material.

b) The allene (143a) (60mg, 0·4m.mol.) was refluxed overnight in THF with lithium aluminium hydride (38mg, 1m.mol.). Subsequent TLC (ethyl acetate:light petroleum, 30:70) and NMR revealed the presence of starting material and minor amounts of about five products.

c) The allene (143a) (45mg, 0·3m.mol.) was refluxed overnight in pyridine with lithium aluminium hydride (12mg, 0·3m.mol.). After work-up, TLC (ethyl acetate: light petroleum, 30:70) and NMR showed only unreacted

starting material.

d) The allene (143a) (36mg, 0·24m.mol.) was refluxed overnight in ether in the presence of lithium aluminium hydride (19mg, 0·5m.mol.) and aluminium chloride (67mg, 0·5m.mol.). No reaction was observed.

Oxidation of Chrysanthemyl Alcohol (146a).

AnalaR chromium trioxide (1g, 0·01mol.) was added carefully to dry pyridine (10ml) at 0°. The alcohol (146a; 380mg, 2·5m.mol.) in dry pyridine (3ml) was added in one portion and the reaction left to stir at room temperature for 24 hours, at the end of which time the oxidation had progressed to the aldehyde stage (TLC). Five drops of water were now added and the reaction left stirring for a further four days.

The reaction mixture was poured into water (25ml) and ether added (5ml). Powdered sodium bisulphate was added until the pH reached 3 or 4 and the product extracted with ether (3 x 50ml). The combined ether extracts were washed with brine, dried over magnesium sulphate and warmed under reduced pressure to remove the solvent. The product (300mg) was shown (TLC, ethyl acetate:light petroleum, 40:60, IR and NMR) to comprise about 25% chrysanthemyl aldehyde and 75% racemic chrysanthemic acid (147a; trans:cis =3:1), the latter being obtained in a yield of 55% based on chrysanthemyl

alcohol. Preparative TLC (ethyl acetate:light petroleum, 40:60) followed by sublimation, afforded (±)-trans-chrysanthemic acid, identical in every respect with a genuine sample (IR, NMR, MS, TLC); m.p. 46-48°, not depressed on admixture with genuine material.

Oxidation of 2-Cyclohexylidenemethyl-3,3-dimethylcyclopropanemethanol (146b).

AnalaR chromium trioxide (370mg, 3·7m.mol.) was added carefully to dry pyridine (5ml) at 0°. The alcohol (146b; 175mg, 0·9m.mol.) in dry pyridine (2ml) was added in one portion and the reaction left stirring at room temperature for 24 hours, at the end of which time three drops of water were added and the reaction left stirring for a further four days. The work-up was as described above for the oxidation of chrysanthemyl alcohol. The product (100mg) was shown (TLC, ethyl acetate:light petroleum 40:60, IR and NMR) to comprise about 90% of (±)-2-cyclohexylidenemethyl-3,3-dimethylcyclopropanecarboxylic acid (147b; trans:cis =3:1) and 10% of the corresponding aldehyde, the yield of acid being 50% based on 146b. Although 147b solidified on standing, selective crystallization of the trans- isomer could not be induced. The compound was characterized by NMR, IR and MS.

Oxidation of 2-Cyclopentylidenemethyl-3,3-dimethyl-cyclopropanemethanol (146c).

AnalaR chromium trioxide (1g, 0·01mol.) was added carefully to dry pyridine (15ml) at 0°. The alcohol (146c; 495mg, 2·9m.mol.) in dry pyridine (5ml) was added in one portion and the reaction left to stir at room temperature for 24 hours, at the end of which time five drops of water were added and the reaction left stirring for a further six days. The work-up was as described for the oxidation of chrysanthemyl alcohol. The product (336mg) was shown (TLC, ethyl acetate:light petroleum 40:60, IR and NMR) to comprise about 70% of the acid (147c; trans:cis =3:1) and 20% of the corresponding aldehyde, the yield of acid being 45% based on 146c. Purification was achieved using preparative TLC (ethyl acetate:light petroleum 40:60) prior to spectroscopic confirmation of the structure.

Oxidation of 2-(2'-methylpropenylidene)-3,3-Dimethyl-cyclopropanemethanol (143a).

AnalaR chromium trioxide (1·1g, 0·011mol.) was added carefully to dry pyridine (15ml) at 0°. The alcohol (143a; 460mg, 3·0m.mol.) in dry pyridine (5ml) was added in one portion and the reaction left stirring at room temperature for 24 hours, at the end of which time five drops of water were added and the reaction left to stir for a further

fourteen days. The work-up was as described for the oxidation of chrysanthemyl alcohol. The product (265mg) was shown (TLC, ethyl acetate:light petroleum 40:60, NMR) to comprise about 80% of the acid (156) and 20% of the corresponding aldehyde, the yield of the acid being 40% based on 143a. The compound (156) was purified by preparative TLC (ethyl acetate:light petroleum 40:60) prior to spectroscopic confirmation of its structure (IR, NMR and MS). Although an oil at normal temperatures, 156 solidified on standing in the refrigerator.

Oxidation of 2-Cyclohexylidenemethylene-3,3-dimethyl-cyclopropanemethanol (143b).

AnalaR chromium trioxide (570mg, 5·7m.mol.) was added carefully to dry pyridine (6ml) at 0°. The allenic alcohol (143b; 200mg, 1·0m.mol.) in dry pyridine (4ml) was added in one portion and the reaction left to stir at room temperature for 24 hours, at the end of which time three drops of water were added and the reaction left stirring for a further fourteen days. The work-up was as described for the oxidation of chrysanthemyl alcohol. The product (75mg) was shown (TLC, ethyl acetate:light petroleum 40:60, IR and NMR) to comprise about 75% of the desired acid (158) and about 25% of the corresponding aldehyde. Preparative TLC (ethyl acetate:light petroleum 40:60) yielded the pure acid (56mg, 25%) m.p. 138-139° (prisms

from ether-light petroleum) (Found: C, 75·6; H, 8·9. $C_{13}H_{18}O_2$ requires C, 75·7; H, 8·8%).

A number of other possible methods for effecting the oxidation of chrysanthemyl alcohol and its analogues to the corresponding acids were examined. A brief summary of these now follows.

Methods Showing no Apparent Reaction.

a) Chrysanthemyl alcohol (31mg, 0·2m.mol.) was dissolved in dimethylsulphoxide (0·33ml) and benzene (0·66ml) with dicyclohexylcarbodiimide (184mg, 0·6m.mol.). A 1M solution of orthophosphoric acid in dimethylsulphoxide (0·1ml) was added and the solution stirred at room temperature for 24 hours[179].

b) Chrysanthemyl alcohol (30mg, 0·2m.mol.) in ethyl acetate (4ml) was shaken under oxygen in the presence of 4% platinum-charcoal at room temperature for five days[180].

c) Chrysanthemyl alcohol (20mg) in methylene dichloride (1ml) was added to a solution of ruthenium trichloride (1mg) in water (1ml) followed by 0·52ml of an approximately molar solution of sodium hypochlorite in water. The solution was stirred overnight at room temperature[181].

d) Chrysanthemyl alcohol (25mg) was dissolved in acetone (20ml) containing 3M sodium hydroxide (1ml).

10% platinum-charcoal (30mg) was added and the mixture refluxed under oxygen for 24 hours[182].

e) By means of the chromium trioxide/pyridine method previously discussed, chrysanthemyl alcohol could be converted in high yield (85%) to the corresponding aldehyde, which was isolated by working up the reaction after 12 hours without the addition of water. To a solution of the aldehyde (168mg) in 10% aqueous THF (10ml) was added silver peroxide (560mg). Stirring the suspension for 24 hours at room temperature or under reflux produced no reaction; after several days, slow formation of minor amounts of two or three products was observed (TLC), none of which proved to be the desired acid. Similar results were obtained with the allenic alcohol (143a).[183]

Destructive Oxidations.

a) Quantitative treatment of chrysanthemyl alcohol in acetone at 0° with Jones' reagent, (10·3g chromium trioxide in 30ml water and 8·7ml conc. sulphuric acid), led to the formation of the required acid along with a number of other products which probably resulted from reaction of sulphuric acid on the chrysanthemyl molecule.

b) Chrysanthemyl alcohol (20mg) in carbon tetrachloride (4ml) was treated with a suspension of ruthenium dioxide (8mg) in carbon tetrachloride (2ml). A drop of 10% sodium periodate in water was added and the mixture stirred

at room temperature. TLC indicated the formation of very polar products which were obviously the result of over-oxidation[184].

c) Chrysanthemyl alcohol (35mg) was suspended in 15% potassium hydroxide solution (0·75ml) and stirred at 0° with slow, dropwise addition of a solution of potassium permanganate (30mg) in water (6ml). Work-up yielded only very polar material which did not contain the desired acid.[54]

d) To a solution of chrysanthemyl alcohol (17mg) in acetone (1ml) immersed in an acetone/solid CO_2 bath, was added a small amount of Jones' reagent. Subsequent TLC showed several polar compounds along with unreacted starting material, indicating that the oxidation was proceeding slowly and non-selectively.

Partial Oxidations.

a) Chrysanthemyl alcohol (50mg) was refluxed for 24 hours in dry benzene (6ml) in the presence of Fetizon's reagent[185](600mg). Clean conversion to the aldehyde was obtained, but further oxidation was extremely slow.

b) A solution of chromium trioxide (500mg) in water (2ml) was added slowly to pyridine (5ml) at 0°. A solution of chrysanthemyl alcohol (100mg) in pyridine (2ml) was added and the reaction stirred at room temperature for 13 days. Work-up gave a poor yield of

a chrysanthemic acid/aldehyde mixture[186].

c) Chrysanthemyl alcohol (84mg) was dissolved in methylene dichloride (10ml) and treated with Collins' reagent[187] (850mg). Overnight stirring at room temperature produced the corresponding aldehyde, but prolonged stirring led to only very slow formation of the acid.

d) Chrysanthemyl alcohol (90mg) was dissolved in acetone (15ml) containing platinum oxide (Adams' catalyst) which had been previously hydrogenated[188]. Shaking under oxygen for six days resulted in slow conversion to the aldehyde.

e) Chrysanthemyl alcohol (40mg) and chromium trioxide (100mg) were stirred in DMF (5ml) containing a catalytic amount of sulphuric acid[189]. Continued stirring at room temperature produced the aldehyde, while refluxing caused the formation of several undesired by-products.

f) Chrysanthemyl alcohol was oxidized to the aldehyde by the chromium trioxide/pyridine method previously discussed. The aldehyde (440mg) was treated with 1M sodium hydroxide (3ml) and 90% hydrogen peroxide (135mg) in water (3·3ml). The reaction was stirred for 24 hours at room temperature to produce a poor yield of chrysanthemic acid, apparently in a trans:cis ratio of 2:3, and minor amounts of more polar products. The method suffered from irreproducibility[190].

g) Chrysanthemyl alcohol (20mg) was dissolved in ether (2ml) and stirred with water under nitrogen. After the addition of a few drops of an oxidizing solution containing potassium dichromate (2g), sulphuric acid (2·3ml) and water (7·7ml), the reaction was stirred at room temperature. Rapid formation of the aldehyde was followed by slower oxidation to chrysanthemic acid along with a considerable number of polar impurities[191].

Formation of 5-Benzyl-3-furylmethyl 2-(2'-methyl-propenylidene)-3,3-Dimethylcyclopropanecarboxylate (160).

The allenic acid (156; 200mg, 1·2m.mol.) was dissolved in dry benzene (5ml). Pyridine (170mg, 2·1m.mol.) was added and the solution cooled to 0° before addition of oxalyl chloride (500mg, 4·0m.mol.) in dry benzene (5ml). After one hour, excess oxalyl chloride was removed under reduced pressure and the resultant acid chloride redissolved in benzene (5ml). A solution of 5-benzyl-3-furylmethanol (159; 380mg, 2·1m.mol.) in benzene (5ml) containing pyridine (170mg, 2·1m.mol.) was added and the reaction left overnight at room temperature. The pyridinium chloride was filtered off, and the solvent removed under reduced pressure. After preparative TLC (ethyl acetate:light petroleum 12:88) the residue yielded the pure ester (160; 110mg, 27%), b.p. 95° at

0·05mm. (Found: C, 78·45; H, 7·2. $C_{22}H_{24}O_3$ requires C, 78·5; H, 7·2%).

3,3-Dimethylacrylyl Chloride.

3,3-Dimethylacrylic acid (11·2g, 0·11mol.) was dissolved in dry benzene (45ml), cooled to 0° and treated with oxalyl chloride (45ml). After thirty minutes refluxing, the solution was allowed to cool and the benzene and excess oxalyl chloride removed under reduced pressure to yield 3,3-dimethylacrylyl chloride (12·8g, 95%).

1,1-Dimethyl-2-hydroxyethyl 3',3'-Dimethylacrylamide (164).

3,3-Dimethylacrylyl chloride (12·8g, 0·11mol.) in methylene chloride (30ml) was added at 0° to a solution of 2-amino-2-methylpropan-1-ol (163; 19·2g, 0·22mol.) in methylene chloride (30ml)[194]. Reaction was instantaneous and exothermic. After removal of the precipitated amine hydrochloride by filtration, the solvent was distilled off under reduced pressure to yield the amide (164; 17·8g, 95%).

1-(2'-methylbut-1'-enyl)-5,5-Dimethyloxazoline (165)[195].

The amide (164; 17·8g, 0·105mol.) was dissolved in freshly distilled thionyl chloride (90g). The solution was refluxed over a water-bath for two hours, cooled and poured into dry ether (400ml). After being left for 48 hours at 0°, the solution was extracted with water

(3 x 300ml). The aqueous extracts were combined, neutralized with concentrated sodium hydroxide solution, and extracted with ether (3 x 400ml). The combined ethereal extracts were washed and dried in the normal manner, and the ether removed under reduced pressure to yield the crude oxazoline, (165; 7g, 45%), which was purified by distillation under vacuum (b.p. 32°, 1·0mm).

Attempted Carbene Addition with 3-Chloro-3-methylbut-1-yne and the Oxazoline, (165).

3-Chloro-3-methylbut-1-yne (334mg, 3·26m.mol.) in n-pentane(4ml) was added dropwise with stirring to a mixture of oxazoline (165; 500mg, 3·26m.mol.), potassium t-butoxide (366mg, 3·26m.mol.) and n-pentane (10ml) at -18° (CCl_4/solid CO_2) under nitrogen. The reaction was stirred for three hours, during which time it was slowly allowed to attain room temperature. The reaction mixture was then filtered and the pentane removed under reduced pressure. TLC (ethyl acetate:light petroleum 15:85) of the residue showed only very non-polar material and unreacted oxazoline, while the IR spectrum showed no allene band which could be associated with the desired product (169).

The above reaction was carried out in the absence of pentane at the same temperature, and at elevated temperatures both with and without solvent. In none of

the cases, however, was the desired allenic compound detected.

3-Methylcrotononitrile (170)[196].

Acetone (5·8g, 0·1mol.) and cyanoacetic acid (8·5g, 0·1mol.) in benzene (50ml) were heated under reflux (Dean and Stark) for 24 hours in the presence of ammonium acetate (1g) and acetic acid (1ml). On cooling, white crystals of 2-cyano-3,3-dimethylacrylic acid (171) appeared (IR). The benzene was removed under reduced pressure and the cyano-acid (171) dissolved in a 0·03M solution of cupric acetate in pyridine (40ml pyridine containing 220mg cupric acetate). On heating the solution to reflux, facile decarboxylation occurred, the evolution of carbon dioxide being monitored by linking the reaction vessel to a Dreschel bottle containing calcium hydroxide solution. After 45 minutes, the reaction solution was cooled and poured into dilute hydrochloric acid (200ml). Extraction with ether and conventional work-up yielded 3-methylcrotononitrile (170; 5·0g, 65%) which was purified by distillation (b.p. 31°, 15mm).

Attempted Formation of the Ortho-ester (162) from 3-Methylcrotononitrile[178].

Concentrated hydrochloric acid (2g) was added to a water-cooled solution of 3-methylcrotononitrile (3g, 0·037mol.) in absolute ethanol (2·3g) and chloroform (2ml).

After allowing the temperature to rise to 40°, the mixture was stirred at room temperature for three days. Absolute ethanol (10ml) was added and the reaction left stirring for a further two days. The resultant solution was poured into 5% sodium hydroxide (15ml) and extracted with chloroform. After conventional work-up, only unaltered starting material was obtained.

Attempted Formation of 1-Cyano-2-(2'-methylpropenylidene)-3,3-dimethylcyclopropane (172).

Potassium t-butoxide (330mg, 3·0m.mol.) was added to a stirring solution of 3-chloro-3-methylbut-1-yne (300mg, 2·9m.mol.) in 3-methylcrotononitrile (348mg, 4·3m.mol.) at -18° (CCl_4/solid CO_2) under nitrogen. The reaction mixture was stirred for three hours, during which time it was slowly allowed to attain room temperature. n-Pentane (5ml) was added and the solution filtered. The solvent was removed under reduced pressure. TLC (ethyl acetate:light petroleum 40:60) of the residue indicated the presence of a complex mixture of non-polar material along with unreacted nitrile. The IR spectrum showed no allene band which could be associated with the desired product (172).

Attempted Carbene Addition with 3-Chloro-3-methylbut-1-yne and the Ethylene Glycol Ketal of Mesityl Oxide (161).

3-Chloro-3-methylbut-1-yne (730mg, 7·1m.mol.) in

n-pentane (5ml) was added dropwise with stirring to a slurry of potassium t-butoxide (0·8g, 7·1m.mol.) and ketal (16l; 1g, 7·1m. mol.) in pentane (10ml) at -18° (CCl_4/solid CO_2) under nitrogen. The reaction mixture was allowed to stir for three hours, during which time it was slowly allowed to attain room temperature. The solution was filtered and the pentane removed under reduced pressure. TLC (ethyl acetate:light petroleum 7:93) of the residue indicated the presence of non-polar material and unreacted ketal. Preparative TLC afforded no compound whose IR spectrum exhibited the characteristic allene band associated with the desired product (173), while distillation of the crude reaction product yielded only unreacted ketal.

The above reaction was attempted in refluxing benzene but produced the same negative result.

Attempted Formation of the p-Toluenesulphonate of 3-Methyl-1-butyn-2-ol.

3-Methyl-1-butyn-2-ol (1g, 12m.mol.) was dissolved in dry, freshly distilled pyridine (10ml) and cooled to 0°. To the solution was added freshly crystallized p-toluenesulphonyl chloride (4·6g, 24m.mol.) in dry pyridine (10ml). When solution was complete, the reaction flask was stored at 0° for 20 hours, during which time a pink colour developed and crystals of pyridinium chloride

formed. The solution was poured into ice/water (100ml) and the resultant white precipitate (1g) filtered and washed with water before drying at room temperature under vacuum. The IR spectrum of the product showed the presence of acidic material; the melting point, however, was much lower than that of p-toluenesulphonic acid, so it was considered possible that a significant amount of p-toluenesulphonate (174) was present. On this assumption, the material was used for allene carbene generation experiments.

Attempted Carbene Addition with p-Toluenesulphonate of 3-Methyl-1-butyn-2-ol (174) and 3,3-Dimethylallyl Alcohol.

The supposed sulphonate (174; 620mg, 2·6m.mol.), 3,3-dimethylallyl alcohol (2g, 23m.mol.) and potassium t-butoxide (400mg, 3·5m.mol.) were stirred in n-pentane (10ml) at -18° under nitrogen for three hours, during which time the temperature was slowly allowed to rise. The reaction mixture was filtered and the solvent removed under reduced pressure. TLC (ethyl acetate: light petroleum 15:85) of the residue showed only non-polar material and unreacted 3,3-dimethylallyl alcohol. The IR spectrum showed no allene band which could be associated with the desired product (143a).

Attempted Preparation of Ethyl 2-Hydroxy-2-methylbut-3-ynoate (167, R= $-CH_2CH_3$)[192].

A stream of dry acetylene was passed into a stirred suspension of lithium aluminium hydride (5·7g, 0·15mol.) in dry refluxing THF (120ml) for two days. To the resulting acetylide was added, under nitrogen, a solution of ethyl pyruvate (5·8g, 0·02mol.) in ether (25ml). The reaction was stirred for a further 24 hours. After treatment with saturated sodium sulphate solution, the reaction mixture was filtered; conventional work-up led to the isolation of a product (350mg) whose spectral properties (IR, NMR) were consistent with the structure of the desired compound (167, R= $-CH_2CH_3$). The yield, however, was only 5%.

Attempted Preparation of 2-Hydroxy-2-methylbut-3-ynoic Acid (167, R= H)[193].

A stream of dry acetylene was passed into a stirring solution of pyruvic acid (2g, 0·023mol.) in N,N-dimethylacetamide (100ml) at room temperature for thirty minutes. Lithium acetylide-ethylenediamine complex (4·5g, 0·05mol.) was added and stirring continued for a further 2 hours. After treatment with saturated sodium sulphate solution, the reaction mixture was poured into 5N sodium hydroxide (100ml) and N,N-dimethylacetamide removed by washing with

ether. Neutralization and extraction with ethyl acetate led to the recovery of a small amount of pyruvic acid. None of the desired product was obtained. The experiment was repeated using ether as solvent, and was also attempted with ethyl pyruvate in place of pyruvic acid, but in neither case was the desired product observed.

Deuteration of 2-(2'-methylpropenylidene)-3,3-Dimethylcyclopropanemethanol (143a).

The allenic alcohol (143a; 165mg) was dissolved in dry chloroform (20ml, AnalaR, purified with silica gel) and shaken with deuterium oxide (2·5ml) at room temperature for three minutes. The solvent was removed under reduced pressure and the process repeated four times. The product was finally dried azeotropically with benzene.

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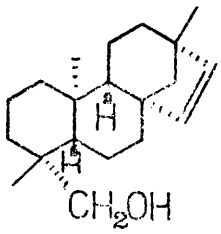
S E C T I O N b.

Acid-catalysed Rearrangement of a Diterpenoid Epoxide.

Acid-induced Rearrangement of Erythroxylol A Epoxide.



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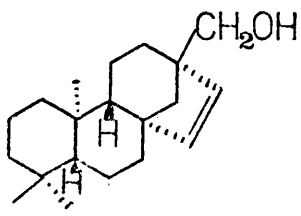

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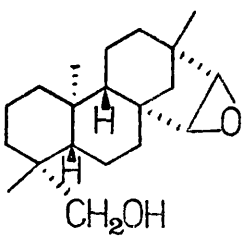

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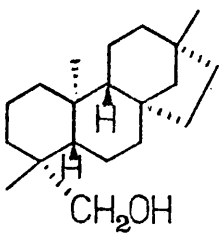


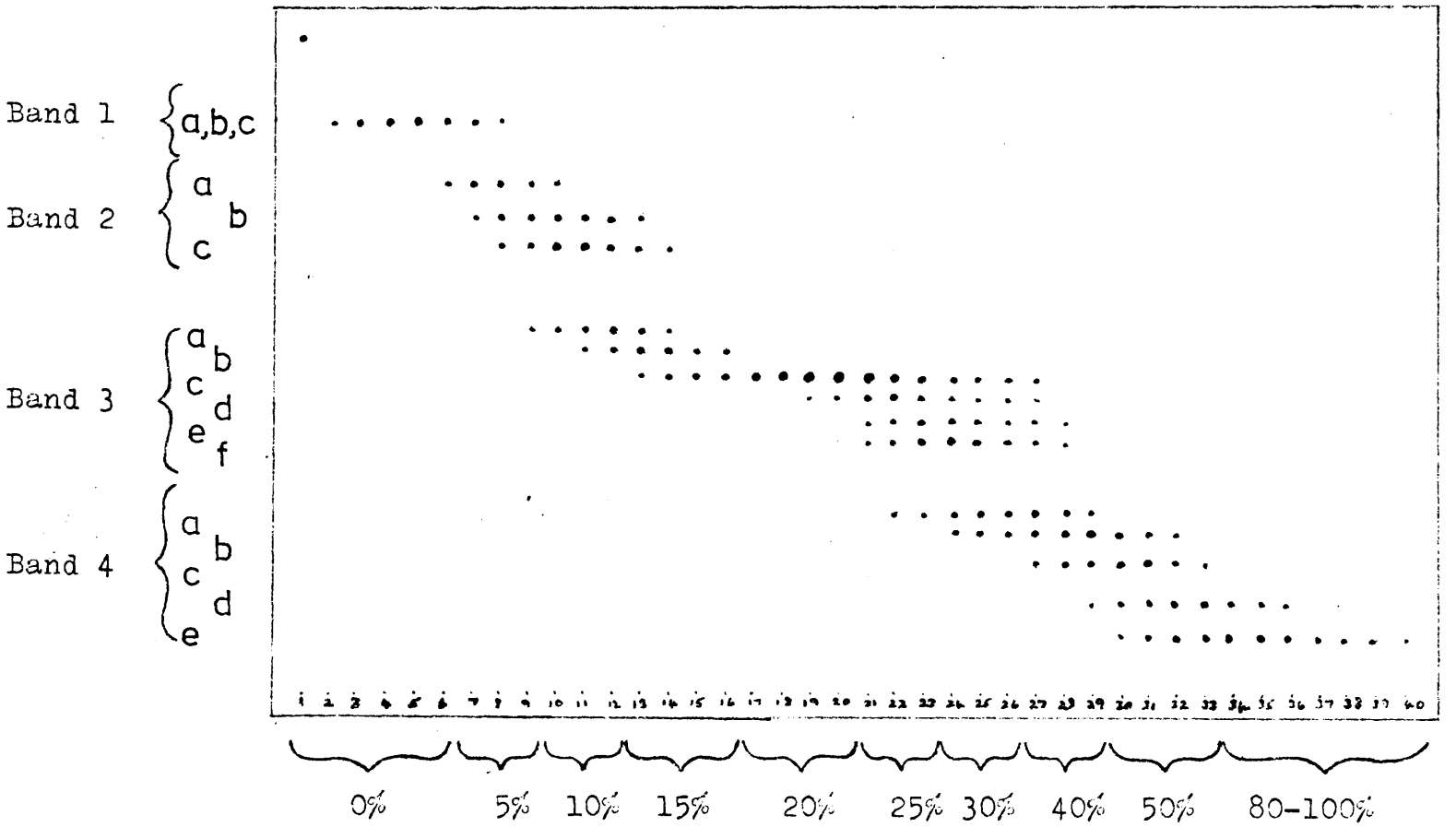
14

From the diterpenoid constituents of Erythroxylon monogynum Roxb., a small tree native to Ceylon and certain parts of India[1], two primary alcohols, erythroxylol A[2,3] (11) and erythroxylol B[3] (12), have been isolated and identified. A further component was shown to be erythroxylol A epoxide (13). The observation that the latter, on subjection to chromium trioxide-acetic acid oxidation, underwent carbon-carbon bond cleavage, prompted the use of formic acid as solvent. Under these conditions, at least seventeen products were formed which, surprisingly, were also observed in the absence of chromium trioxide. Since treatment of dihydroerythroxylol A (14) with 95% formic acid afforded only the derived formate, these products must necessarily have resulted from fission of the epoxide ring.

In order to investigate the origin and nature of this complex mixture of compounds, it was necessary to aquire substantial quantities of the epoxide (13). This was achieved by epoxidation of erythroxylol A (11), which was readily available from column chromatography of the crude extract of Erythroxylon monogynum.

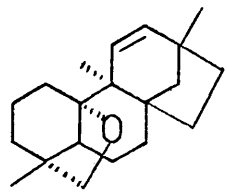
After reaction of the epoxide (13) with 95% formic acid, TLC (ethyl acetate-light petroleum, 20:80), showed the aforementioned range of compounds distributed among four bands according to polarity, (fig. 1). This feature

Fig. 1

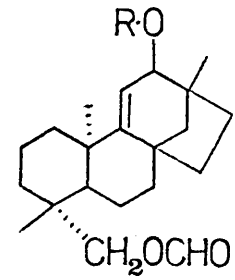

Band 1
a,b,c
Band 2
a
b
c
Band 3
a
b
c
d
e
f
Band 4
a
b
c
d
e
0%
5%
10%
15%
20%
25%
30%
40%
50%
80–100%
ether-light petroleum
yl acetate

was utilized as a means of reference, each compound being accorded the number 1, 2, 3 or 4 depending on the band in which it occurred, followed by a letter (a, b etc.), allocated in order of increasing polarity. Thus band 1, the least polar, was resolved (chloroform-light petroleum, 25:75) into three purple-staining compounds (1a, 1b and 1c), while band 2 showed three brown spots, associated with compounds 2a, 2b and 2c. Band 3 showed spots due to products 3a and 3b (grey), 3c (rose), 3d (yellow-brown) and 3e and 3f (grey-brown). Finally, band 4 contained five compounds, namely 4a (rose-staining), 4b (grey), 4c (yellow-brown) and 4d and 4e (rose).

It was observed that the addition of ether a few seconds after the treatment of epoxide (13) with formic acid led to quenching of the reaction, a phenomenon which can be attributed to hydrogen bonding between the ether and the carboxylic acid[4] preventing further participation of the latter in the reaction. It was hoped that this effect could be utilized to facilitate separation of the products, since it caused a considerable reduction in the number of compounds formed; however low yields, irreproducibility and the problem of choosing the correct instant for the addition of ether in order to control the number of products observed, rendered



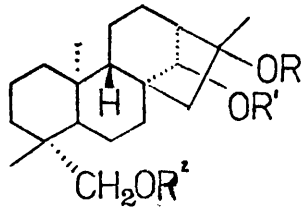
1 (1c)



2

(i) R = CHO (3b)

(ii) R = H (4b)



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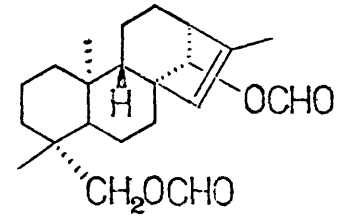


4 (3c)

(i) $R = R' = R^2 = CHO$ (4a)

(ii) $R = H$, $R' = R^2 = CHO$ (4d)

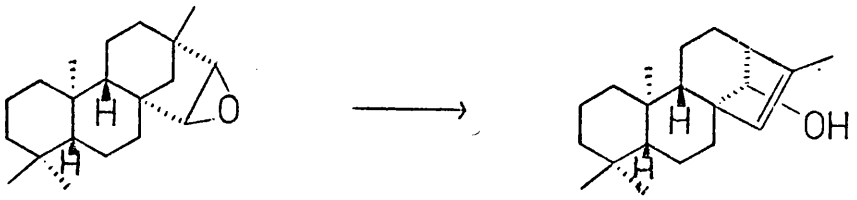
(iii) $R = R' = H$, $R^2 = CHO$ (4e)

Fig. 2

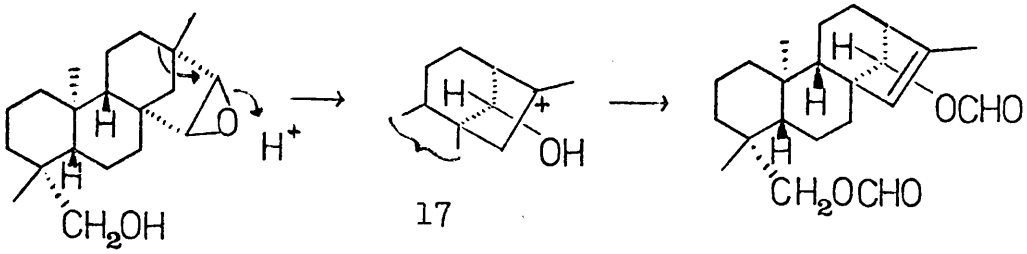
this technique somewhat impractical.

After separation, using a combination of column chromatography and preparative TLC, spectroscopic examination of the isolated components pointed to their derivation from opening of the epoxide ring followed by molecular rearrangement. In all cases except one, (1c), the reaction was accompanied by esterification of the primary hydroxyl group, the grouping $-CH_2OCHO$ being indicated by IR (ν_{max} 1731 and 1175cm^{-1}) and NMR spectra (τ 5·6 and 6·1, 2H, ABq, J= 11Hz).

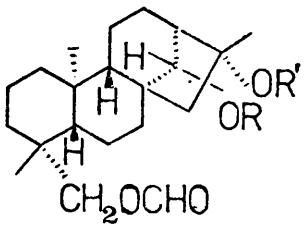
On performing the reaction with varying amounts of acid, it was observed that the relative yields of the products changed markedly, and it became apparent that two distinct concentration dependent rearrangement processes were operative. The first to be elucidated occurred on exposure of epoxide (13) to 95% formic acid for five minutes at a concentration of 85mg/ml, when the main product was 3c, an enediol diformate, the NMR spectrum of which reveals two tertiary methyls (τ 9·05 and 8·87) and a vinyl methyl (τ 8·28, d, J= 1Hz), shown by double resonance experiments to be adjacent to one vinyl proton (τ 4·98, m). The compound possesses both a primary and secondary formate group, the methine proton associated with the latter being considerably deshielded (τ 4·50, bs), probably as a result of its through-space proximity to



15 16



13 17 4



3

(i) R =R'=CHO

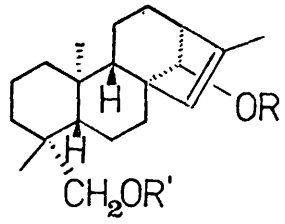
(ii) R =CHO, R'=H

(iii) R =R'=H

SCHEME 1

the C-10 methyl. The mass spectrum exhibits a molecular ion peak at m/e 360, while a peak at m/e 314 indicates the facile loss of formic acid. The spectroscopic data is consistent with structure (4), whose formation can be rationalized on the basis of the hibaene epoxide rearrangement[5] established by Kapadi and Sukh Dev, who demonstrated the chemical transformation of (+)-hibaene into (-)-kaurene. Thus treatment of (+)-hibaene epoxide (15) with BF_3-Et_2O in benzene at 0° gave a high yield of the isokaurene alcohol (16). By analogy, one can postulate (4) arising from the carbonium ion (17) by deprotonation and esterification (scheme 1).

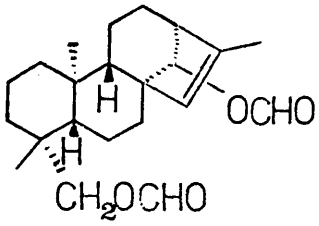
Treatment with lithium aluminium hydride readily converted (4) into the corresponding enediol (6i), the NMR spectrum of which shows resonances at τ9·03 and 8·97 (each 3H, s; tertiary methyls), 8·26 (3H, d, J=1·5Hz; vinyl methyl), 5·0 (1H, m; vinyl proton) and 5·87 (1H, bs). The AB quartet associated with the primary hydroxyl group appears at τ6·58 and 6·25 (2H, J=11Hz). The IR spectrum indicates the presence of both free and bonded hydroxyl functions with bands at ν_{max} 3610 and 3400cm^{-1} respectively, while the mass spectrum exhibits the expected peaks at m/e 304 (molecular ion peak) and m/e 286 (M-18, loss of water). Acetylation of (6i) yielded the enediol diacetate (6ii), whose structure was



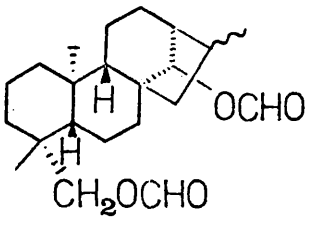
6

(i) R =R' =H

(ii) R =R' = $OCOCH_3$



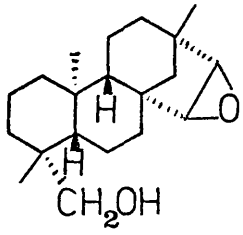
$\xrightarrow[Pd/C]{H_2}$



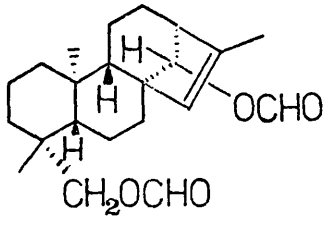
4 8

verified by its NMR spectrum (100MHz; $CDCl_3$) which shows resonances at τ9·06 and 8·86 (each 3H, s; tertiary methyls), 8·26 (3H, d, J=2Hz; vinyl methyl), 7·96 (6H, s; acetate methyls), 5·0 (1H, bs; vinyl proton), 4·60 (1H, bs) and 6·15 and 4·79 (2H, ABq, J=11Hz). The IR spectrum shows the carbonyl band of the acetate functions at ν_{max} 1735cm^{-1}, while the mass spectrum exhibits a molecular ion peak at m/e 388 and a peak at m/e 328 indicating facile loss of acetic acid.

Catalytic hydrogenation of the enediol diformate (4) resulted in an approximately 3:2 mixture of dihydro epimers (8), which were resolved by analytical GLC. The NMR spectrum of the mixture, which was inseparable by TLC, has signals at τ9·12 (6H, s; tertiary methyls) and 8·91 (3H, s; tertiary methyl), while resonances at 4·60 and 4·50 (each 1H, bs) are probably associated with the C-14 methine protons of the two epimers. Both the NMR and IR spectra indicate that the primary and secondary formate groupings have been unaffected, while the molecular weight is confirmed by the mass spectrum with a peak at m/e 362. A further slightly more polar compound, partially isolated in low yield by preparative TLC (ethyl acetate-light petroleum, 15:85), was not identified, but may have resulted from hydrolysis of the C-14 secondary formate grouping. The NMR spectrum (100MHz;$CDCl_3$)



13



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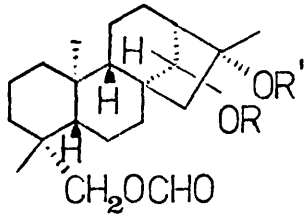
+



3

(i) R =R' =CHO

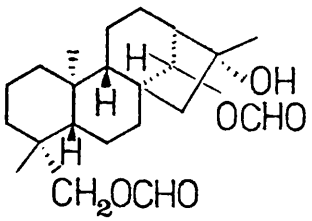
(ii) R =CHO, R' =H

(iii) R =R' =H

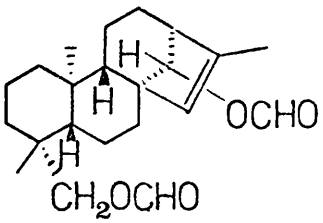
shows resonances at τ9·04, 8·90 and 8·74 (all 3H, s; tertiary methyls), while a signal at 5·87 (1H, d, J= 8Hz) has the chemical shift expected for a methine proton associated with a C-14 hydroxyl; a less intense signal at τ4·61 (1H, bs) may be due to a residual vinyl proton. The presence of the primary formate group was verified by the anticipated AB quartet and a signal due to the formyl proton at τ1·90. An additional less intense signal at τ1·94 would appear to indicate an unreacted secondary formate group.

The rearrangement of epoxide (13) yielded three compounds closely related to (4), namely 4a, 4d and 4e (fig. 1), which like (4), gave rise to rose-coloured spots on TLC. The former, 4a, was shown to be the triol triformate (3i) by its NMR spectrum (100MHz; $CDCl_3$) which shows resonances at τ9·08, 8·94 and 8·36 (all 3H, s; tertiary methyls), 4·54 (1H, bs; C-14 methine), 2·06 (1H, s; formate) and 1·89 (2H, s; formate) as well as the AB quartet associated with the primary formate at 5·66 and 6·11 (2H, J= 11Hz). The IR spectrum exhibits strong carbonyl absorptions at ν_{max} 1730 and 1722cm^{-1}, while the mass spectrum predictably does not reveal a molecular ion peak, the highest signals at m/e 360 and 314 indicating facile loss of formic acid.

Compound 4d was found to be the corresponding triol



3ii



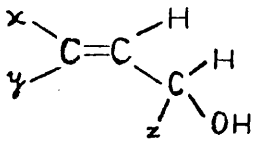
4

diformate (3ii), the NMR spectrum showing signals at τ9·07, 8·90 and 8·75 (all 3H, s; tertiary methyls), 4·41 (1H, bs; C-14 methine), 6·20 and 5·60 (2H, ABq, J= 11Hz), 2·04 (1H, s; formate) and 1·93 (1H, s; formate), while the IR spectrum has a strong carbonyl absorption at ν_{max} 1728cm^{-1}, a free hydroxyl band at ν_{max} 3600cm^{-1} and bands at ν_{max} 3400 and 3500cm^{-1} indicating respectively an inter- and intramolecularly hydrogen bonded hydroxyl function, the former disappearing on dilution. The mass spectrum exhibits no molecular ion peak, but has diagnostic peaks at m/e 332 (M-46) and 314 (332-18) due to successive loss of formic acid and water. The compound (3ii) was cleanly dehydrated to the enediol diformate (4) with phosphoryl chloride in pyridine.

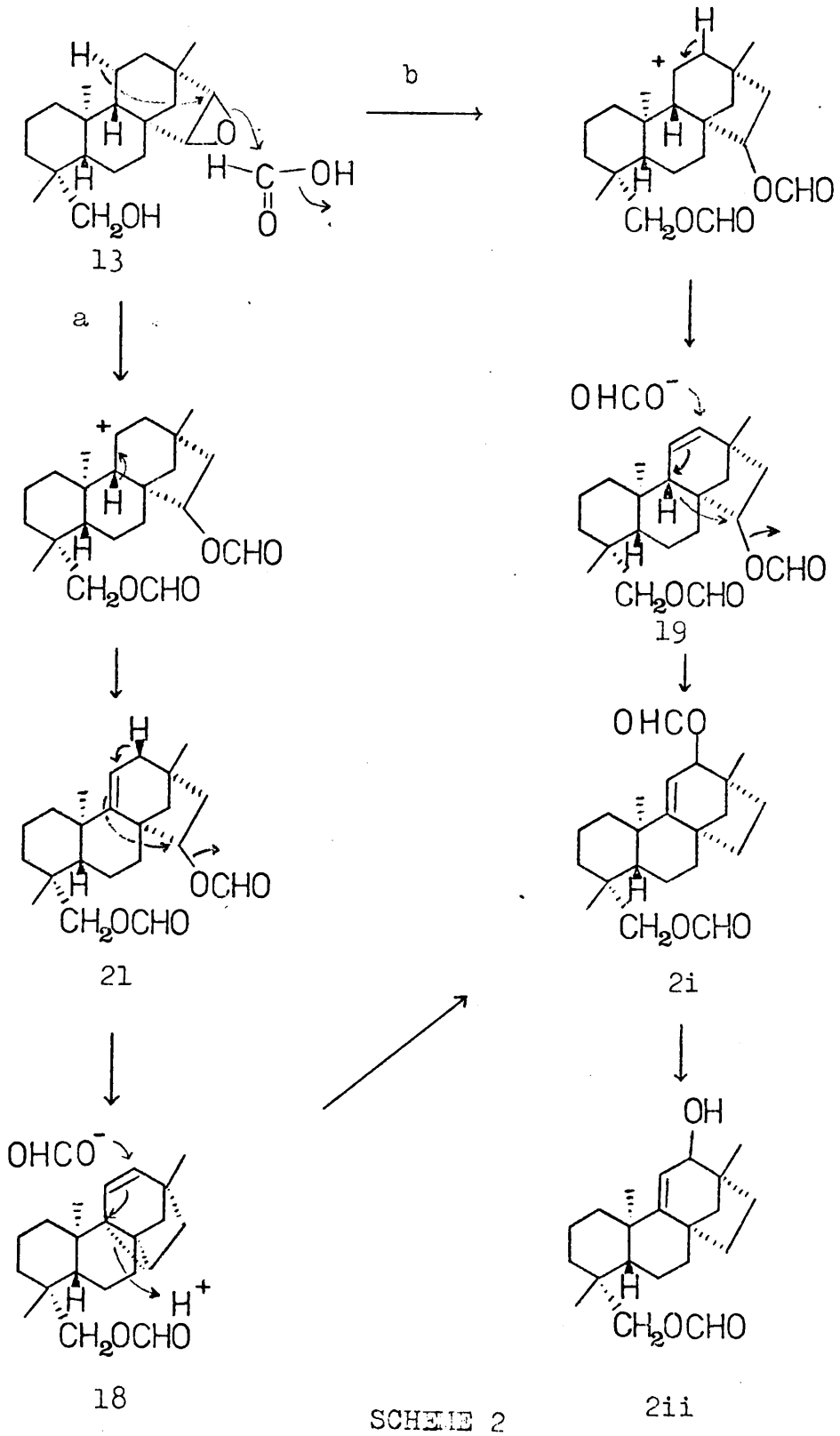
Rearrangement product 4e, to which (3ii) slowly hydrolyses on standing, was assigned the structure of the triol monoformate (3iii) on the basis of its NMR spectrum which exhibits resonances at τ9·04, 9·01 and 8·65 (all 3H, s; tertiary methyls), 5·79 (1H, bs; C-14 methine), 1·95 (1H, s; formate) and 6·06 and 5·64 (2H, ABq, J= 11Hz), and its IR spectrum with bands at ν_{max} 1728 (carbonyl) and 3628 (free hydroxyl) cm^{-1}, further bands at ν_{max} 3603 and 3510cm^{-1} being attributed respectively to a non-bonded and intramolecularly hydrogen bonded hydroxyl function which remained observable on dilution. The

highest peak in the mass spectrum appears at m/e 332 (M-18), indicating facile elimination of water.

At higher concentrations of epoxide (13) in formic acid (750mg/ml), a more deep-seated rearrangement predominated. The main product (35%) was compound 4b, a diol monoformate which was not formed when (4), (3ii) or (3iii) were resubjected to formic acid and which must therefore arise from (13) by an alternative pathway. From the NMR spectrum the compound contains a primary formate grouping (τ5·53 and 5·85, 2H, ABq, J=11Hz) necessarily located at C-19, three tertiary methyls (τ9·03, 8·89 and 8·88, all 3H, s) and the grouping



with one vinyl hydrogen (τ4·58, d, J= 4Hz) coupled to the methine proton (τ6·38, d, J= 4Hz) of a secondary alcohol (ν_{max} 3600cm^{-1}); since the former signal appears as a sharp doublet (while double resonance mutually decouples both protons) and the latter doublet is only slightly broadened, probably by 'W' coupling[6], the groups x, y and z are probably all  . The presence of the primary formate group was further confirmed by the NMR (τ1·87, 1H, s) and IR (ν_{max} 1728cm^{-1}) spectra, while the mass spectrum, with no molecular ion peak, shows a highest detectable fragment ion at m/e 314 (M-18), indicating ready loss of water. On the basis of the



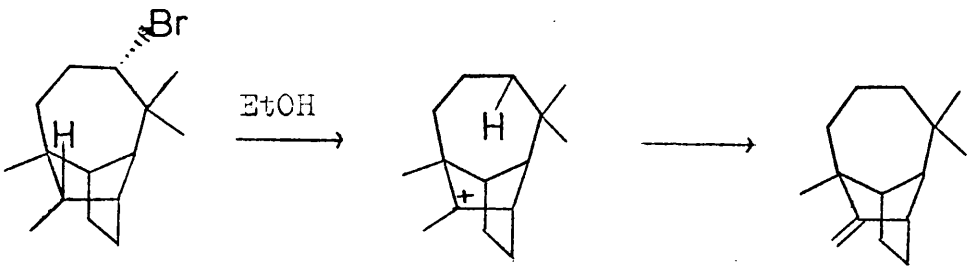
13 19 21 2i 18 2ii

SCHEME 2

available evidence, compound 4b can be provisionally assigned structure (2ii). Although the mechanism of its formation has by no means been established, one possible route is given in scheme 2a, the postulation of the initial hydride shift being inspired by analogy with the observations of Ourisson[7], who reported the participation of a trans-annular 1-5 hydride shift during the ethanolysis of medium-size ring bromides in the longifolene series. Thus 3α-bromo-(7βH)-longifolane (24) gave longifolene (25) by a C-7→ C-3 hydride shift (scheme 3).

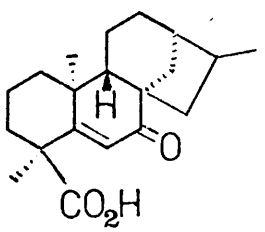
Molecular models show that the C-11 α-hydrogen is only about 3Å from C-16 (through space), while the cyclopropane ring in (18) is not unduly strained. Attack by formate at C-12 from the α-face of (18) would result in a concerted transformation to the diformate (2i), which hydrolyses readily to (2ii). Route 2b is not so feasible, since the antiperiplanar relationship of the C-9 hydrogen and C-8—C-15 bond in (19) would render the required hydride shift sterically unfavourable.

Although the main product of the new rearrangement is believed to be, in the first instance, compound 3b, to which was assigned the diol diformate structure (2i), the allylic secondary formate group hydrolysed so readily on TLC and on heating in ethyl acetate, that it could not be isolated in the absence of (2ii). The NMR spectrum



24 25

SCHEME 3



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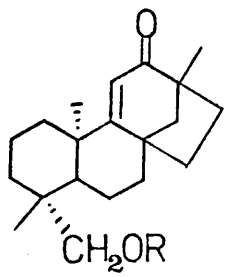


7

(i) R =CHO

(ii) R =H

of (2i) immediately after isolation reveals an approximately 1:1 mixture of the diol mono- and diformates, the resonances resulting from the latter (2i) appearing at τ9·06, 8·94 and 8·90 (all 3H, s; tertiary methyls), 4·87 (1H, d, J~3Hz; C-12 methine), 4·35 (1H, diffuse; vinyl hydrogen), 1·90 (1H, s; formate) and 2·00 (1H, s; formate). This facile hydrolysis provided a convenient method for the isolation of the pure diol monoformate (2ii); the diformate obtained from the reaction by preparative TLC was inevitably contaminated with rearrangement products of similar polarity, but the separation procedure induced hydrolysis to (2ii) which, being considerably more polar, could be cleanly isolated by further preparative TLC.

The allylic nature of the secondary alcohol (2ii) was verified by its ease of oxidation to an α,β-unsaturated ketone, the IR spectrum of which shows an absorption at ν_{max} 1676cm^{-1}, consistent with the expected conjugated cyclohexenone (7i). The UV spectrum (λ_{max}^{EtOH} 245nm, ε 12,900) compares very favourably with the value of λ_{max}^{EtOH} 244nm predicted by Woodward's rules for such a conjugated system, while the value (λ_{max}^{EtOH} 241 nm, ε 7,450) has been reported for the very similar structure (20)[8]. The NMR spectrum (100MHz; $CDCl_3$) shows resonances at τ 9·00, 8·82 and 8·76 (all 3H, s; tertiary methyls) while the lone vinyl proton resonates as a sharp singlet at τ 4·22. The primary formate

5

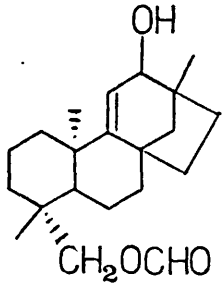
(i) R = R' = H

(ii) R = $OCOCH_3$, R' = CHO

(iii) R = CH_3, R' = H

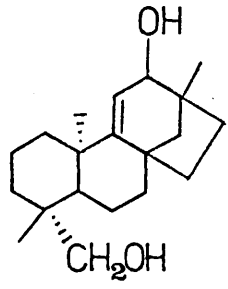
(iv) R = CH_3, R' = CHO

(v) R = CHO, R' = H



2ii

$LiAlH_4$ →

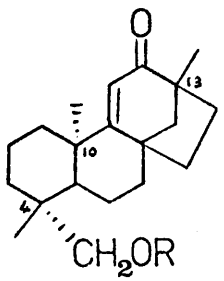


5i

is indicated by signals at τ1·88 (1H, s; formate) and 5·82 and 5·57 (2H, ABq, J= 11Hz) and in the IR spectrum by a band at ν_{max} 1731cm^{-1}. The mass spectrum shows a molecular ion peak at m/e 330. Support for structure (7i) is provided by the NMR spectrum (100MHz; $CDCl_3$) of the derived hydrolysis product (7ii) which discloses three tertiary methyls at τ9·05, 8·90 and 8·83 (all 3H, s), one vinylic proton at τ4·28 (s) and a hydroxy-methylene group at τ6·20 and 6·44 (2H, d, ABq, J= 11Hz), while the IR spectrum shows bands at ν_{max} 1673 (carbonyl) and 3645 (hydroxyl) cm^{-1} with little evidence of hydrogen bonding. The mass spectrum displays a molecular ion peak at m/e 302 and a base peak at m/e 271 (M-CH_2OH).

Reduction of the diol monoformate (2ii) with lithium aluminium hydride afforded an enediol (5i) whose NMR spectrum (100MHz; $CDCl_3$) shows the three expected tertiary methyl singlets at τ9·07, 8·96 and 8·90, the C-11 vinylic and C-12 methine doublets (which were mutually decoupled by double irradiation) at τ4·64 and 6·42 respectively (J= 4Hz), and the AB quartet due to the C-19 methylene group at τ6·16 and 6·42 (J= 11Hz). The IR spectrum reveals hydroxyl bands at ν_{max} 3620 and 3550cm^{-1}, while the molecular weight is confirmed by the mass spectrum with a molecular ion peak at m/e 304.

Further verification for the proposed structure (2ii)



7

(i) R = CHO

(ii) R = H

and those related is available from NMR data, use being made of the semi-empirical theory of aromatic solvent induced shifts (ASIS)[9] in ketones. The chemical shifts of protons in such compounds alter considerably on changing the solvent from carbon tetrachloride or deuteriochloroform to benzene, the reason being that the latter complexes with ketones at the carbon end of the carbonyl function because the partially negative oxygen end inhibits complex formation with an electron donor[10]. Consequently, if a reference plane (P) is drawn through the carbon of the carbonyl group at right angles to the carbon-oxygen bond, then protons close to (P) show very small shifts (benzene - $CDCl_3$); protons in front of P, i.e. on the same side as the oxygen of the carbonyl, are deshielded, while protons behind are shielded[11]. Although largely empirical, this rule has been applied successfully to terpenes and steroids, and was therefore adopted as a means of verifying the positions of the methyl groups in the ketone (7ii). The results of running the NMR spectrum of (7ii) in benzene-$CDCl_3$ solutions varying in composition from 0% to 100% benzene are given in table I, and are expressed in graphical form in fig. 3. The methyl group resonating at τ8·83 in 100% $CDCl_3$ experiences only a small negative shift (0·07ppm) on changing the solvent to 100% benzene, a result which one would expect from

C-4 CH_3	C-10 CH_3	C-13 CH_3	%$CDCl_3$
9·05	8·90	8·83	100
9·08	8·94	8·80	90
9·13	9·03	8·84	75
9·12	9·05	8·77	50
9·14	9·12	8·76	25
9·15	9·12	8·76	0

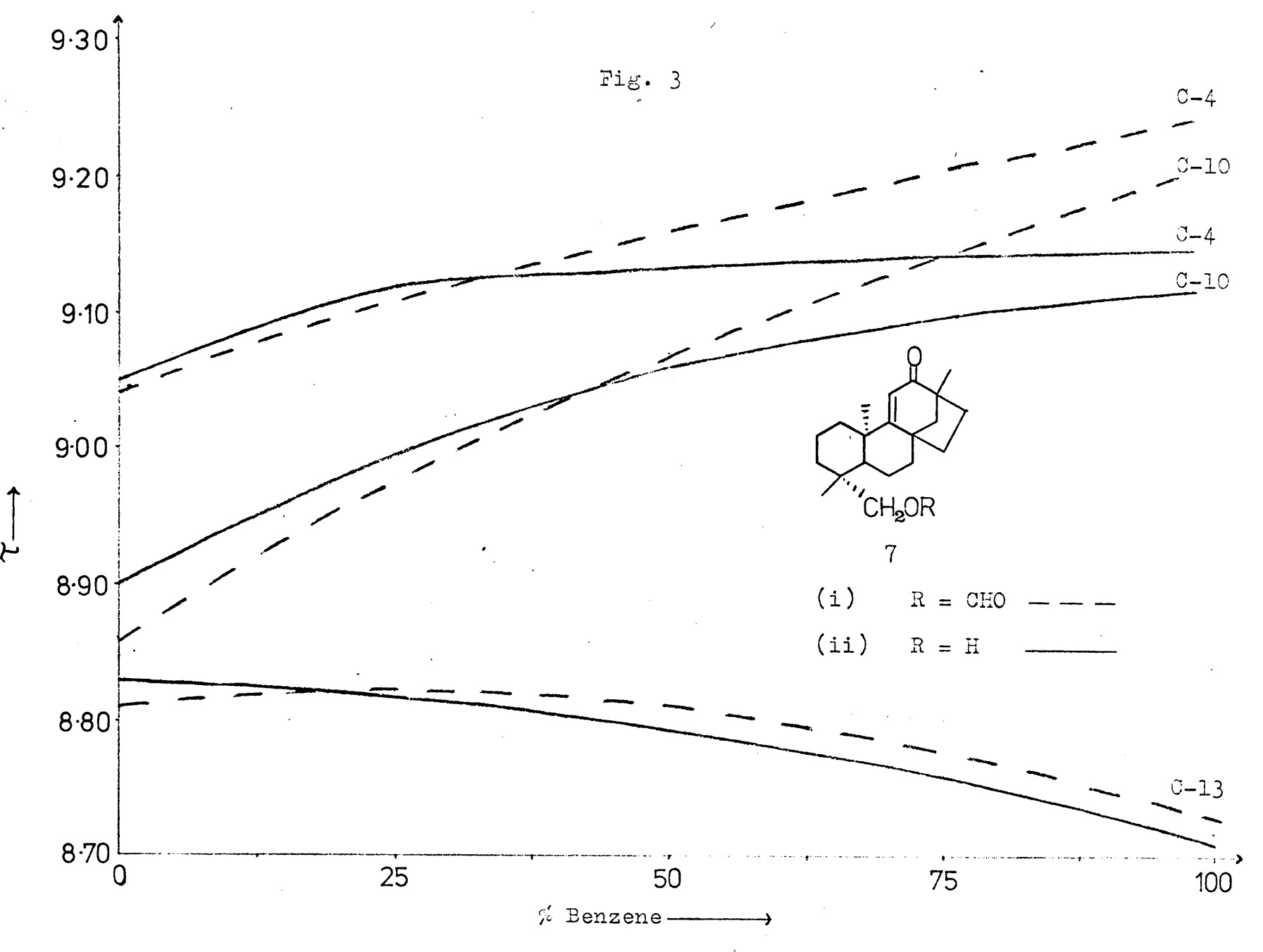
TABLE I

C-4 CH_3	C-10 CH_3	C-13 CH_3	%$CDCl_3$
9·04	8·86	8·81	100
9·08	8·91	8·82	90
9·11	8·98	8·82	75
9·15	9·07	8·81	50
9·20	9·16	8·80	25
9·25	9·21	8·72	0

TABLE II

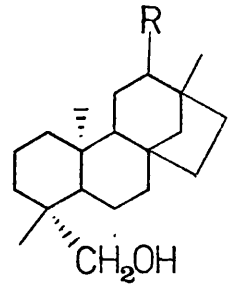
Chemical shift values given on τ scale.

Fig. 3


9·30
9·20
9·10
9·00
8·90
8·80
8·70
τ
0
25
50
75
100
% Benzene
C-4
C-10
C-4
C-10
C-13
O
CH2OR
7
(i) R = CHO
(ii) R = H

a group lying very close to but in front of the plane (P)[11]. Molecular models show that just such a condition is fulfilled by the C-13 methyl group of (7ii). Methyl functions close to but behind P experience small upfield shifts, while those of groups further removed are larger, the effect apparently increasing to a maximum and then decreasing with distance behind the plane. It therefore seems reasonable to assign the signal at τ8·90 ($CDCl_3$) to the methyl group at C-10, since it is within reasonable distance of the carbonyl function and would be expected to exhibit considerable shielding in benzene. The C-4 methyl is remote from the plane (P) and should show the much smaller solvent shift effect associated with the signal at τ9·05 ($CDCl_3$). Similar results (table II) were obtained in the case of the ketone (7i) (fig. 3), the effect of the formate group apparently being to enhance the influence of increased benzene concentration on the C-4 and C-10 methyls above 25%.

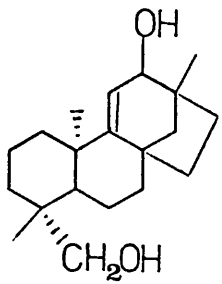
In an attempt to catalytically hydrogenate the double bond of the enediol (5i), the latter was shaken in ethyl acetate under hydrogen in the presence of 10% palladium-charcoal. However, after eight hours, the NMR spectrum of the recovered material indicated that hydrogenolysis of the allylic hydroxy function was proceeding faster than hydrogenation of the olefinic double bond. This was



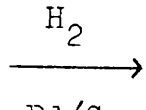
9

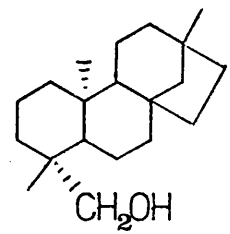
(i) R = H

(ii) R = OH

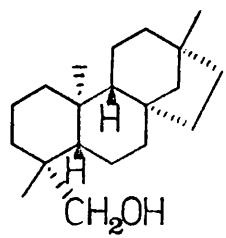


5i



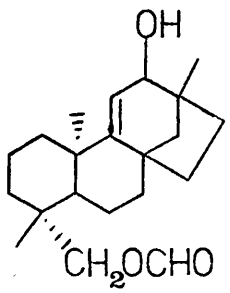


9i

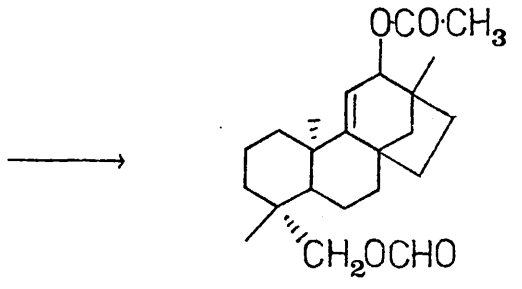


14

inferred from a triplet at τ 4·89 (J= 4Hz) which was clearly due to an isolated vinylic proton coupling to an adjacent methylene group. On resubjecting the material to hydrogenation conditions for a further 48 hours, a fully saturated alcohol was obtained. The NMR spectrum shows resonances at τ 9·04 (9H, s; three tertiary methyls) and 6·58 and 6·22 (2H, ABq, J= 11Hz), the IR spectrum bands at ν_{max} 3640 and 3480cm^{-1}, indicative of a non-bonded and hydrogen bonded hydroxyl function, and the mass spectrum a molecular ion peak at m/e 290. On the basis of the spectroscopic evidence, the compound was assigned structure (9i), with, however, the stereochemistry at C-9 undefined. If the stereochemistry of ring D in the diol monoformate (2ii) is as postulated, and hydrogenation of (5i) has occurred from the more accessible β face, then (9i), which gives rise to one peak on GLC, should be identical to dihydroerythroxylol A (14). The two compounds were, in fact, inseparable on GLC, and gave rise to identical mass spectra, but their IR spectra were slightly different. In the NMR spectrum of (9i), the three tertiary methyls resonate as a 9H singlet, while in that of (14) they are fractionally separated. Again, the melting points were identical, but admixture resulted in depression. These observations suggest that the hydrogenolysis product (9i) is very similar to (14), differing however in stereochemistry. The difference



2ii

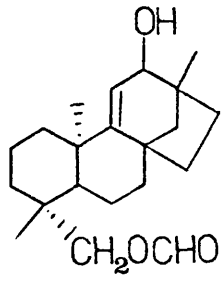


5ii

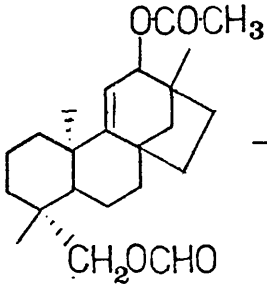
could be due either to the stereochemistry of ring D in (9i) being opposite to that postulated, in which case the mechanism proposed in scheme 2a is incorrect, or to hydrogenation of the C-9 — C-11 double bond in (5i) having occurred at the α face.

The C-12 position of the allylic alcohol (2ii) proved to be particularly reactive, this at first becoming apparent when incautious use of acetic acid while attempting to oxidise the compound to the ketone, led to facile formation of the derived acetate (5ii). The NMR spectrum (100MHz; $CDCl_3$) shows signals at τ 9·11, 9·02 and 8·96 (all 3H, s; tertiary methyls), 8·05 (3H, s; acetate), 4·78 (1H, d, J= 4Hz; vinylic hydrogen), 5·17 (1H, d, J= 4Hz; C-12 methine), 1·96 (1H, s; formate) and 5·65 and 5·95 (2H, ABq, J= 11Hz; C-19 methylene), while the IR spectrum exhibits a strong carbonyl absorption at ν_{max} 1729cm^{-1}. The molecular weight is confirmed by the mass spectrum with a molecular ion peak at m/e 374, while a further peak at m/e 314 indicates facile loss of acetic acid. (5ii) was presumably formed as a result of protonation of the secondary hydroxyl group followed by nucleophilic substitution by the acetate anion, this reaction being apparently faster than oxidation.

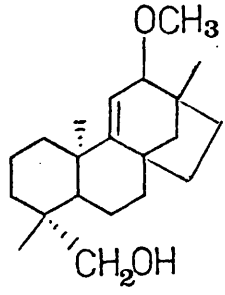
Treatment of the acetate (5ii) with methanol and aqueous sodium bicarbonate resulted in methanolysis,



2ii

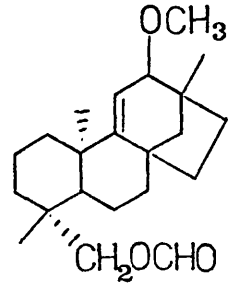


5ii



5iii

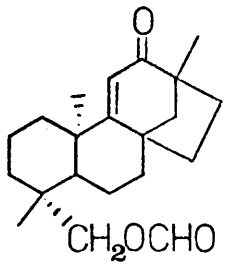
+



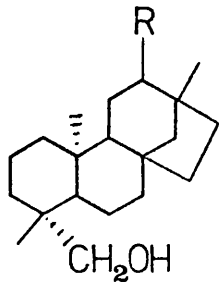
5iv

thirty minutes reflux producing the methoxy-alcohol (5iii) along with a small quantity of the corresponding primary formate (5iv). Separation was achieved by preparative TLC (ethyl acetate-light petroleum, 15:85). The alcohol (5iii) was also obtained cleanly by allowing a solution of the diol monoformate (2ii) in 50% methanolic/aqueous sodium bicarbonate to stand at room temperature for 48 hours. The NMR spectrum of (5iii) discloses the three tertiary methyls at τ 9·05, 8·90 and 8·87 (all 3H, s) and the ether-methyl at τ 6·59 (1H, s). Signals at τ 4·52 and 6·88 (each 1H, d, J= 4Hz) which were mutually decoupled by double irradiation, correspond to the vinylic and C-12 methine protons respectively, while the C-19 methylene group gives rise to the expected AB quartet at τ 6·38 and 6·09 (J= 11Hz). The IR spectrum has bands at ν_{max} 1730 (carbonyl), 3620 (free hydroxyl) and 3480 (hydrogen bonded hydroxyl) cm^{-1} while the mass spectrum shows the expected molecular ion peak at m/e 318. The corresponding formate (5iv) was similarly characterized, the formate grouping being disclosed by a singlet at τ 1·90 and the shifting of the AB quartet of the C-19 methylene to τ 5·90 and 5·58 (J= 11Hz).

It was hoped to reduce the α,β-unsaturated ketone (7i) to the corresponding allylic alcohol and to ascertain whether the product was (2ii) or a mixture of C-12 epimers.



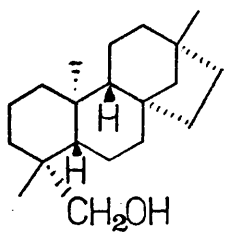
7i



9

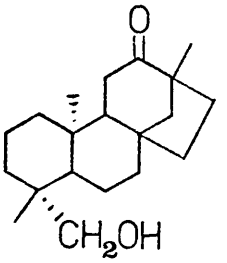
(i) R = H

(ii) R = OH



14

Reaction of (7i) with sodium borohydride in ethanol yielded two inseparable products of very similar polarity on TLC (ethyl acetate-light petroleum, 60:40), which proved not to be the C-12 epimers but comprised at least one carbonyl-bearing compound. The NMR and IR spectra disclosed a primary alcohol grouping and no primary formate, the latter having been removed in the reaction. Due to its inseparability, the mixture was subjected directly to catalytic hydrogenation, to yield three products which proved to be readily separable by preparative TLC (ethyl acetate-light petroleum, 60:40). The least polar was identical on TLC and GLC with the fully saturated primary alcohol (9i) and dihydroerythroxylol A (14). The NMR spectrum (100MHz; $CDCl_3$) of the most polar discloses three tertiary methyls at τ 9·07 (6H, s) and 8·99 (3H, s), while a broad signal at τ6·4 is of the correct chemical shift for the methine hydrogen associated with a secondary alcohol function at C-12. The expected AB quartet at τ 6·30 and 6·62 (J= 11Hz) reveals the C-19 methylene group, while the associated primary hydroxyl function gives rise to a band in the IR spectrum at ν_{max} 3646cm^{-1}. The mass spectrum displays a molecular ion peak at m/e 306. On the basis of the spectroscopic data, the compound appears to be the fully saturated diol (9ii), perhaps occurring as a mixture of C-12 epimers,



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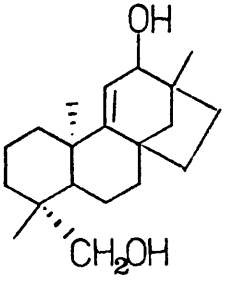
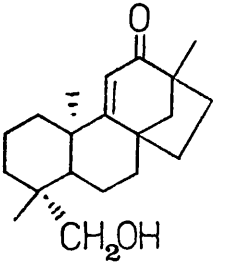
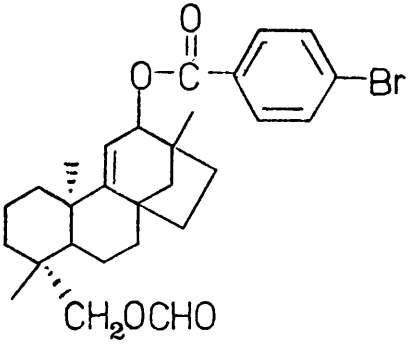


5i



7ii



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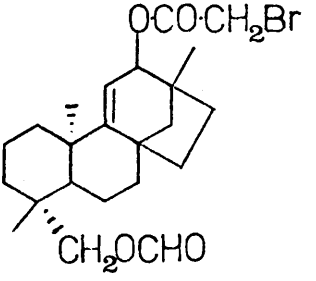
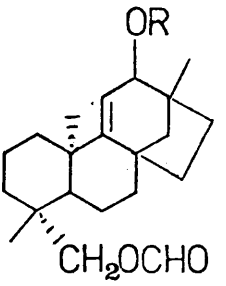


23

since it melts with a certain amount of preliminary weeping. The third hydrogenation product was assigned the ketone structure (10), its NMR spectrum showing resonances at τ9·20, 9·03 and 8·93 (all 3H, s; tertiary methyls), 7·66 (2H, bm; C-11 methylene) and 6·31 and 6·60 (2H, ABq, J= 11Hz), while the IR spectrum displays absorptions at ν_{max} 1708 (carbonyl), 3650 and 3500 (hydroxyl) cm^{-1}. The molecular weight of 304 is confirmed by the corresponding molecular ion peak in the mass spectrum. On the basis of the structures assigned to the hydrogenation products, the two compounds isolated from the borohydride reaction would be expected to be the enediol (5i), which on catalytic reduction could yield (9i) and (9ii), and the conjugated ketone (7ii) which on hydrogenation could give rise to (10). However, TLC comparison showed that neither (5i) nor (7ii) was a product of the borohydride reaction, a result which is difficult to rationalize in the light of former conclusions. The problem remains unresolved.

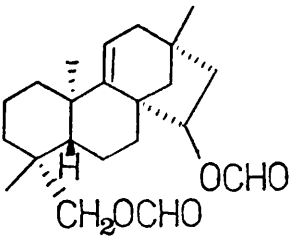
In order to completely prove the structure of (2ii), X-ray analysis was attempted on the compound itself in the absence of a heavy atom, but solution of the problem ultimately proved mathematically impossible. The p-bromobenzoate (22) and bromoacetate (23) were prepared, but their crystal forms rendered them unsuitable for X-ray analysis.



2

(i) R = CHO

(ii) R = H

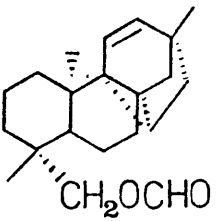


21

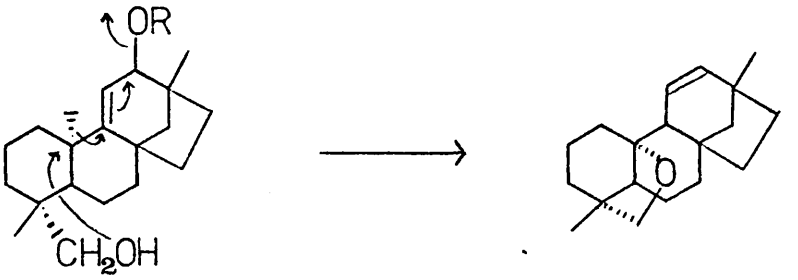
Examination of the remaining products emanating from the rearrangement of epoxide (13) was hindered by separation difficulties and their occurrence in low yields. However, the compounds of both bands 1 and 2 (fig. 1) appear to result from the same reaction pathway as (2ii), since resubjection of the latter to formic acid leads initially to the diformate (2i), followed by slow formation of products which are TLC identical with bands 1 and 2. Partial separation of the three compounds constituting band 2 was achieved by preparative TLC (ethyl acetate-benzene, 95:5) using 20 x 50cm plates left to run overnight. This technique afforded compound 2b, slightly contaminated with 2a (a very minor component) and 2c, while compound 2c was obtained containing a little 2b as an impurity. The NMR spectrum of 2b (100MHz; $CDCl_3$) shows resonances at τ9·02, 8·97 and 8·90 (all 3H, s; tertiary methyls), 1·86 and 1·89 (each 1H, s; formate hydrogens), 4·80 (1H, d, J= 4Hz; vinylic hydrogen), 5·80 (1H, bd) and 6·06 and 5·56 (2H, ABq, J= 11Hz), while the IR spectrum contains a carbonyl band at ν_{max} 1725cm^{-1}. The spectroscopic data is consistent with structure (21) which was proposed as an intermediate in the formation of the diformate (2i). It would be unwise, however, to categorically claim this structure to be correct, since it seems unlikely that it would arise from resubjection

of (2ii) to the reaction conditions; it is of course possible that the compounds resulting from formic acid treatment of (2ii) are not the products in bands 1 and 2 (fig. 1), but simply compounds of similar R_f. The NMR spectrum of 2c (100MHz; $CDCl_3$) was of poor quality due to lack of material and the presence of 2b, but it discloses three tertiary methyls at τ 9·02, 8·92 and 8·86 (all 3H, s), an AB quartet at τ 5·50 and 5·90 (J~11Hz) attributable to the C-19 methylene group, and one or two formate hydrogens at τ 1·88 (s). Broad singlets at τ 4·20 and 5·80 may be due to a vinylic hydrogen and the methine of a secondary formate respectively. The exact structure of 2c is not immediately obvious, but is presumably closely related to that of 2b.

Band 1 yielded an inseparable mixture of two oils, 1a and 1b. Although appearing as one spot on TLC, it was resolved by GLC into two components occurring in the approximate ratio of 3:1. The NMR spectrum of the mixture shows a broad singlet at τ 8·94, presumably attributable to coincident resonance of three tertiary methyls, while an AB quartet at τ 6·06 and 5·80 (J= 11Hz) and a rather broad singlet at τ 1·93 point to the presence of a primary formate. An unsymmetrical vinylic doublet at τ 4·53 (J= 4Hz) may not be genuine, but may in fact be two very close singlets, while a further signal at τ 5·9 is badly



18



5 1

(i) R =H

(v) R = CHO

SCHEME 4

obscured by the AB quartet. The IR spectrum contains the expected carbonyl band at ν_{max} 1728cm^{-1}. While the structure of 1a or 1b is by no means clear, there is a certain amount of evidence to suggest that they may be closely allied to (18), one of the intermediates in the postulated rearrangement mechanism. The mixture analyses correctly for $C_{21}H_{30}O_2$, the molecular formula of (18), while the mass spectrum contains the required molecular ion peak at m/e 314. The NMR spectrum contains a sharp singlet at τ9·18, one of the highest signals observed in any of the spectra so far examined, and may indicate a cyclopropyl hydrogen, one of which is contained by structure (18) at C-15; this, however, would be expected to resonate as a triplet.

Band 1 yielded one further compound, 1c, which was interesting insomuch that it contained neither carbonyl nor hydroxyl functions and appeared to contain a cyclic ether. It was tentatively assigned structure (1), and its derivation from (5i) or (5v) proposed according to scheme 4, which involves nucleophilic attack by the C-19 oxygen at C-10, resulting in a methyl shift, double bond migration and overall elimination of water or formic acid. Although scheme 4 implies a concerted mechanism, it is possible that formation of the ether ring occurs only after migration of the C-10 methyl, since the latter,

being α, is not ideally disposed for concerted displacement by the C-19 oxygen. The mass spectrum of (5i) shows that it eliminates water readily. Support for the proposed structure (1) is provided by the NMR spectrum which discloses three tertiary methyls at τ9·15 (3H, s) and 8·98 (6H, s); a sharp singlet at τ6·43 (2H) implies the grouping $-CH_2OR$, while a further singlet at τ4·64 (2H) is indicative of two vinylic hydrogens. Further evidence for the olefinic double bond is the band at ν_{max} 3010cm^{-1} in the IR spectrum, while a band at ν_{max} 1046cm^{-1} may be due to the ether linkage. The mass spectrum supports the suggested structure ($C_{20}H_{30}O$), the molecular ion peak occurring at m/e 286.

EXPERIMENTAL

Melting points (uncorrected) were determined on a Reichert hot-stage apparatus. IR spectra were run in carbon tetrachloride solutions (0·1mm cell), unless otherwise stated, on Perkin-Elmer 257 and 225 and Unicam SP100 Mark II spectrophotometers. NMR spectra were recorded on a Varian T-60 spectrometer, unless otherwise stated, using deuteriochloroform solutions and tetramethylsilane as internal standard. Mass spectra were recorded with an AEI-GEC MS12 mass spectrometer. Analytical GLC separations were performed using Pye-Argon chromatographs with a 1% OV-1 column at 175°.

Kieselgel G (Merck) was used for analytical (0·25mm) and HF 254 for preparative (1mm) TLC. Plates were sprayed with a solution of ceric ammonium sulphate (10g) in dilute sulphuric acid (330ml) diluted to 990ml with water, and then warmed at 150° for approximately 3 minutes. Light petroleum refers to the fraction b.p. 60-80°. Solutions were dried over anhydrous magnesium sulphate.

Extraction of Erythroxylol A (11).

A mixture of erythroxylol A (11) and erythroxylol B (12) (8·18g), obtained from the extraction of Erythroxylon monogynum with ether, was chromatographed over alumina (grade H) (320g). Gradient elution [ether-light petroleum (3:1) dropping into ether-light petroleum (1:9)] gave

almost pure erythroxylol A (2·86g) followed by a mixture (approximately 1:2) of erythroxylols A and B (4·40g).

Erythroxylol A Epoxide (13).

Erythroxylol A (1·0g, 3·5m.mol.) and m-chloroperbenzoic acid (0·65g, 3·8m.mol.) were dissolved in chloroform (20ml). After being allowed to stand at room temperature for two hours, the solution was passed through a short column of alumina (Woelm, grade 3). Removal of solvent under reduced pressure afforded erythroxylol A epoxide (13; 0·89g, 85%), m.p. 115-116·5° (needles from methanol).

Acid-Catalysed Rearrangement of Erythroxylol A Epoxide.

i) Erythroxylol A epoxide (510mg, 1·7m.mol.) was warmed with 95% formic acid (6ml) for five minutes. Most of the acid was then removed by heating under reduced pressure and the residue taken up in ether. TLC (ethyl acetate-light petroleum, 15:85 and 30:70) revealed the presence of at least seventeen compounds.

ii) Erythroxylol A epoxide (1·13g, 3·7m.mol.) was warmed with 95% formic acid (1·5ml) for five minutes. Most of the acid was then removed by heating under reduced pressure and the residue taken up in ether. TLC (ethyl acetate-light petroleum, 15:85 and 30:70) showed the formation of the same range of compounds as above, but occurring in different relative proportions.

Isolation of Products.

Rearrangement (i). Partial separation of the products was effected by chromatography of the crude residue (700mg) over silica (28g), eluting with ether-light petroleum. Subsequent TLC of the fractions (ethyl acetate-light petroleum, 20:80), showed four distinct bands of compounds, (fig. 1), which were classified accordingly and whose ultimate structural assignments, where possible, are shown in fig. 2.

The material (120mg) constituting band 1 (the least polar) was combined. Preparative TLC (20 x 20 x 0·1cm plate run twice in 25% chloroform-light petroleum) yielded an inseparable mixture of two oils, 1a and 1b (82mg, 19%, R_f= 0·7), and compound 1c, (20mg, 5·5%, R_f= 0·5), b.p. 60-63° (0·02mm). The mixture of 1a and 1b distilled at 125° (0·35mm). (Found: C, 79·8; H, 9·8. $C_{21}H_{30}O_2$ requires C, 80·2; H, 9·6%).

Band 2 (52mg) comprised three products which proved very difficult to separate. Partial resolution was achieved using preparative TLC (50 x 20 x 0·1cm plate run in 2·5% ethyl acetate-light petroleum) which yielded impure quantities of compounds 2a (5mg, 1·5%), 2b (14mg, 3·5%) and 2c (10mg, 8%), all of R_f 0·4 to 0·5.

Band 3 (234mg) contained six compounds, of which one, (3c), was very much predominant. Preparative TLC

(100 x 20 x 0·1cm plate in 10% ethyl acetate-light petroleum) yielded inseparable mixtures of 3a and 3b (12mg, 3%, R_f= 0·6) and 3e and 3f (7mg, 1·5%, R_f= 0·3), 3d (3mg, 1%, R_f= 0·4) and 3c (196mg, 40%, R_f= 0·5), m.p. 135-136° (from ether-light petroleum) (Found: C, 72·7; H, 9·1. $C_{22}H_{32}O_4$ requires C, 73·3; H, 9·0%).

Preparative TLC of band 4 (91mg) (20 x 20 x 0·1cm plate in 50% ethyl acetate-light petroleum) yielded five compounds, namely (i) 4a (4mg, 1%, R_f= 0·8), m.p. 124-125° (from ether-light petroleum) (Found: C, 67·9; H, 8·3. $C_{23}H_{34}O_6$ requires C, 68·0; H, 8·4%), (ii) 4b (18mg, 4%, R_f= 0·7), m.p. 105-106° (from ether-light petroleum) (Found: C, 75·5; H, 9·5. $C_{21}H_{32}O_3$ requires C, 75·9; H, 9·7%), (iii) 4c (3mg, 1%, R_f= 0·6), (iv) 4d (32mg, 7%, R_f= 0·5), m.p. 126-128° (from ether-light petroleum) (Found: C, 70·1; H, 9·2. $C_{22}H_{34}O_5$ requires C, 69·8; H, 9·1%) and (v) 4e (17mg, 4%, R_f= 0·4), m.p. 161-164° (from ether-light petroleum) (Found: C, 71·5; H, 9·7. $C_{21}H_{34}O_4$ requires C, 71·95; H, 9·8%).

Rearrangement (ii). Preparative TLC of the crude residue (two 100 x 20 x 0·1cm plates in 10% ethyl acetate-light petroleum) yielded 4b (80mg) and a mixture of 3b and 3c The latter, after warming in ethyl acetate for ten minutes and further preparative TLC (100 x 20 x 0·1cm plate in 20% ethyl acetate-light petroleum), afforded 4b (178mg,

overall yield 25%).

The compounds isolated have hitherto been designated according to the system in fig. 1. They are hereafter referred to by the number of their structural assignment.

Reduction of the Enediol Diformate (4).

The enediol diformate (4) (60mg, 0·17m.mol.) was stirred at room temperature overnight in dry ether (5ml) with an excess of lithium aluminium hydride (19mg, 0·5 m.mol.). Treatment with saturated sodium sulphate solution followed by filtration and drying afforded the diol(6i) (49mg, 97%), m.p. 195-196° (from ether-light petroleum) (Found: C, 78·5; H, 10·6. $C_{20}H_{32}O_2$ requires C, 78·9; H, 10·6%).

Acetylation of the Enediol (6i).

The enediol (6i) (38mg, 1·2m.mol.) was dissolved in pyridine (2ml). A slight excess of acetic anhydride was added and the reaction allowed to stand overnight at 0°. The solution was poured into a mixture of ice and dilute hydrochloric acid (5ml) and extracted with ethyl acetate to yield, after washing with brine and drying in the usual manner, the enediol di-acetate (6ii) (37mg, 75%), b.p. 140° (0·004mm) (Found: C, 74·4; H, 9·3. $C_{24}H_{36}O_4$ requires C, 74·2; H, 9·3%).

Catalytic Hydrogenation of the Enediol Diformate (4).

The enediol diformate (4) (84mg, 0·3m.mol.) was dissolved in ethyl acetate (15ml) and shaken with 10% palladium-charcoal (12mg) under hydrogen at room temperature for 20 hours. The solution was filtered and the solvent removed under reduced pressure. Preparative TLC (ethyl acetate-light petroleum, 15:85) afforded a 3:2 mixture of the dihydro epimers (8) (54mg, 65%) which were separated by GLC, along with 14mg of an unidentified compound. The epimeric mixture (8) crystallized with difficulty from ether-light petroleum and melted, after considerable weeping, at 154-158°. (Found:C, 72·9; H, 9·45. $C_{22}H_{34}O_4$ requires C, 72·6; H, 9·1%).

Dehydration of the Triol Diformate (3ii).

The triol diformate (3ii) (80mg, 0·2m.mol.) was dissolved in pyridine (0·5ml). Phosphoryl chloride (0·2ml) was added and the reaction allowed to stand overnight. The solution was poured into water (10ml), filtered and extracted with ether to yield the enediol diformate (4) (72mg, 94%) which was identical (NMR, IR and mixed m.p.) with an authentic sample.

Reduction of the Enediol Monoformate (2ii).

The enediol monoformate (2ii) (53mg, 0·16m.mol.) was stirred in ether (4ml) with an excess of lithium aluminium hydride (10mg, 0·25m.mol.) at room temperature for thirty

minutes. Conventional work-up afforded the enediol (5i) (47mg, 97%), m.p. 150-152° (from ether-light petroleum) (Found: C, 78·4; H, 10·4. $C_{20}H_{32}O_2$ requires C, 78·9; H, 10·6%).

Oxidation of the Enediol Monoformate (2ii).

A solution of the enediol monoformate (2ii) (20mg, 0·06m.mol.) in benzene (4ml) was treated at 1-6° with a cold solution of sodium dichromate and sulphuric acid containing a little acetic acid until the orange colour of the reaction medium persisted[12]. The solution was then poured into ice-water (10ml) and the product extracted with benzene. After washing with brine and drying in the usual manner, the solvent was removed under reduced pressure to yield the enone (7i) (19mg, 95%), m.p. 130-131° (from ether-light petroleum) (Found: C, 76·9; H, 8·8. $C_{21}H_{30}O_3$ requires C, 76·3; H, 9·15%).

Hydrolysis of the Enone Formate (7i).

The formate (7i) (39mg, 1·2m.mol.) was stirred overnight at room temperature in 1:1 methanol-water (3ml) containing sodium bicarbonate (20mg). Removal of the methanol under reduced pressure followed by extraction with ether and conventional work-up yielded the primary alcohol (7ii) (30mg, 85%), m.p. 133-134° (from ether-light petroleum) (Found: C, 79·4; H, 9·8. $C_{20}H_{30}O_2$ requires C, 79·4; H, 10·0%).

Acetylation of the Enediol Monoformate (2ii).

A solution of the enediol monoformate (2ii) (98mg, 0·3m.mol.) in benzene (10ml) was treated at 1-6° with a cold solution made from saturating 30ml of 50% sulphuric acid with sodium dichromate and adding 5ml of acetic acid. When the orange colour persisted, the benzene solution was poured into ice-water (20ml) and the product extracted with benzene. Work-up in the normal manner afforded the acetate (5ii) (93mg, 85%), m.p. 134-136° (from ether-light petroleum) (Found: C, 73·7; H, 9·0. $C_{23}H_{34}O_4$ requires C, 73·8; H, 9·15%).

Methanolysis of the Acetate (5ii).

A solution of the acetate (5ii) (40mg, 1·1m.mol.) in 50% methanolic/aqueous sodium bicarbonate (10ml) was heated under reflux for thirty minutes. The methanol was removed under reduced pressure and the product extracted with ether. Preparative TLC (ethyl acetate-light petroleum, 18:82) yielded the methoxy-alcohol (5iii) (23mg, 65%), m.p. 158-160° (from ether-light petroleum) (Found: C, 79·0; H, 10·6. $C_{21}H_{34}O_2$ requires C, 79·2; H, 10·8%), along with the methoxy-formate (5iv) (3mg, 8%).

Methanolysis of the Enediol Monoformate (2ii).

The enediol monoformate (2ii) (50mg, 0·15m.mol.) was allowed to stand in 50% methanolic/aqueous sodium bicarbonate (10ml) at room temperature for two days, at

the end of which time normal work-up yielded the methoxy-alcohol (5iii).

Hydrogenolysis of the Enediol (5i).

The enediol (5i) (47mg, 1·5m.mol.) was dissolved in ethyl acetate (15ml) and shaken under hydrogen at room temperature in the presence of 10% palladium-charcoal (13mg). After eight hours, the NMR spectrum of the recovered material indicated that hydrogenolysis of the allylic hydroxy function was proceeding faster than hydrogenation of the olefinic double bond. The material was resubjected to the reaction conditions for a further 48 hours. Work-up followed by preparative TLC (ethyl acetate-light petroleum, 15:85) afforded the fully saturated alcohol (9i) (20mg, 45%), m.p. 130-131° (from light petroleum) (Found: C, 82·5; H, 11·5. $C_{20}H_{34}O$ requires C, 82·7; H, 11·8%)..

Reduction of the Enone (7i).

The enone (7i) (51mg, 1·5m.mol.) was stirred in ethanol (5ml) with an excess of sodium borohydride (22mg) at room temperature for one hour. Addition of water (20ml) followed by extraction with ethyl acetate yielded a mixture of two compounds (43mg) which could not be separated by preparative TLC. The mixture was dissolved in ethyl acetate (15ml) and shaken under hydrogen in the presence of 10% palladium-charcoal (10mg) for 18 hours

at room temperature. After work-up, preparative TLC (ethyl acetate-light petroleum, 40:60) afforded three crystalline compounds, the least polar of which (4mg) was identical on TLC and GLC with the fully saturated alcohol (9i). The compound of intermediate polarity (17mg), m.p. 177-179° (from ether-light petroleum), had spectroscopic properties consistent with the proposed structure (10), while the most polar compound (6mg), m.p. 195-197° (from ether-light petroleum), was similarly assigned the structure (9ii).

p-Bromobenzoate of (2ii).

The diol monoformate (2ii) (33mg, 0·1m.mol.) and p-bromobenzoyl chloride (120mg, 0·55m.mol.) were heated in refluxing benzene (20ml) containing pyridine (2ml) for 20 minutes. Ether (30ml) was added to the cooled solution, which was then washed with dilute acid followed by dilute alkali and water. After drying in the normal manner, the solvent was removed under reduced pressure to yield, after preparative TLC (ethyl acetate-light petroleum, 15:85), the p-bromobenzoate (22) (30mg, 65%), m.p. 194-196° (needles from light petroleum).

Bromoacetate of (2ii).

To a solution of the diol monoformate (2ii) (77mg, 0·23m.mol.) in benzene (4ml) was added bromoacetyl bromide (100mg, 0·5m.mol.) in benzene (4ml) followed by pyridine

(1ml). After refluxing for ten minutes, the solution was cooled and ether (20ml) added. Work-up and preparative TLC as above yielded the bromoacetate (23) (20mg, 20%), m.p. 112·5-114·5° (prisms from ether-light petroleum), and unreacted or regenerated diol monoformate (2ii) (30mg).

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