SYNTHETIC AND CONFIGURATIONAL STUDIES OF BIOSYNTHETIC PRECURSORS.

THESIS

presented to the University of Glasgow

for the degree of M.Sc.

by

George W. Francis

1967

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

SYNTHETIC AND CONFIGURATIONAL STUDIES OF BIOSYNTHETIC PRECURSORS.

George W. Francis M.Sc. Thesis - 1967

Summary.

A synthesis of 7-^{14}C-shikimic acid was attempted. It was hoped to decarboxylate the closely related quinic acid to yield a 3:4:5-trihydroxy-cyclohexanone. Suitable recarboxylation of such a derivative using labelled reagents would yield a product which on dehydration and hydrolysis would provide 7-^{14}C-shikimic acid.

It was not found possible to repeat a Hunsdieker reaction on the silver salt of tetra-acetyl quinic acid which had previously been described as resulting in 3:4:5-triacetoxy-cyclohexanone.

The two known modifications of 3:4-isopropylidene-3:4:5-trihydroxy-cyclohexanone were prepared and, contrary to the claims in the literature, found to be two crystalline modifications of the same free ketone. A number of cyanohydrin reactions were attempted on this ketone and its acetyl derivative without success. Ethynylation of these ketones also failed. When an attempt was made to form the pyrrolidine enamines of the ketones the product isolated was found to be N-(p-hydroxyphenyl)-pyrrolidine.

Acetic anhydride dehydration of tetra-acetyl-quinamide and of 3-acetyl-4:5-isopropylidene-quinamide yielded the respective acetyl cyanohydrins as described in the literature.

An alternative route to 3:4:5-triacetoxy-cyclohexanone was successfully repeated. This involved the lead tetra-acetate cleavage of 3:4:5-triacetyl china alcohol. There was unfortunately no time available to undertake recarboxylation of this ketone, either by the previously reported cyanohydrin reaction or otherwise.

It was decided to obtain derivatives of geraniol and nerol suitable for x-ray analysis in order to establish the respective configurations of the alcohols beyond doubt. The p-iodobenzoates and p-bromobenzoates of the alcohols were prepared and found to be liquids.

p-(p-Bromophenylazo)-benzoic acid was prepared by coupling p-bromo-nitrosobenzene with p-aminobenzoic acid. Reaction of geraniol and nerol with the acid chloride gave the esters. These esters were submitted for x-ray analysis as crystalline solids. As a check against isomerisation the esters of α-terpineol and citronellol were also prepared.

The proton magnetic resonance spectra of all the compounds prepared were analysed.

I wish to express my gratitude to Professor R. A. Raphael and Doctor K. H. Overton for their encouragement and assistance during the past two years.

My thanks are also due to Mr. J. M. L. Cameron and his staff for micro-analyses, to Mrs. F. Lawrie for infra-red spectra, and to Mrs. S. Hamilton and Messrs. J. Gall and J. Lennon for nuclear magnetic resonance spectra.

I am also indebted to the University of Glasgow for financial assistance in the form of a Demonstratorship during the last year.

CONTENTS.

Shikimic Acid.

Shikimic acid (1) was first isolated in 1885 by Eykman[1] from Illicium religiosum. It exists in nature as D-(-)-shikimic acid which when pure is a white solid m.p. 190-1° and $[\alpha]_D$ -157°.[2]

Shikimic acid has been found to occur in nature in a wide variety of plants and in a wide variety of their tissues. A complete list of the plants examined for shikimic acid is given in a review article by Bohm[3]; suffice it to say that the list includes Bryophytes, Pteridophytes, Gymnosperms and Angiosperms, and numbers several hundred in all. Shikimic acid has also been found to be a metabolite in a number of bacteria. Indeed, some of these furnish a source of labelled shikimic acid when labelled precursors are used. A full account of the occurrence and metabolic involvement of shikimic acid is found in the above paper[3] and only an outline will be given here. An excellent review of the biochemistry of shikimic acid is given by Sprinson[4]. What follows is taken from the above sources[3,4].

Studies on Escherichia coli strains have shown that D-glucose (B1) is the precursor of the shikimate pathway. In the presence of unlabelled D-glucose there was no significant incorporation of labelled acetate, pyruvate and formate in the resultant shikimate.

It is believed that the first stage in the shikimate pathway is the formation by separate paths of phosphoenol-pyruvate (B2) and D-erythrose 4-phosphate (B3). From these is formed 3-deoxy-D-arabino-heptulosonate 7-phosphate (B4) and this is then cyclised to 5-dehydroquinate (B5). This latter is now metabolised either to quinate (B6) or 5-dehydroshikimate (B7), each of these steps being reversible. The enzyme responsible for the conversion of 5-dehydroquinate to 5-dehydroshikimate has been partially purified and characterised by Mitsuhasi and Davis[5]. This 5-dehydroquinase is quite specific and does not affect quinate itself. The conversion of 5-dehydroshikimate (B7) to shikimate (B8) is carried out by 5-dehydroshikimate reductase which has been found to be absent in mutants of E. coli which accumulate 5-dehydroshikimate (B7). Phosphorylation of shikimate (B8) leads to shikimate 5-phosphate (B9).

The next place in the pathway is occupied by 3-enolpyruvyl-shikimate 5-phosphate (B10) and this was at one time thought to be a branch-point. Recent work has however suggested that branching occurs after this stage and chorismate (B11) has been proposed as the branch-point.

It is believed that in the presence of glutamine, as an amino-donor, anthranilate (B12) is formed from chorismate (B11). Anthranilate (B12), by enzymatic incorporation of a ribose unit followed by cyclisation, yields the indole derivative (B13) which

in the presence of L-serine is further metabolised to give L-tryptophan (B14).

In the absence of glutamine chorismate (B11) is converted to prephenate (B15). Prephenate (B15) is then converted to phenyl-pyruvate (B16) by loss of water and carbon dioxide by either acidic or enzymatic catalysis. Alternatively prephenate may be metabolised to give p-hydroxyphenyl-pyruvate (B17). Enzymatic transamination with glutamate with both keto-acids (B16 and B17) has been shown[6] to yield phenylalanine (B18) and tyrosine (B19) in strains of E. coli.

Labelling studies have shown that shikimate metabolites are incorporated into the flavenoids and lignin. The flavenoid quercetin (B20) is formed in the buck-wheat plant and when this plant was fed[7] with labelled phenylalanine or cinnamic acid these were incorporated into ring B and atoms C2, C3, C4 as a unit. Further studies showed[8] that the carbon atoms in ring A were derived from the acetate pathway.

Lignins are the polymeric condensation products of the cinnamyl alcohols and are widespread in nature. When sugar-cane plants were fed[9] with p-hydroxyphenyl-pyruvate (B17) labelled at the carboxyl position and the lignins obtained from the plant were hydrolysed, the products showed a high level of incorporation of the label.

Eykman's initial paper[1] showed that shikimic acid had the formula $C_7H_{10}O_5$ and that it was capable of being aromatised. The fact that it differed only by the elements of water from the already known[10] quinic acid (2) and that the products of aromatisation were the same in each case suggested that the two acids might well be closely related.

In a second paper[11] Eykman considered six possible structures for the compound. The chemical evidence which he had showed that the compound was a cyclohexene-carboxylic acid with three hydroxyl groups, one of which was para to the carboxyl group. On the basis of conductivity measurements he was able to place the double bond in the position α to the carboxyl group and so reduce the number of possible structures to three, one of which was in fact the true structure.

Although a considerable amount of work was done on shikimic acid and the related quinic acid in the following years its structure and configuration were not elucidated until the work of Fischer and Dangschat in the 1930's. In the first paper of a series they described[12] the oxidation of methyl dihydroshikimate (3) to the dialdehyde (4) by means of periodic acid. This was further oxidised to the diacid (5) with bromine water and saponification then yielded carballylic acid (6). This proved that the three hydroxyl groups must be in the 3, 4 and 5 positions.

Fischer and Dangschat, in a second paper[13], repeated the above series of reactions on methyl shikimate (7) itself. The product in this case was trans-aconitic acid (8) and the position of the double bond was thus shown to be α to the carboxyl group.

Further work[14] by Fischer and Dangschat showed that distillation of dihydroshikimic acid (9) at 220° under reduced pressure gave a lactone which was unaffected by lead tetra-acetate. This lactone must therefore no longer contain hydroxyl groups on adjacent carbon atoms and have the structure (10). Since acetonides of shikimic acid and its derivatives could be prepared it was demonstrable that at least one of the two remaining hydroxyl groups must be cis to the one on C4.

Conversion[15] of the acetyl acetonide methyl ester of shikimic acid (11) to glucodesonic acid (16) proved the stereochemistry and the position of the double bond beyond all doubt. The ester (11) was hydroxylated with potassium permanganate to give the substituted pentol (12) which on saponification yielded the free acid (13). Periodate cleavage of the acid (13) produced the open-chain acid (14) which on mild oxidation gave the hemi-acetal (15). Catalytic hydrogenation of (15) gave glucodesonic acid (16), identical with the naturally-occuring material.

Recent work by Hall[16] on the n.m.r. of shikimic acid has shown that it exists in the half-chair form (17) rather than the boat form (18). Corse et al.[17] have studied the n.m.r. of the related quinic acid and a number of its derivatives and have found that the preferred conformation is a chair with the carboxyl group in the equatorial position (19). In a second paper Corse[18] reported n.m.r. and o.r.d. measurements on quinic acid and a number of its derivatives. The axial conformer (20) was found only in the esters of quinic acid (2) and chlorogenic acid (21) where all the hydroxyl groups had been trimethyl-silylated.

The syntheses of shikimic acid may be divided into two groups. Firstly the total syntheses, which have so far all been by a Diels-Alder reaction, and secondly there are the conversions of quinic acid into shikimic acid.

The first total synthesis was that of McCrindle et al.[2]. The Diels-Alder adduct (24) was obtained by reacting trans,trans-1:4-diacetoxybutadiene (22) acrylic acid (23) at 85°. Osmylation of (24) gave the cis-diol (25) which was first methylated with diazomethane to give the ester (26) and then converted to the acetonide (27). Base-promoted elimination of acetic acid was accomplished by heating with magnesium oxide. The substituted racemic shikimic acid (28) was hydrolysed to give (±)-shikimic acid (1). This was resolved as the quinine methohydroxy-salt of

the triacetate to give D (-) shikimic acid identical with the natural material.

The above synthesis has since been repeated by Chabannes et al.[19] who used 2,3 -^{14}C methyl acrylate as starting material and obtained 1,2 -^{14}C (±) shikimic acid. Chabannes does not report the resolution of the acid but gives the overall yield as 11 %.

Smissman et al.[20] have reported a synthesis similar to that above. Resolution was carried out by them using α-phenylethylamine.

A somewhat different sequence of reactions was used by Grewe and Hinrichs[21] in their synthesis of shikimic acid. The Diels-Alder adduct (29) of acetylene-carboxylic acid and butadiene was methylated to give the ester (30). Epoxidation of the isolated double bond afforded the epoxide (31) which was then hydrolysed to the trans-diol (32). Acetylation and allylic bromination gave the trans,trans bromo-derivative shown (33). Treatment of this with silver acetate produced the hydroxy-compound (34) with inversion of configuration. Hydrolysis of the acetyl groups gave (±) methyl shikimate (7) in 20 % yield from (29).

This synthesis has been modified by Grewe and Kersten[22,23] to give much improved yields. The adduct (29) was treated with silver acetate and iodine in aqueous acetic acid to give a partially acetylated cis-diol (35) which was reacetylated to give (36). Treatment of (36) with N-bromo-succinimide, then with potassium

acetate in refluxing acetic acid, and finally with refluxing methanolic hydrochloric acid yielded (37). This was acetylated to give the triacetate (38) with the wrong configuration. When this was hydrolysed in liquid hydrogen flouride for 24 hours and re-esterified with methanolic hydrogen chloride (±)-methyl shikimate (7) was obtained.

Yet another approach was that of Doshi[24]. Reacting 2-acetoxy-furan with maleic anhydride gave the adduct (39) and osmylation of this yielded the cis-diol (40). Stirring in water for three days converted (40) to (41) and this on borohydride reduction and treatment with acetic anhydride gave the lactone (42). Cleavage of the lactone with acidic methanol, followed by acetylation yielded the tetra-acetyl methyl ester (43) which on pyrolysis gave methyl 3,4,5-triacetyl-shikimate (44). Alkaline hydrolysis of this last (44) gave (±)-shikimic acid (1). A somewhat similar scheme was outlined by McCrindle et al.[2] but they were unable to find conditions for the cleavage of the acetonide of the diol (40) which avoided aromatisation.

Quinic acid (2) has been converted to shikimic acid (1) by Fischer and Dangschat[25,26]. The amide of 3-acetyl-4,5-methylene quinic acid (45) was converted to the unsaturated nitrile (46) by treatment with p-toluenesulphonyl chloride in pyridine. Hydrolysis of the nitrile with sodium hydroxide gave 4,5-methylene shikimic

acid (47) identical with that prepared from natural shikimic acid.

Grewe and Vangermain[27] described a method of converting quinic acid to shikimic acid which depended upon a Hunsdieker reaction carried out on the silver salt of tetra-acetyl quinic acid (48). The product of this reaction was the triacetyl ketone (49) which then underwent a cyanohydrin reaction to give (50). The cyanohydrin (50) was dehydrated to give triacetyl-shikimic acid nitrile identical with that synthesised from the natural material (51).

In an earlier paper Grewe et al.[28] treated tetra-acetyl-quinic acid chloride (52) with sodium trimethoxy borohydride to give the tetra-acetyl alcohol (53). This alcohol was dehydrated to give (54) which was then converted to the primary trityl ether (55). Removal of the trityl group gave triacetyl-shikimic alcohol (56) which on chromic acid oxidation furnished (-)-triacetyl-shikimic acid (57).

The reverse transformation has been accomplished by Grewe and Lorentzen[29]. Chemical work carried out on dibromo-shikimic acid showed it to have the configuration shown (58). Careful hydrolysis with silver acetate replaced one bromine atom to give (59). This was readily lactonised to give (60) which on acetylation gave (61). Catalytic reduction of the triacetyl bromo-compound gave bromine-free triacetyl-quinide (62) identical with the authentic material.

Since these transformations have been carried out the synthesis of quinic acid by Smissman and Oxman[30] may also be regarded as a as a synthesis of shikimic acid, and the syntheses given above as syntheses of quinic acid.

References.

(1) J.F.Eykman, Rec. trav. chim., 4, 32, (1885).

(2) R.McCrindle, K.H.Overton and R.A.Raphael, J. Chem. Soc., 1560, (1960).

(3) B.A.Bohm, Chem. Revs., 65, 435, (1965).

(4) D.B.Sprinson, Advan. Carbohydrate Chem., 15, 235, (1960).

(5) S.Mitsuhasi and B.D.Davis, Biochim. Biophys. Acta, 15, 54, (1954).

(6) D.Rudman and A.Meister, J. Biol. Chem., 200, 591, (1953).

(7) E.W.Underhill, J.E.Watkin and A.C.Neish, Can. J. Biochem. and Physiol., 35, 219, (1957).

(8) J.E.Watkin, E.W.Underhill and A.C.Neish, Can. J. Biochem. and Physiol., 35, 229, (1957).

(9) S.N.Acerbo, W.J.Schubert and F.F.Nord, J. Amer. Chem. Soc., 80, 1990, (1958).

(10) M.S.Baup, Ann., 1, 6, (1833).

(11) J.F.Eykman, Ber., 24, 1278, (1891).

(12) H.O.L.Fischer and Gerda Dangschat, Helv. Chim. Acta., 17, 1200, (1934).

(13) H.O.L.Fischer and Gerda Dangschat, Helv. Chim. Acta, 18, 1204, (1935).

(14) H.O.L.Fischer and Gerda Dangschat, Helv. Chim. Acta, 18, 1206, (1935).

(15) H.O.L.Fischer and Gerda Dangschat, Helv. Chim. Acta, 20, 705, (1937).

(16) L.D.Hall, J. Org. Chem., 29, 297, (1964).

(17) J.Corse, R.E.Lundin, E.Sondheimer and A.C.Waiss Jr., Phytochemistry, 5, 767, (1966).

(18) W.Gaffield, A.C.Waiss Jr. and J.Corse, J. Chem. Soc., 1885, (1966).

(19) B.Chabannes, L.Pichat, M.Herbert and H.Pacheo, J. Lab. Comp., 1, 102, (1966).

(20) E.E.Smissman, J.T.Suh, M.Oxman and R.Daniels, J. Amer. Chem. Soc., 84, 1040, (1962).

(21) R.Grewe and I.Hinrichs, Ber., 97, 443, (1964).

(22) R.Grewe and S.Kersten, Angew. Chem. Internat. Edn., 4, 871, (1965).

(23) R.Grewe and S.Kersten, Ber., 100, 2546, (1967).

(24) M.M.Doshi, Dissert. Abs., 24, 3998, (1964).

(25) Gerda Dangschat and H.O.L.Fischer, Biochim. and Biophys. Acta, 4, 199, (1950).

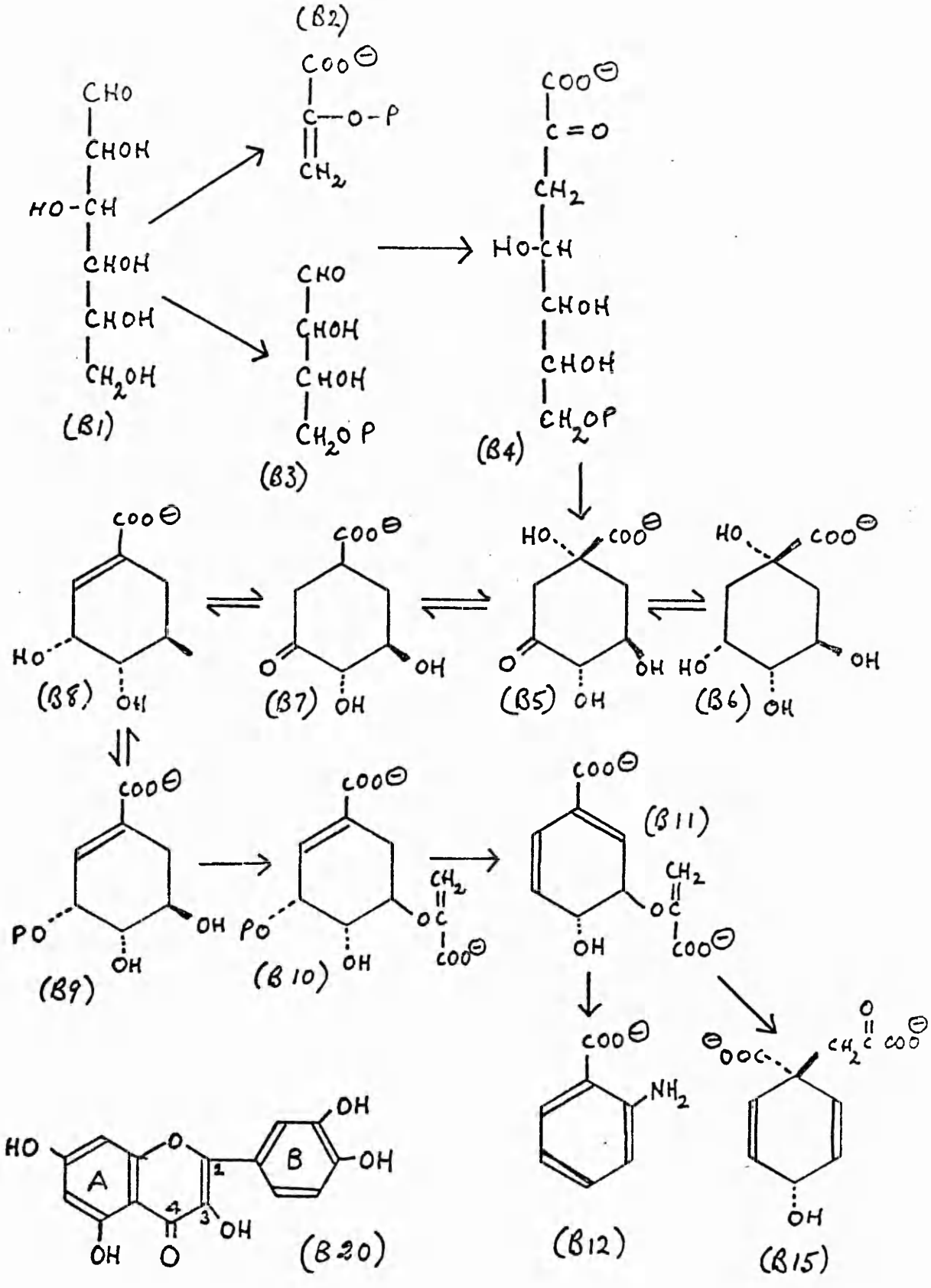
(26) H.O.L.Fischer and Gerda Dangschat, Naturwiss, 26, 562, (1938).

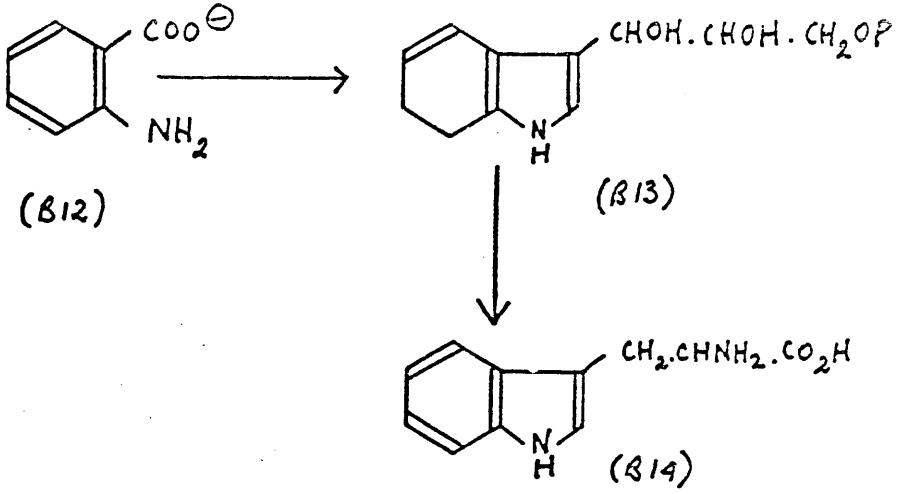
(27) R.Grewe and E.Vangermain, Ber., 98, 104, (1965).

(28) R.Grewe and H.Haendler, Ann., 658, 113, (1962).

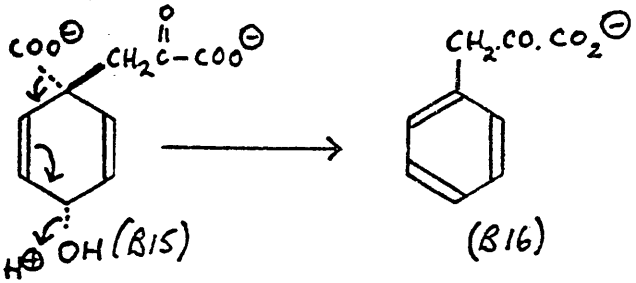
(29) R.Grewe and W.Lorentzen, Ber., 86, 928, (1953).

(30) E.E.Smissman and M.A.Oxman, J. Amer. Chem. Soc., 85, 2184, (1963).

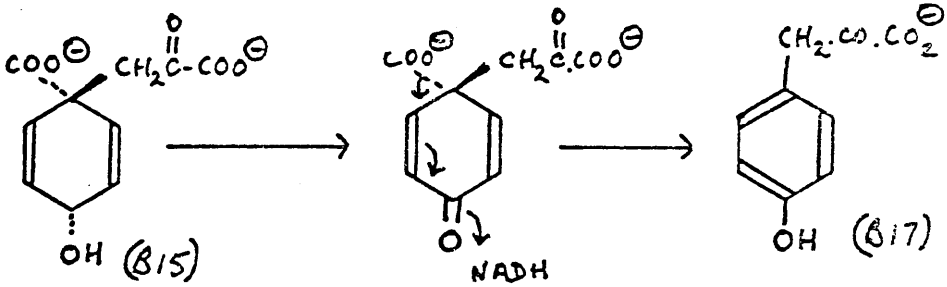

(B2)
(B1)
(B3)
(B4)
(B8)
(B7)
(B5)
(B6)
(B9)
(B10)
(B11)
(B20)
(B12)
(B15)
A
B



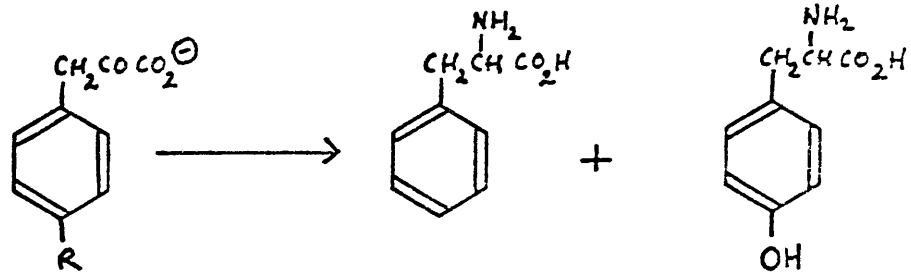
(B12) (B13) (B14)



(B15) (B16)

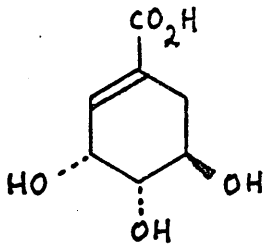


(B15) (B17)

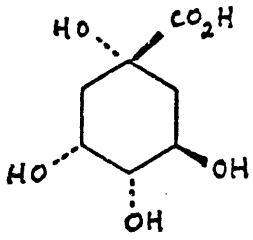


(B16) R = H
(B17) R = OH

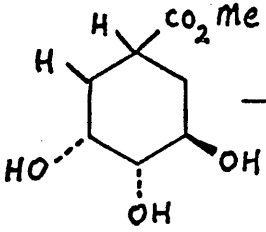
(B18) (B19)



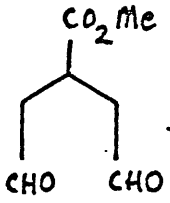
(1)



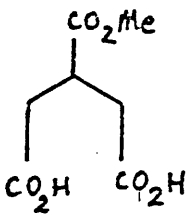
(2)



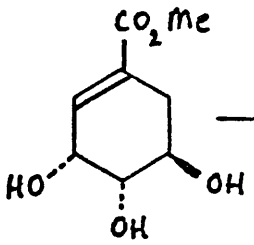
(3)



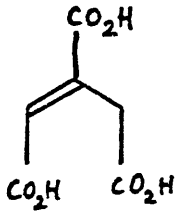
(4)



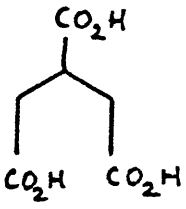
(5)



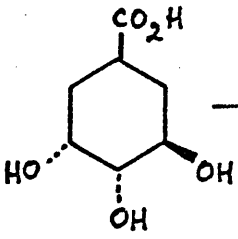
(7)



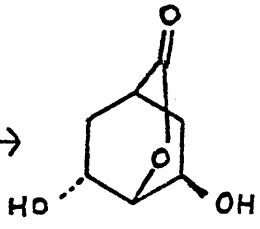
(8)



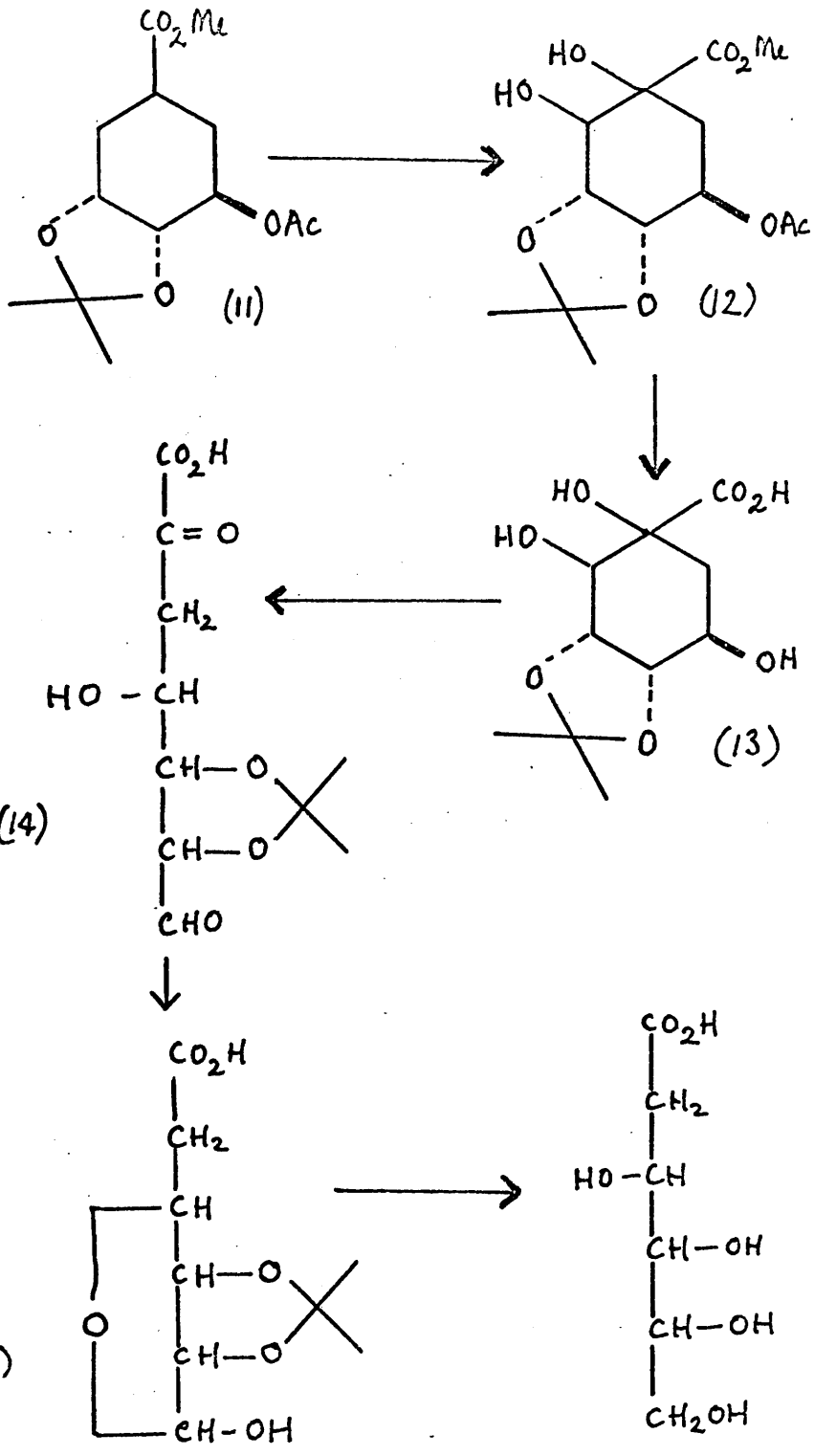
(6)

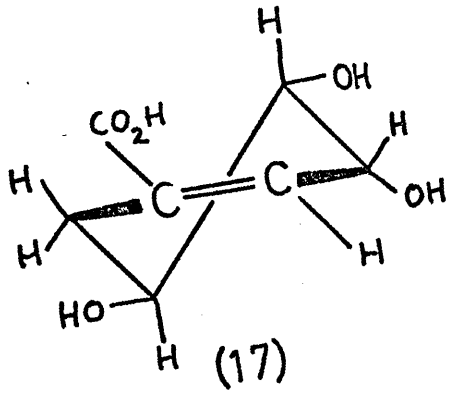


(9)

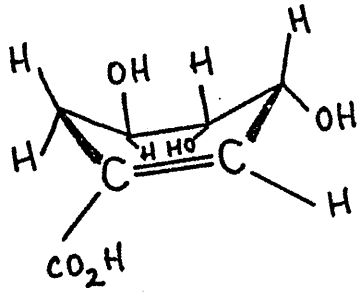


(10)

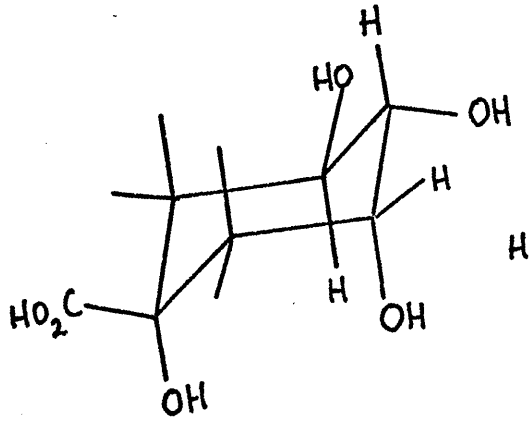

CO2Me
OAc
O
O
(11)
HO
HO
CO2Me
OAc
O
O
(12)
HO
HO
CO2H
OH
O
O
(13)
CO2H
C=O
CH2
HO-CH
CH-O
CH-O
CHO
(14)
CO2H
CH2
CH
CH-O
CH-O
O
CH-OH
(15)
CO2H
CH2
HO-CH
CH-OH
CH-OH
CH2OH
(16)


H
OH
CO2H
H
H
C
C
OH
H
H
HO
H

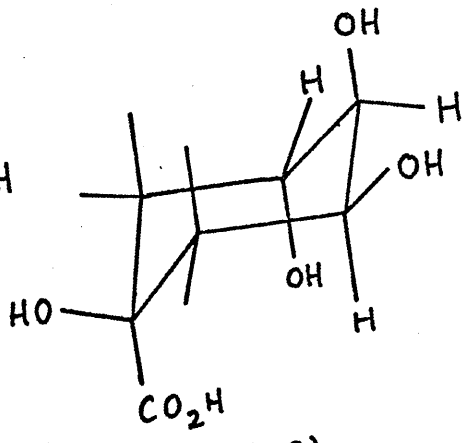
(17)


H
H
OH
H
H
OH
H HO
C
C
H
CO2H

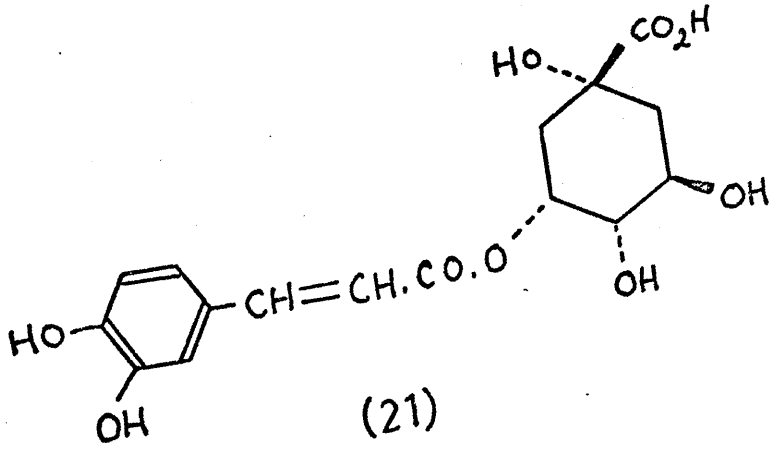
(18)


H
HO
OH
H
H
HO2C
OH
OH

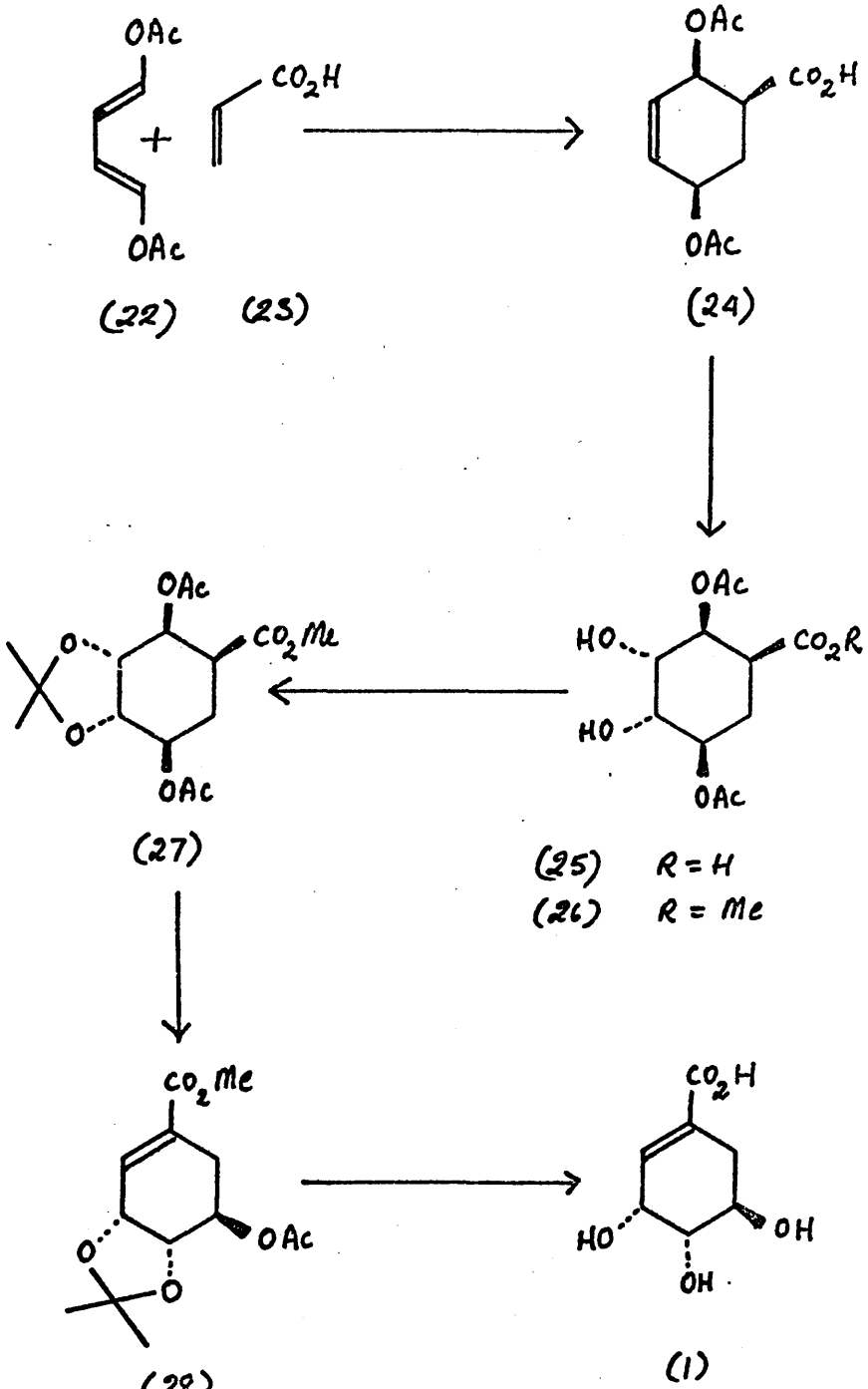
(19)

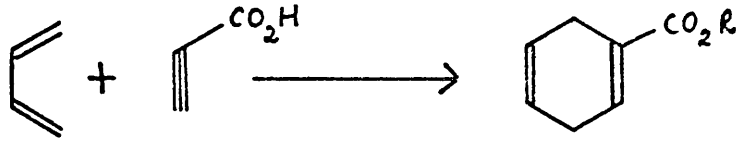

OH
H
H
OH
OH
HO
H
CO2H

(20)

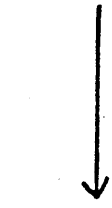

CO2H
HO
OH
CH=CH.CO.O
OH
HO
OH

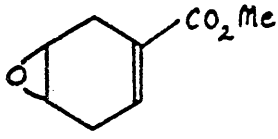
(21)


OAc
OAc
CO_2H
OAc
CO_2H
OAc
(22)
(23)
(24)
OAc
HO
HO
CO_2R
OAc
(25) R = H
(26) R = Me
OAc
O
O
CO_2Me
OAc
(27)
CO_2Me
O
O
OAc
(28)
CO_2H
HO
OH
OH
(1)

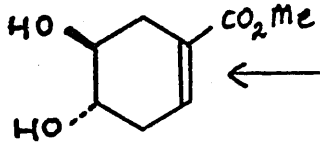


(29) R = H
(30) R = Me

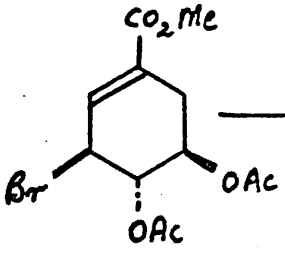




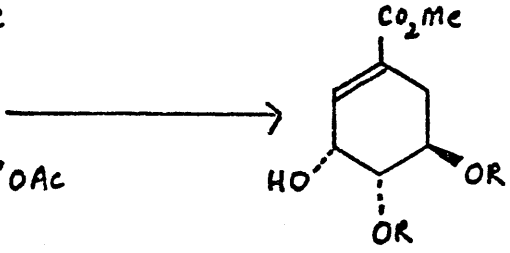
(31)



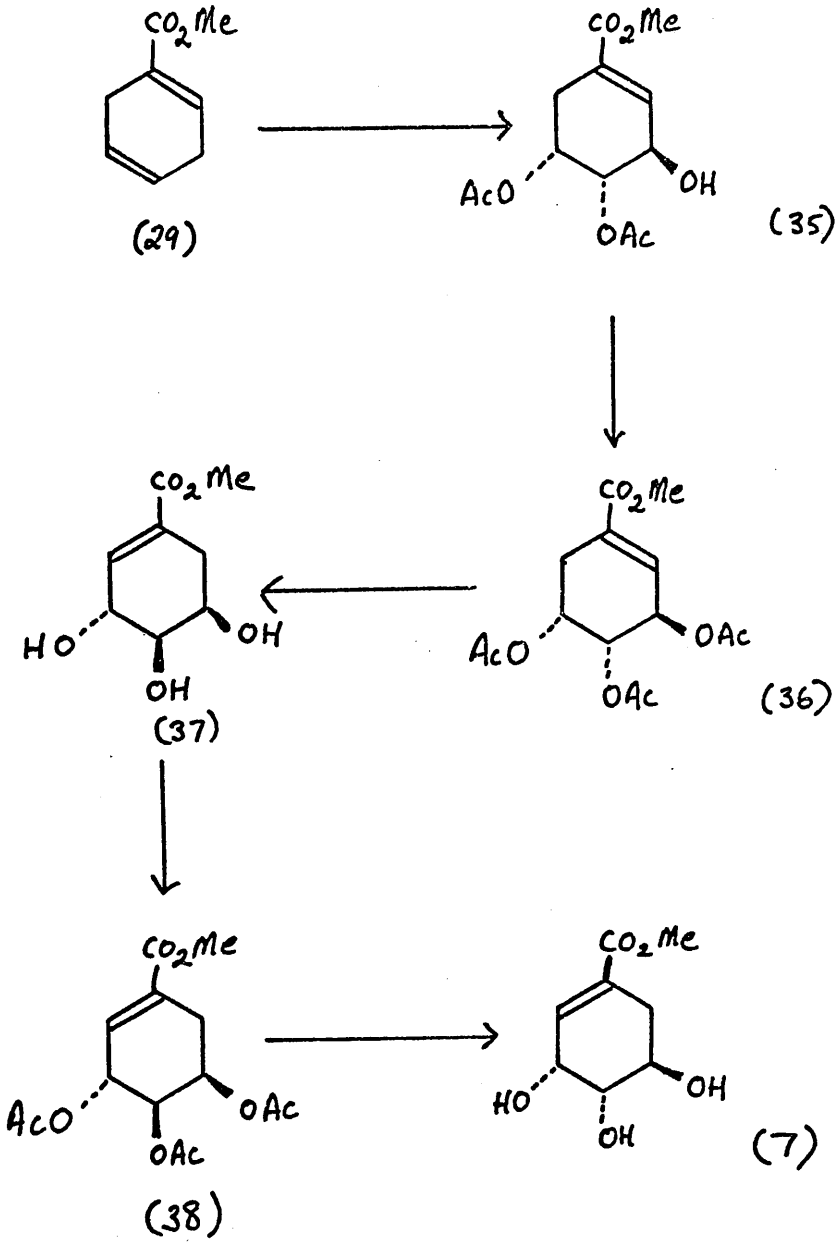
(32)



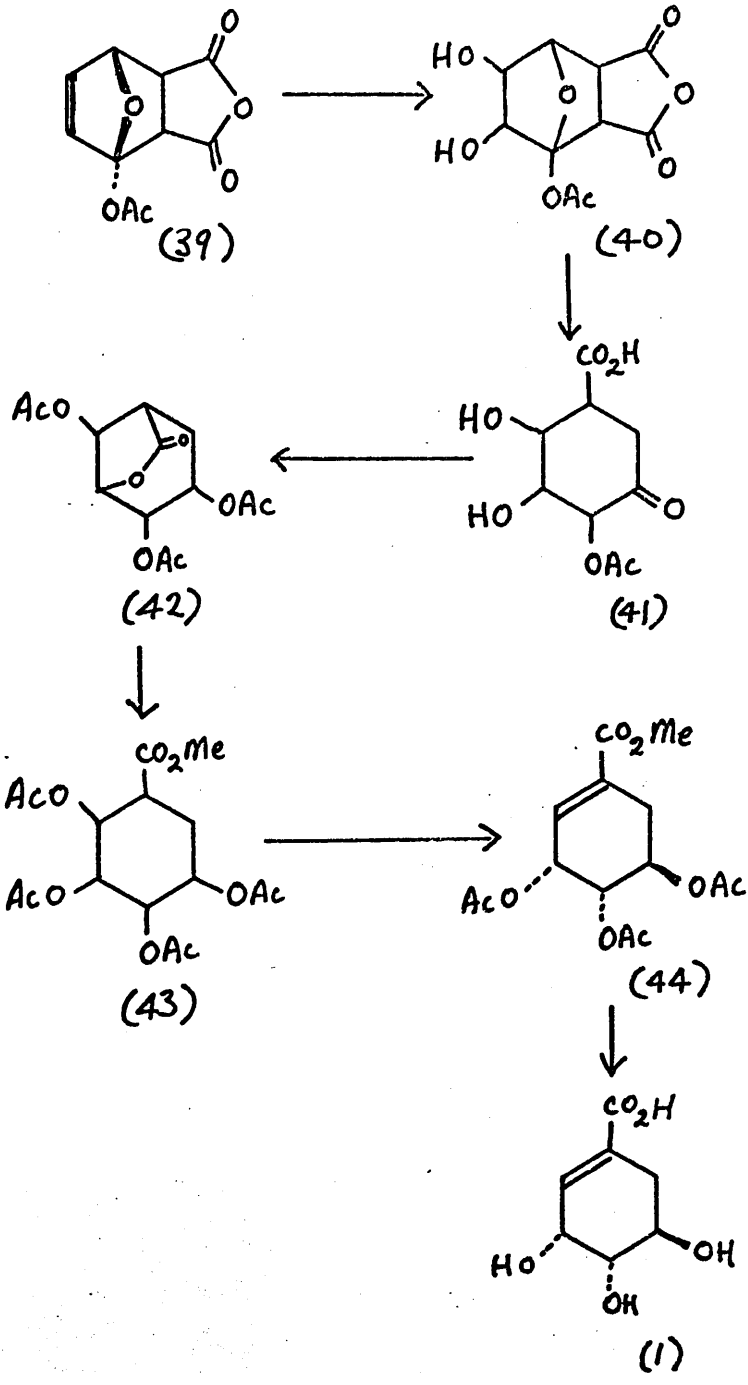
(33)

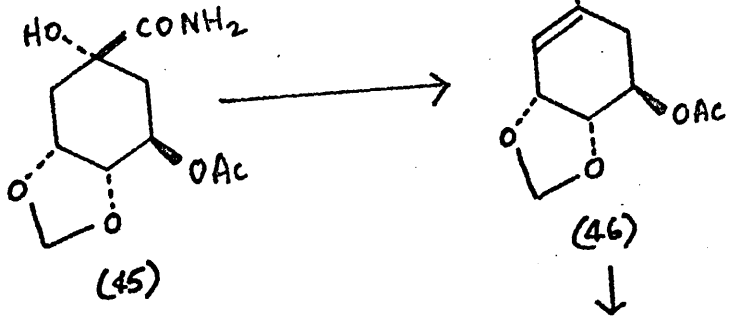


(34) R = Ac
(7) R = H



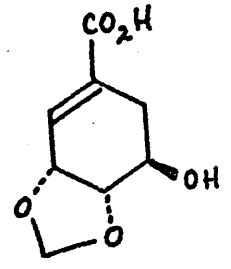
(29) (35) (36) (37) (38) (7)


OAc
(39)
HO
HO
OAc
(40)
CO_2H
HO
HO
OAc
(41)
AcO
OAc
OAc
(42)
CO_2Me
AcO
AcO
OAc
OAc
(43)
CO_2Me
AcO
OAc
OAc
(44)
CO_2H
HO
OH
OH
(1)

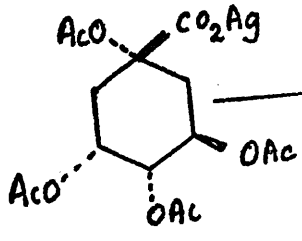


(45)

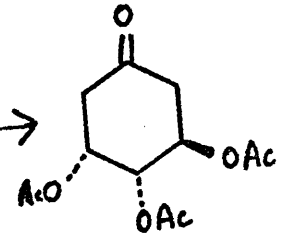
(46)



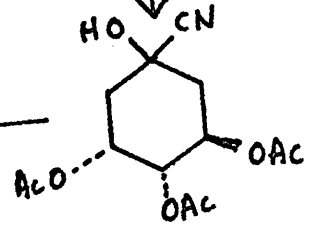
(47)



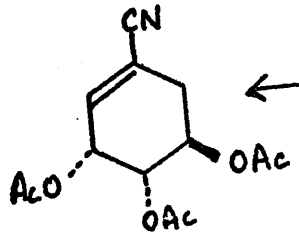
(48)



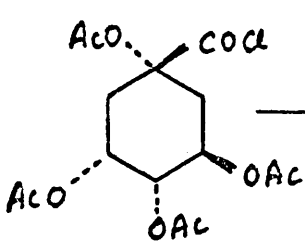
(49)



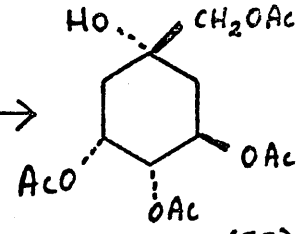
(50)



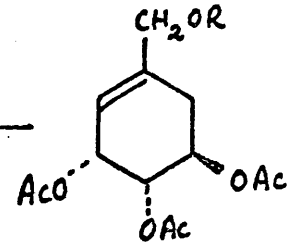
(51)



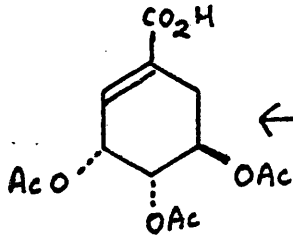
(52)



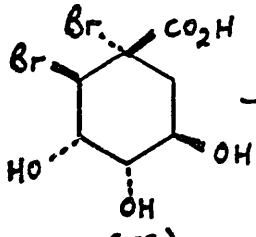
(53)



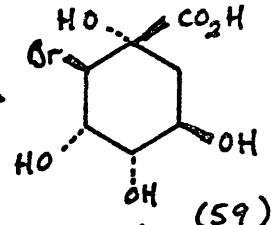
(54) R = Ac
(55) R = Tr
(56) R = H



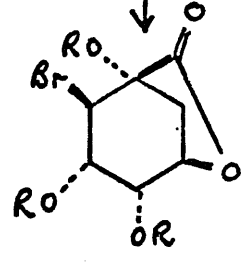
(57)



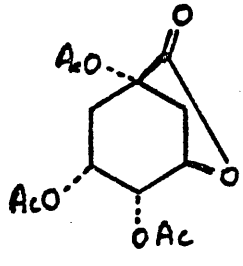
(58)



(59)



(60) R = H
(61) R = Ac



(62)

Discussion.

The purpose of the experimental work was to synthesise 7-^{14}C-shikimic acid (1). The route chosen was based on the work of Grewe and Vangermain[1] and took advantage of the stereochemical similarity of quinic acid (2) and shikimic acid.

Quinic acid could be converted to a ketone (3) and this made to undergo a cyanohydrin reaction to give a compound of the type (4). This would then dehydrate to give a substituted shikimic acid nitrile (5) which on suitable hydrolysis would give (-)-shikimic acid.

Acetylation of quinic acid with pyridine and acetic anhydride gave tetra-acetyl quinic acid[2](6). The silver salt (7) was formed by stirring the tetra-acetate in acetone[1] with freshly prepared silver oxide.

A Hunsdieker reaction was then attempted using bromine, the silver salt (7) and silver acetate in ethyl bromide. The conditions given by Grewe and Vangermain[1] were rigorously observed but the product isolated by them, 3:4:5-triacetoxy-cyclohexanone (8) was not obtained. The product obtained appeared to be one spot on t.l.c. but it showed only acetate absorption in the carbonyl region of the i.r.. On analysis it contained about 10 %. of bromine and catalytic hydrogenation did not affect it. Many runs were made using materials which had been dried in vacuo

for weeks and freshly redistilled dried bromine. Alteration of the relative quantities[3] of the silver salt and silver acetate did not change the result significantly.

The silver salt (7) was refluxed in methyl iodide and tetra-acetyl quinic acid methyl ester (9) resulted. This compound had the $[\alpha]_D$ and m.p. described for it by Zemplen et al.[4], who obtained it by a different route. There thus seemed little doubt that the silver salt (7) was genuine.

3:4-Isopropylidene-3:4:5-trihydroxy-cyclohexanone (10) was now considered as a possible alternative on which to carry out the re-carboxylation. This ketone was readily available by the route of Fischer and Dangschat[5].

Acetone-quinide (11) was prepared[6] by shaking quinic acid (2) in acetone containing 1 % of hydrogen chloride for about three days. When the lactone (11) was heated with hydrazine hydrate 4:5-iso-propylidene quinic acid hydrazide (12) was formed.[5] Treatment of (12) with nitrous acid gave the corresponding azide (13) which was not purified but immediately pyrolysed[5] in xylene to give the ketone (10a) m.p. 72°. Acetylation[5] of this ketone furnished 3-acetyl-4:5-isopropylidene-3:4:5-trihydroxy-cyclohexanone (14).

An alternative method of preparing the ketone (10) was then carried out as described by Zemplen et al.[7]. 1-Acetyl-4:5-iso-propylidene-quinide (15) obtained by the acetylation[8] of acetone-

quinide (11), was reduced[9] with lithium aluminium hydride to give acetone china alcohol (16). Treatment of this 1:2-diol with lead tetra-acetate yielded the ketone (10b) m.p. 79° . Grewe et al.[10] described substantially the same reaction and product m.p. 79°.

Zemplen[7] described the two modifications of the ketone as being the chair (10c) and boat (10d) conformations of the hemi-acetal (10e). In support of his claim he showed that the two forms had a different rate of mutarotation,although the initial and final values were the same,and that (10a) and (10b) had different crystal forms. Examination of models of the conformers (10c and 10d) suggests however that the conformational problem is analogous to that in cyclohexane. There is considerable strain in the four-membered hemi-acetal ring, but this would be expected to have the same effect in each conformer. Further, no particularly bad interaction has to be overcome in going from one conformer to the other. Thus no large energy barrier is to be expected between (10c) and (10d) and they would consequently not exist as separable entities.

Grewe[10] suggested that the modifications (10a and 10b) were in fact the free ketone (10) and the hemi-acetal (10e).

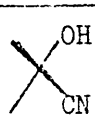
Examination of samples of each showed that they had in fact identical i.r., n.m.r., and $[\alpha]_D$ values. In each case the i.r., whether as a nujol mull or in solution, showed ketone absorption and the n.m.r. could only be explained in terms of the free ketone. When a sample having m.p. 79° was distilled the melting

point decreased with each successive distillation. On the other hand when a sample having m.p. 72° was dissolved up and seeded with a crystal of the modification with m.p. 79° the crystals formed had m.p. 79°. The conclusion reached was thus that the two forms were in fact only different crystalline modifications of the same free ketone (10a = 10b)

Having obtained the ketones (10 and 14) the next stage was to recarboxylate them ; the most obvious method being by a cyanohydrin reaction. The cyanohydrin reaction on the ketone (10) was reported to go in 6 % yield at best by Cornthwaite and Haslam[11] who gave a reference to Zemplen[4] as their source. This reference was however cited wrongly no mention being made in Zemplen's paper of the cyanohydrin.

A number of cyanohydrin reactions were attempted by both direct and exchange methods. In almost every case unchanged ketone was recovered (see Table 1). The action of acetone cyanohydrin on the ketone (10) in the presence of ethanol and triethylamine was the only reaction which showed any promise. When this was carried out two products were isolated. The more polar of these bands showed both nitrile and ketone bands in the i.r. and was assumed to be a cyanide adduct like (17). The less polar compound appeared from its i.r. and u.v. to be an unsaturated carbonyl compound and it was not further investigated.

TABLE 1.

Conditions	Ref.	Product from	
		Ketone (10)	Ketone (14)
Bisulphite, KCN	1	82 % s.m.	85 % s.m.
EtOH, AcOH, KCN	12	95 % s.m.	84 % s.m.
EtOH, H_2O, KOAc, KCN	13	tar	tar
 , 2 hrs., R.T.	14	94 % s.m.	84 % s.m.
 , $2\frac{1}{2}$ hrs., 60°	15	67 % s.m.	79 % s.m.
 , D.M.F., 24 hrs., R.T.	-	83 % s.m.	81 % s.m.
 , Et_3N, 5 hrs., R.T.	16	75 % s.m.	complex mixture
 , EtOH, 2 hrs., R.T.	-	82 % s.m.	80 % s.m.
 , EtOH, Et_3N, 24 hrs. R.T.	16	35 % s.m. 52 % C=O, C≡N 14 % C=C-C=O	complex mixture

The results of the various reactions are shown opposite in tabular form. It should be explained that when any run was finished the first step was to run the product on a thin-layer t.l.c. plate. If this showed only ketone the reaction product was dried and evaporated in vacuo. If the i.r. then obtained was identical with that of the starting material and the R_f was the same this was taken as proof of recovery and the yield so quoted. When a mixture of products was obtained this was run on a preparative scale t.l.c. plate. Often small amounts of very polar material were found which could not be re-extracted from the plate and there always seemed to be some decomposition of the ketones on the plate.

The failure of the above reactions is hard to reconcile with Grewe and Vangermain's report[1] of a successful cyanohydrin reaction on 3:4:5-triacetoxy-cyclohexanone (8). Our results strongly suggest that the equilibrium in this reaction was on the wrong side and that any cyanohydrin (18) formed reverted to the ketone.

Since the ketones (10 and 14) appeared not to be amenable to the cyanohydrin reaction it was decided to attempt to form the ethynols of them (19 and 20, respectively). These might then be oxidised and dehydrated to yield shikimic acid derivatives. The reagent used was the ethylenediamine complex of lithium acetylide.

This was stirred with the ketone (10 or 14) in benzene for two hours at 35° under argon cover as described by Beumel and Harris[17]. The reaction wasworked up by the dropwise addition of water and subsequent extraction with benzene. When no product was found in the benzene layer, the aqueous layer was extracted with other organic solvents without success. T.l.c. of the aqueous layer itself showed only very polar materials to be present.

A recent procedure for the introduction of cyanide via the enamine[18] was then considered. The enamine of the ketone (21) is prepared and the perchlorate salt (22) formed. This is then reacted with potassium cyanide to give (23) which in turn is hydrolysed under suitable conditions to give the cyanohydrin (24).

When the hydroxy-ketone (10) was refluxed with pyrrolidine in benzene and the product distilled[19], the compound obtained had an analysis for $C_{10}H_{13}NO$ and the i.r. and u.v. suggested that it was a phenol (25). The n.m.r. of this compound was anomolous due to rapid decomposition in the solvents.

The structure of the phenol (25) was confirmed by forming the acetate (26) which had i.r., u.v. and n.m.r. spectra consonant with the proposed structure and gave the correct analysis. In addition, the melting points of the two compounds (25 and 26) were in reasonable agreement with those quoted in the literature for the authentic materials[20,21]. Time did not allow for the separate

syntheses of the genuine compounds to compare with the materials which were isolated by us.

The same product (25) was obtained when the acetate ketone (14) was used and when the hydroxy-ketone (10) was stirred for a week with potassium carbonate and pyrrolidine in benzene[22].

At this stage it was decided to look for alternative methods of preparing the cyanohydrins of the series. Fischer and Dangschat described[5] acetic anhydride dehydration of the acetyl acetonide amide (27) and of the tetra-acetyl amide (28) to give the acetyl cyanohydrins (29 and 30) by a simple procedure.

Quinic acid (2) was refluxed for three minutes with acetic anhydride, the solution allowed to cool and pyridine added. This furnished 1-triacetyl-quinide (31) as reported by Zemplen et al.[4]. The triacetyl quinide was then treated with ammonia in methanol to give quinamide (32). This procedure , as claimed by Zemplen, gives a purer product than the older method whereby ethyl quinate was treated with ammonia.[23]

Quinamide (32) was acetylated as described by Fischer and Dangschat[5] using pyridine and acetic anhydride to give tetra-acetyl-quinamide (28). The n.m.r. of the product showed it to be the N-acetyl-3:4:5-tri-O-acetyl-quinamide (28) and not the tetra-O-acetyl-quinamide (33).

4:5-Isopropylidene-quinamide (34) was obtained[24] by

treatment of acetone-quinide (11) with ammonia in ethanol. This was acetylated[5] as above to give 3-acetyl-4:5-isopropylidene-quinamide (27).

Dehydration of the acetonide amide (34) was carried out by refluxing it for two hours in acetic anhydride[5]. The excess reagent was removed under reduced pressure and the product subjected to thick-layer t.l.c.. The two more polar of the three compounds isolated were acetylated amides and were not further investigated. The least polar band was identified by i.r. and t.l.c. as 1-acetyl-4:5-isopropylidene-quinide (15).

Dehydration of acetyl-acetonide-quinamide (27) yielded two products less polar than the starting material. These proved to be 1:3-diacetyl-4:5-isopropylidene-quinamide (35) and the required 1:3-diacetyl-4:5-isopropylidene-quinic acid nitrile (29).

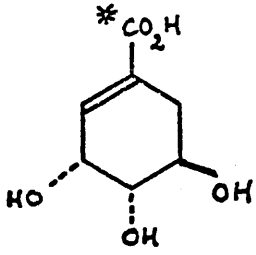
When the same procedure was applied to tetra-acetyl-quinamide (28) three products were obtained. The most polar (36) band was penta-acetyl-quinamide (previously isolated from the same reaction by Grewe et al.[10]) contaminated with a little starting material. The middle band was the required tetra-acetyl nitrile (30). The least polar compound was identified as hydroquinone diacetate (37) by comparison with a genuine sample.

It was now decided to attempt to obtain 3:4:5-triacetoxy-cyclohexanone (8) by an alternative route described by Grewe and

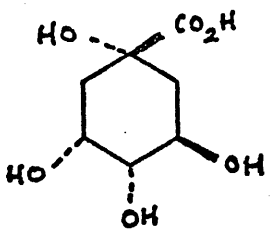
Vangermain.[1] The starting material was acetone china alcohol (16) and it's identity was confirmed by making the ditosyl derivative (38) as described by Grewe and Nolte[9].

Acetone china alcohol (16) was heated in warm water with Amberlite I.R.-120 to remove the acetonide residue and give the crude pentol (39). The pentol was tritylated with trityl chloride in pyridine to give a mixture of the monotrityl ether (40) and the ditrityl ether (41), which were separated by t.l.c.. The monotrityl ether was acetylated with pyridine and acetic anhydride to give the triacetyl derivative (42). This was detritylated with acetic acid to yield the 1:2-diol (43) and this on cleavage with lead tetra-acetate gave 3:4:5-triacetoxy-cyclohexanone (8).

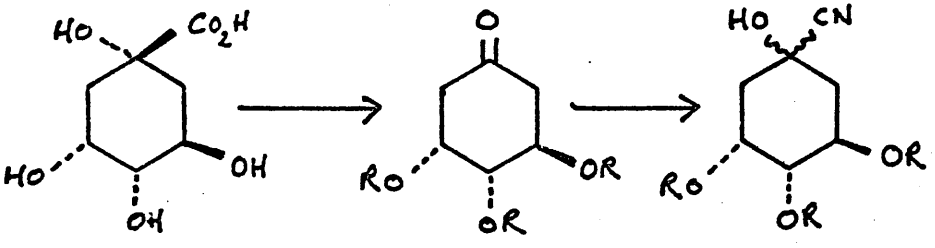
There was unfortunately no time available to attempt the projected cyanohydrin reaction on this ketone.


*CO2H
HO
OH
OH

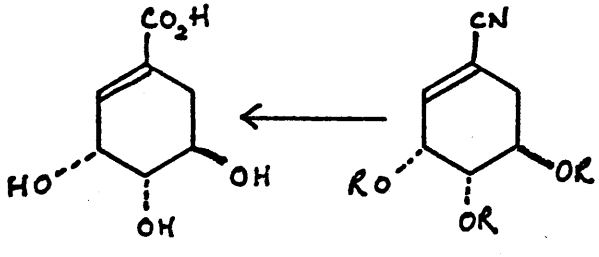
(1)


HO
CO2H
HO
OH
OH

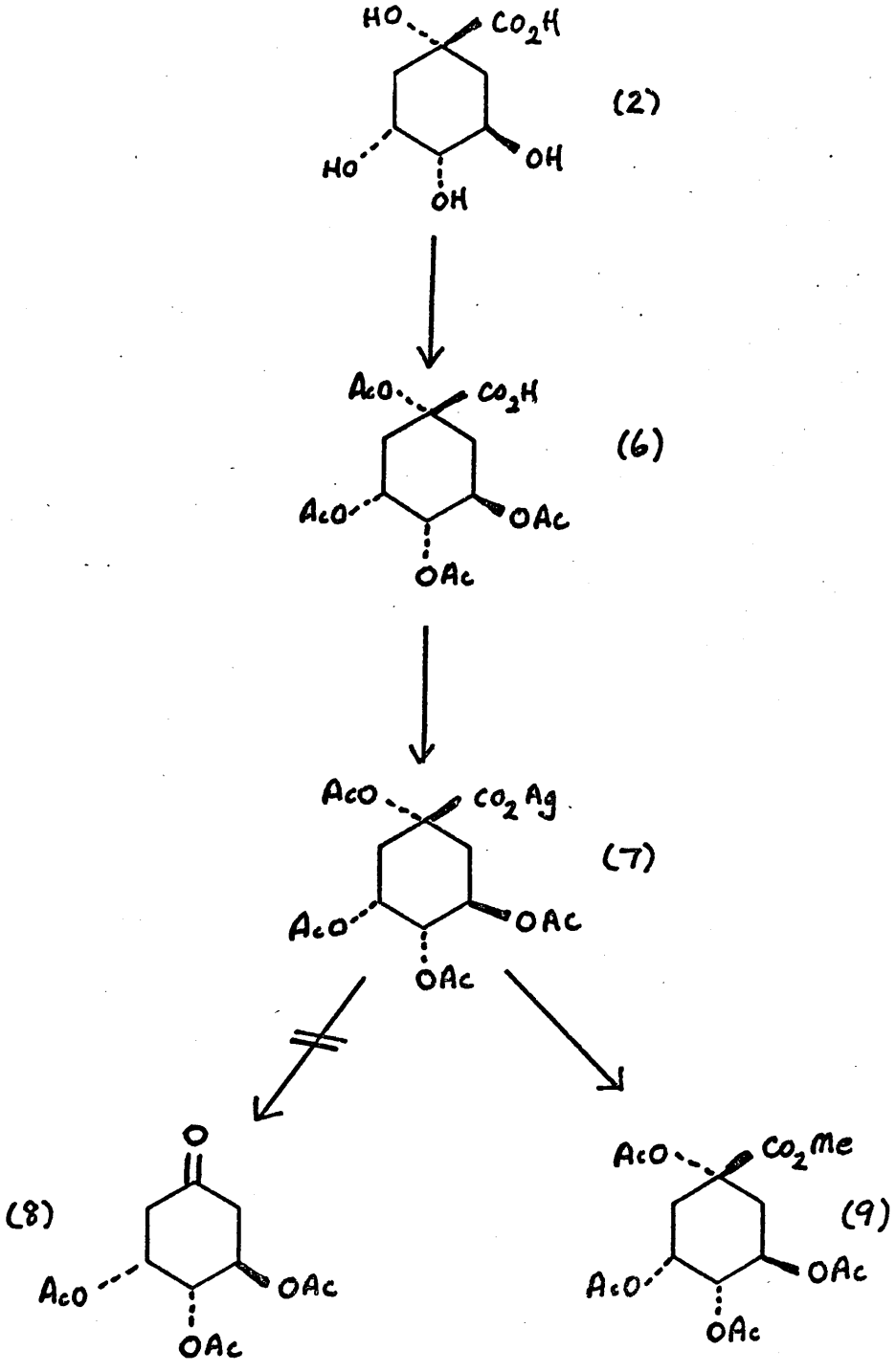
(2)

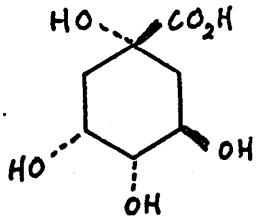

HO
CO2H
HO
OH
OH
O
RO
OR
OR
HO
CN
RO
OR
OR

(2) (3) (4)

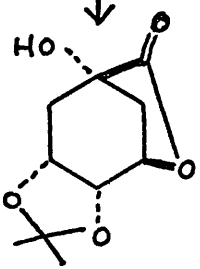

CO2H
HO
OH
OH
CN
RO
OR
OR

(1) (5)

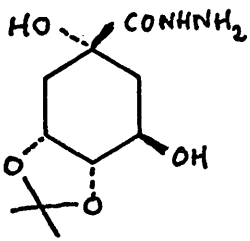

HO
CO2H
HO
OH
OH
(2)
AcO
CO2H
AcO
OAc
OAc
(6)
AcO
CO2Ag
AcO
OAc
OAc
(7)
O
AcO
OAc
OAc
(8)
AcO
CO2Me
AcO
OAc
OAc
(9)



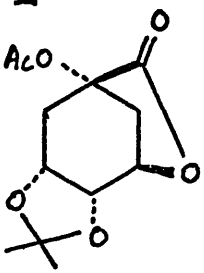
(2)



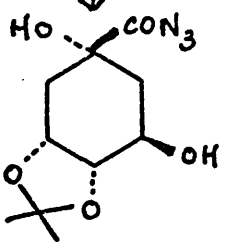
(11)



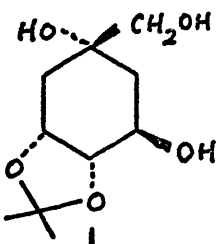
(12)



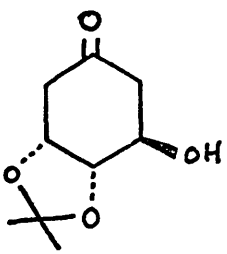
(15)



(13)

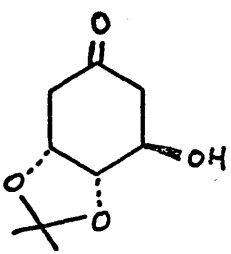


(16)



(10a)

(72°)

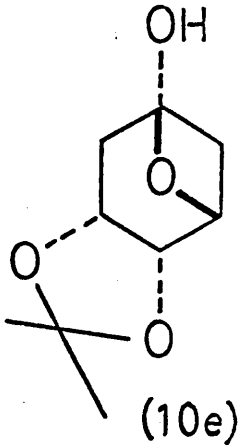


(10b)

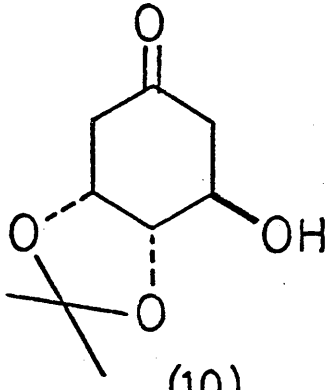
(79°)

(10a) m.p. 72°

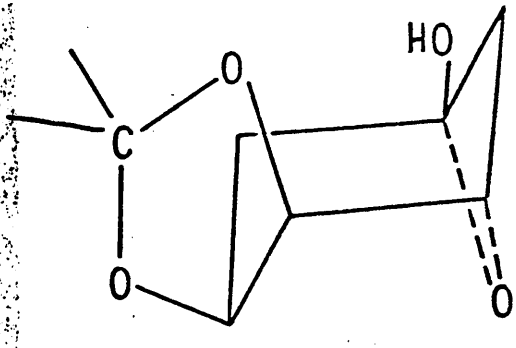
m.p. 79° (10b)



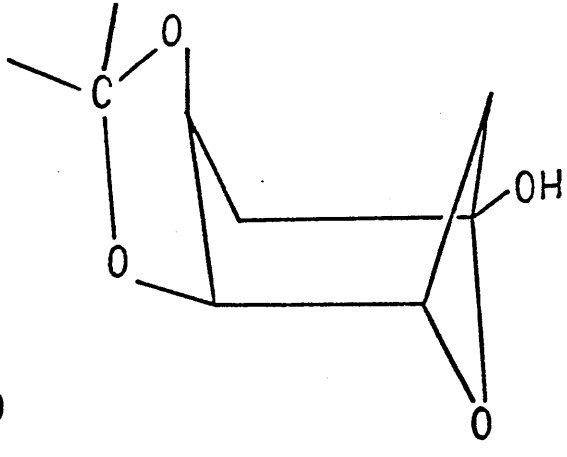
(10e)



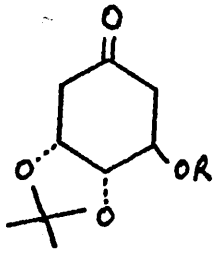
(10)



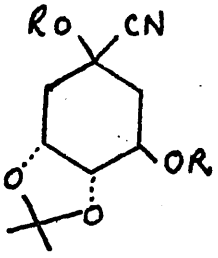
(10c)



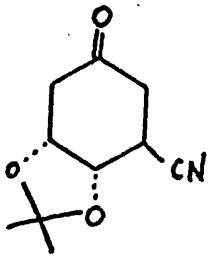
(10d)



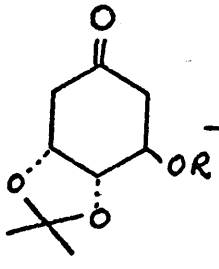
(10) R=H
(14) R=Ac



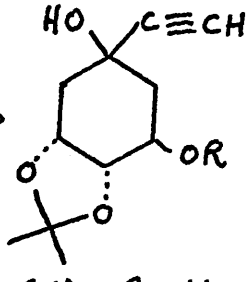
(18) R=H or Ac



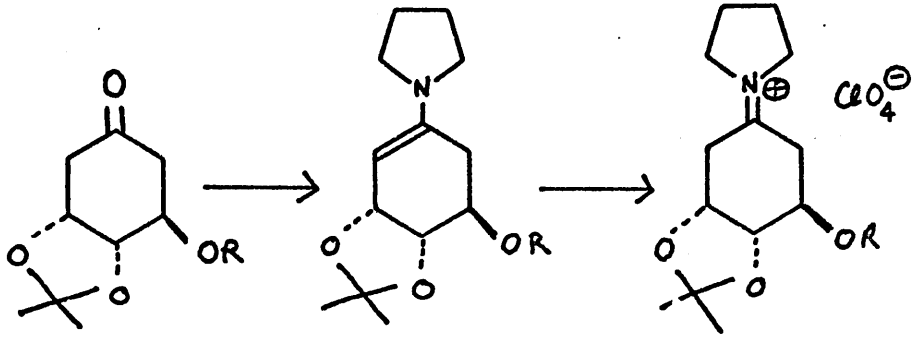
(17)



(10) R=H
(14) R=Ac



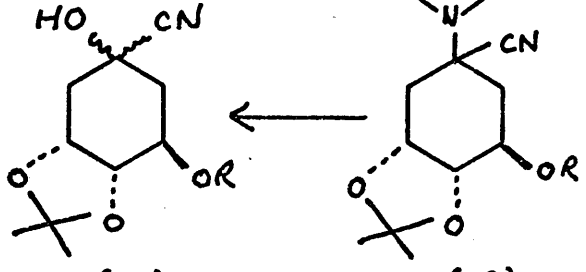
(19) R=H
(20) R=Ac



(10) R=H
(14) R=Ac

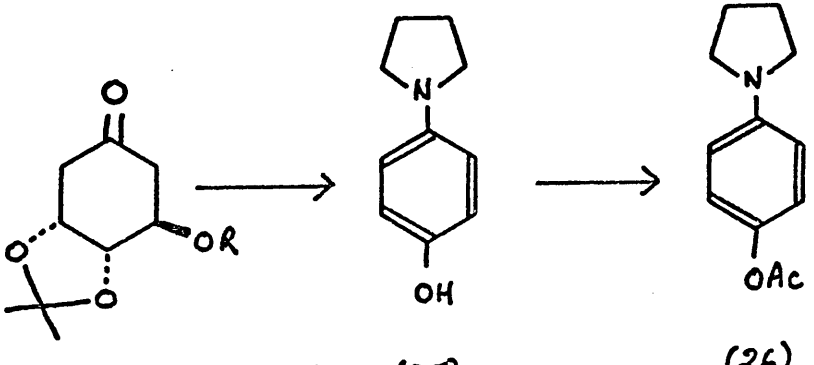
(21)

(22)



(24)

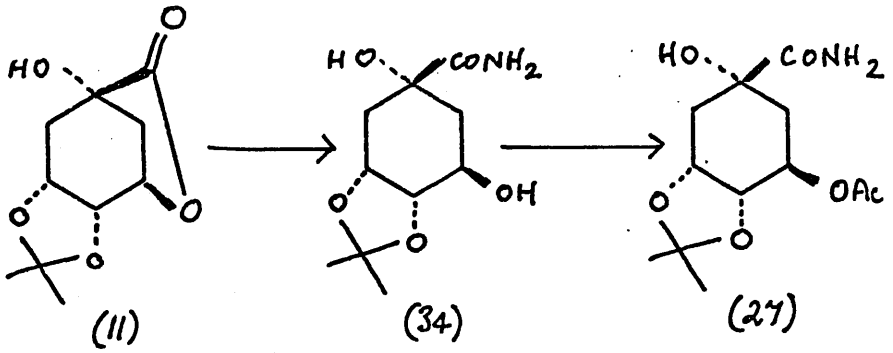
(23)

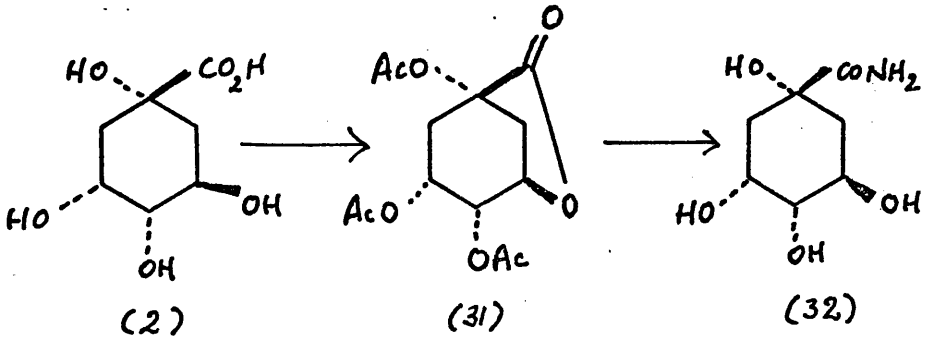


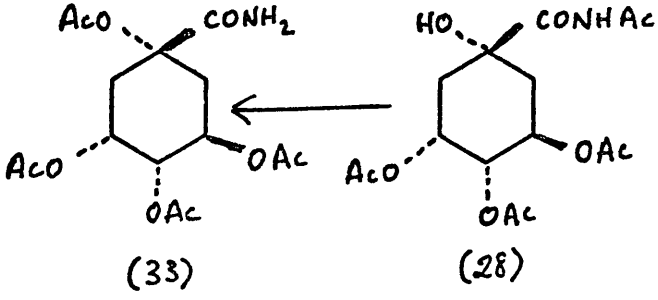
(10) R=H
(14) R=Ac

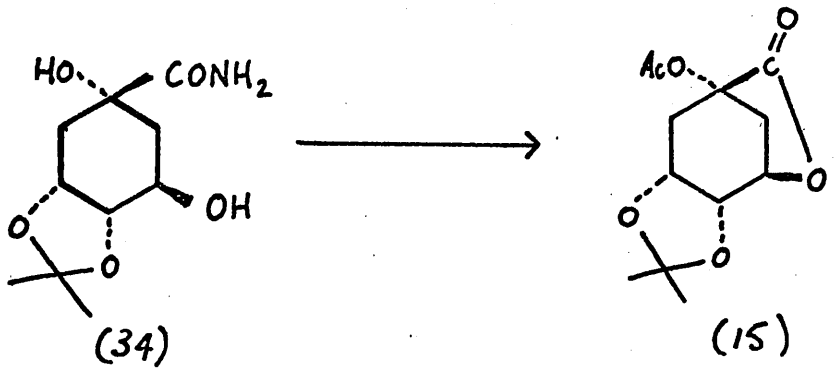
(25)

(26)

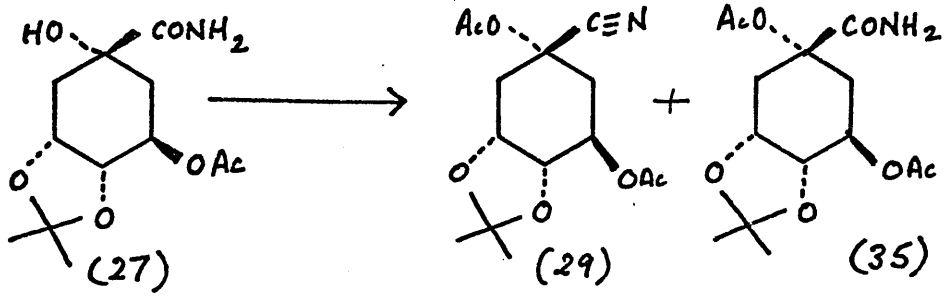

HO
O
O
O
O
(11)
HO
CONH2
OH
O
O
(34)
HO
CONH2
OAc
O
O
(27)


HO
CO2H
HO
OH
OH
(2)
AcO
O
AcO
O
OAc
(31)
HO
CONH2
HO
OH
OH
(32)

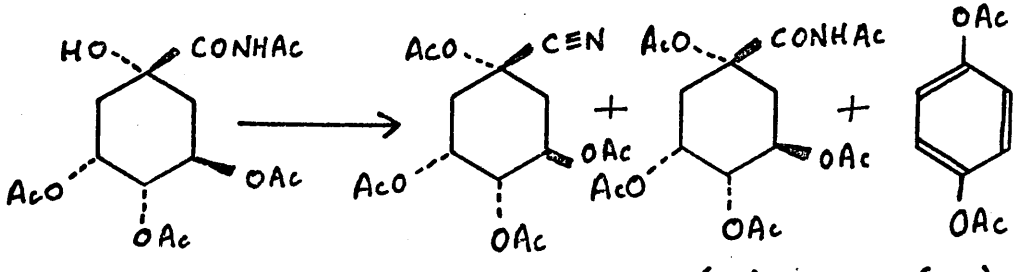

AcO
CONH2
AcO
OAc
OAc
(33)
HO
CONHAc
AcO
OAc
OAc
(28)



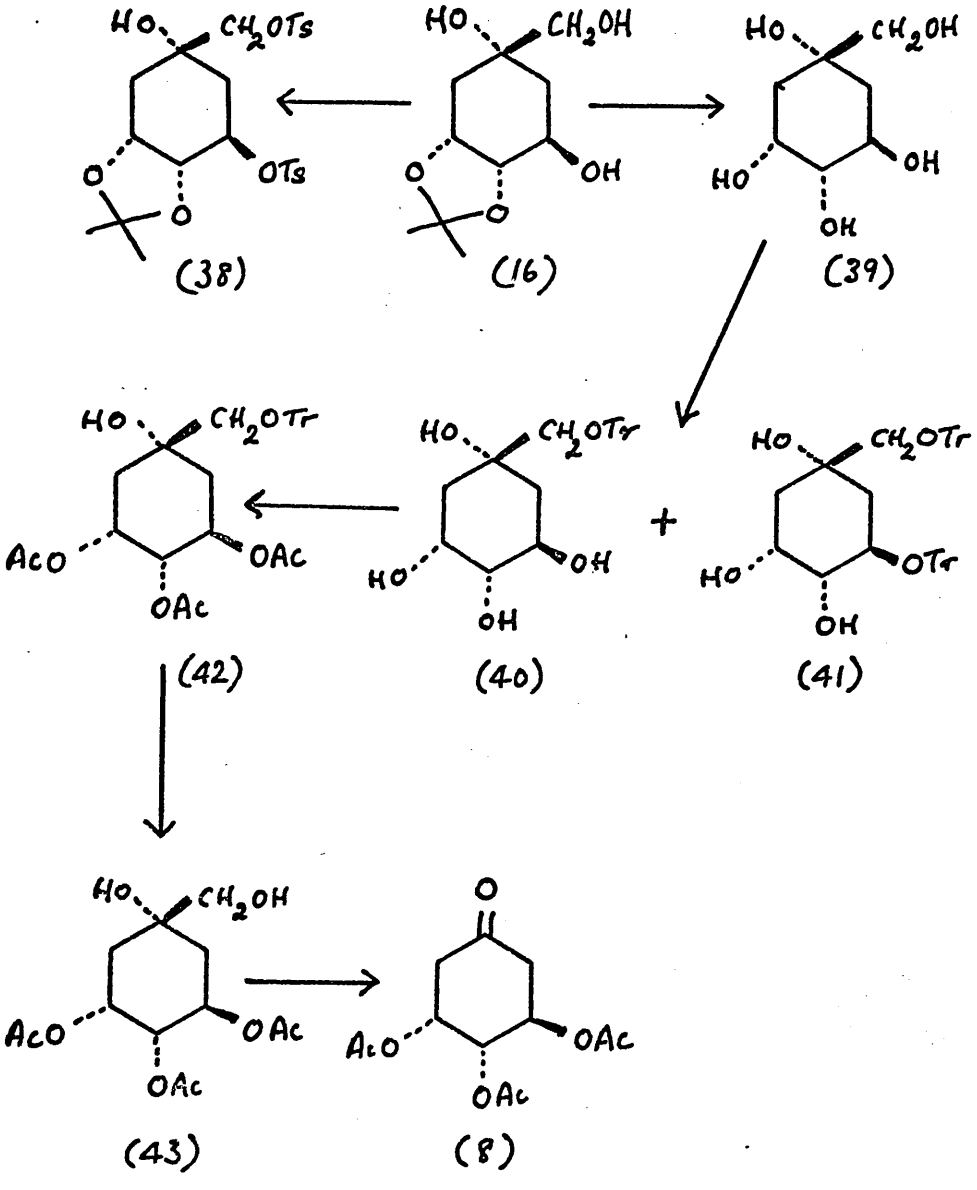
(34) (15)



(27) (29) (35)



(28) (30) (36) (37)


HO
CH2OTs
OTs
O
O
(38)
HO
CH2OH
OH
O
O
(16)
HO
CH2OH
HO
OH
OH
(39)
HO
CH2OTr
AcO
OAc
OAc
(42)
HO
CH2OTr
HO
OH
OH
(40)
+
HO
CH2OTr
HO
OTr
OH
(41)
HO
CH2OH
AcO
OAc
OAc
(43)
O
AcO
OAc
OAc
(8)

Experimental.

Melting points were recorded on a Kofler block and are uncorrected, as are boiling points. T.l.c. refers to thin layer chromatography and the plates used for this were prepared using Merck's "Kieselgel G".

Ultra-violet absorption spectra were measured using an automatic Unicam S.P. 800 instrument. Infra-red spectra run as pressed discs or in solution were recorded linearly in $cm.^{-1}$ as percentage transmission with a Unicam S.P. 100 instrument. Other infra-red spectra were measured on a Unicam S.P. 200 instrument.

Proton magnetic resonance spectra were measured in solution with tetramethylsilane as an internal reference on a Perkin - Elmer 60 Mc/s. spectrometer (values quoted are in τ).

Tetra-acetyl quinic acid[2](6)

Quinic acid (10 g.) was dissolved in pyridine (20 ml.) and acetic anhydride (30 ml.) added to the solution with ice-cooling. After standing overnight at room temperature the solvent was removed by rotary evaporation at about 5 mm.. The residue, a light yellow viscous oil, was taken up in chloroform (30 ml.) and 5N hydrochloric acid (10 ml.) added to ensure acidity. The chloroform layer was separated, washed with saturated brine and then with water. The resulting solution was dried over sodium sulphate and evaporated down under vacuum to give a viscous oil.

This oil was taken up in ethyl acetate (100 ml.) and an equal volume of petrol ether 60-80° added. After shaking vigorously for a few minutes a white oil separated out and this, on scraping with a glass rod began to crystallise. The flask was set aside overnight and the crystals, then removed by filtration, were dried in vacuo for 24 hours. The white micro-crystals (16.1 g., 85%.) had m.p. 138-41° and $[\alpha]_D$ -25.0° in ethanol c = 1.5 (Lit. values[2] 142-3° and -25.4°).

I.R. (CCl_4 soln.) : 1758 $cm.^{-1}$

Tetra-acetyl quinic acid silver salt[1](7).

Tetra-acetyl quinic acid (10 g.) was dissolved in acetone (50 ml.) and an excess of freshly prepared silver oxide added. The resulting suspension was stirred in the dark for 3 hours and the white needles which had formed were then filtered off. These were recrystallised from boiling water, dried at 40° in vacuo for two days, ground up, and then dried at 80° in vacuo for a further week to give a white powder (9.8 g., 75 %.) which did not discolour within an hour on exposure to light and air.

Hunsdieker reaction[1] on the silver salt (7).

Tetra-acetyl quinic acid silver salt (0.5 g.) and silver acetate (2.2 g.) were ground in a mortar until an intimate mixture was obtained and this was dried at 80° in vacuo for 24 hours. The dried mixture was placed in a three-necked flask fitted with a stirrer and ethyl bromide, dried over potassium carbonate, distilled from phosphorus pentoxide onto it. Bromine (2.08 g.), dried over phosphorus pentoxide and freshly distilled, was added slowly under a steady stream of dried nitrogen. Almost at once carbon dioxide was evolved and yellow silver bromide began to precipitate. After a few minutes of vigorous evolution of gas, reaction ceased. The silver bromide was filtered off and the resulting pale yellow-

green solution washed with cold sodium carbonate solution (10ml.) and ice-water (10 ml.). After drying over sodium sulphate the ethyl bromide was removed under vacuum and a colourless oil (0.3 g.) obtained. This appeared to be one spot on t.l.c. and could be distilled at 70°/0.02 mm. without changing the i.r. or R_f values. The i.r. showed only acetate absorption in the carbonyl region. Analysis showed the product to contain ca. 10 %. of bromine. Catalytic hydrogenation with palladium charcoal failed to produce any change. The product was not 3:4:5-triacetyl-cyclohexanone (8) as isolated by Grewe.[1] Alteration of the relative molar quantities of the starting materials did not affect the product obtained.

I.R. (CCl_4 soln.) : 1753 $cm.^{-1}$

Tetra-acetyl quinic acid methyl ester (9)

Tetra-acetyl quinic acid silver salt (1.5 g.) was added to methyl iodide (30 ml.) and the mixture refluxed for 5 hours. The silver iodide formed was filtered off and the filtrate evaporated to dryness under vacuum. The product was one spot on t.l.c. (R_f 0.8 in 20 %. ethyl acetate - petrol ether 60-80°) and was recrystallised from ethyl acetate - petrol ether 60-80° to give colourless needles (1.41 g., 90 %.) m.p. 104-5° and $[\alpha]_D$ -22.1°

in methanol c = 1. (Lit. values[4] m.p. 99-101° and $[\alpha]_D$ -21.9)

I.R. (CCl_4 soln.) : 1744, 1752 $cm.^{-1}$ (methyl ester, acetate)

N.M.R. ($CDCl_3$) 4.4 - 5.1 : 3H multiplet (H-C-OR)

6.29 : 3H singlet (methyl ester)

7.4 - 7.6 : 4H multiplet ($-CH_2-$)

7.9 - 8.0 : 12H 4 singlets (acetates)

Analysis. Found C : 51.47 %. H : 5.77 %.

Calc. for $C_{16}H_{22}O_{10}$ C : 51.34 %. H : 5.92 %.

Acetone-quinide[6](11).

Quinic acid (40 g.) was shaken in acetone (800 ml.) containing dry hydrogen chloride (8 g.) for three days. The insoluble material was filtered off, the solution shaken with lead carbonate (40 g.) for 1 hour and the lead salts filtered off. The acetone was removed under vacuum and the resultant solid recrystallised from ethyl acetate - petrol ether 60-80° to give acetone-quinide as colourless needles (41.2 g., 93 %.) m.p. 140-1°, $[\alpha]_D$ -37.4° in tetrachloroethane c = 3. (Lit. values[6] m.p. 140-1° and $[\alpha]_D$ -36.6)

I.R. (CCl_4 soln.) : 860, 1790, 3450, 3560 $cm.^{-1}$ (acetonide, lactone, bonded hydroxyl, non-bonded OH)

N.M.R. ($CDCl_3$) 5.2 - 5.7 : 3H multiplet (H-C-OR)

7.1 - 7.7 : 4H multiplet ($-CH_2-$)

7.5 : 1H exchanges with D_2O (-OH)

8.5 : 3H singlet (acetonide)

8.7 : 3H singlet (acetonide)

Analysis. Found C : 56.30 %. H : 6.70 %.

Calc. for $C_{10}H_{14}O_5$ C : 56.05 %. H : 6.59 %.

4:5-isopropylidene quinic acid hydrazide[5](12).

Acetone quinide (4 g.) was heated with hydrazine hydrate (1.4 ml.) on a steam bath for 2 hours. On cooling the reaction mixture crystallised as a solid mass. This was rubbed with an ethanol - ethyl acetate mixture, filtered off and recrystallised from ethanol to give white prisms (3.71 g., 81%.) m.p. 148°. (Lit. value[5] m.p. 150-1°)

I.R. (nujol mull) : 850, 1540, 1610, 1680 $cm.^{-1}$

(acetonide, acid hydrazide)

3:4-Isopropylidene-3:4:5-trihydroxy-cyclohexanone[5](10).

4:5-Isopropylidene quinic acid hydrazide (2.5 g.) and sodium nitrite (0.8 g.) were dissolved in water (5 ml.) and the resulting solution cooled to 0° and ice-cold chloroform (40 ml.) added. Ice-cold 1N hydrochloric acid (11 ml.) was then added to the solution dropwise with continuous shaking. Immediately the addition was completed the mixture was saturated with salt. The

chloroform layer was separated and the aqueous layer extracted with two further portions of ice-cold chloroform (2 x 40 ml.). The total chloroform extract was dried with sodium sulphate for 1 hour at 0° and evaporated to dryness at 20° to give a pale yellow oil (1.96 g.). This oil had the correct i.r. (liquid film) with peaks at 865, 1710, 1782, 2240 $cm.^{-1}$ (acetonide, azide) for the acid azide (13).

The oil was dissolved in dry toluene (12.5 ml.) and heated on the water-bath from 40° to 100° over a period of 1 hour with continuous shaking. The toluene was then removed by rotary evaporation and the residual oil was rubbed with petrol ether 30-40°. The resulting oily solid (1.24 g., 67%.) was two spots on t.l.c. (R_f in 4 % methanol in chloroform - 0.52 and 0.46 due respectively to acetone-quinide [5 %.] and ketone [95 %.]). A sample was distilled twice under vacuum at 115°/0.05 mm. to give pure material m.p. 69-72°, $[\alpha]_D$ 116° in water c = 2 (Lit. values[5,7] m.p. 72°, $[\alpha]_D$ 118°).

I.R. (CCl_4 soln.) : 861, 1727, 3500, 3630 (acetonide, ketone, bonded hydroxyl, non-bonded hydroxyl)

N.M.R. ($CDCl_3$)

5.2	:	1H multiplet (H-C-OR)
5.5 - 5.8	:	2H multiplet (H-C-OR)
6.4	:	1H exchanges with D_2O (OH)
7.2 - 7.5	:	4H multiplet ($-CH_2-$)
8.55, 8.62	:	6H 2 singlets (acetonide)

Analysis. Found C : 57.72 %. H : 7.41 %.

Calc. for $C_9H_{14}O_4$ C : 58.03 %. H : 7.58 %.

3-Acetyl-4:5-isopropylidene-3:4:5-trihydroxy-cyclohexanone[5](14).

The hydroxy-ketone (10, 1g.) was dissolved in a mixture of pyridine (7 ml.) and acetic anhydride (6 ml.). The reaction was left overnight at room temperature and the solvent then removed by rotary evaporation at the lowest possible temperature. The last traces of solvent were removed by addition of ethanol and re-evaporation to dryness as above. The resultant oil was crystallised from petrol ether 60-80° as colourless hexagonal plates (0.81 g., 66 %.) m.p. 68° (Lit. value[5] 68-9°). This was one spot on t.l.c. (R_f 0.75 in 2 % methanol in chloroform).

I.R. (CCl_4 soln.) : 882, 1733, 1758 $cm.^{-1}$ (acetonide, ketone, acetate)

N.M.R. ($CDCl_3$)

4.7	:	1H multiplet (H-C-OR)
5.3	:	1H multiplet (H-C-OR)
5.6	:	1H multiplet (H-C-OR)
7.2-5	:	4H multiplet ($-CH_2-$)
7.92	:	3H singlet (acetate)
8.52,8.61	:	6H 2 singlets (acetonide)

Analysis. Found C : 57.71 %. H : 7.23 %.

Calc. for $C_{11}H_{16}O_6$ C : 57.88 %. H : 7.03 %.

1-Acetyl-4:5-isopropylidene-quinide[8] (15).

Acetone-quinide (10 g.) was dissolved in a mixture of acetic anhydride (10 ml.) and pyridine (15 ml.) in the cold and allowed to stand overnight. Water (100-120 ml.) was then added slowly and with continuous shaking. The product began to crystallise as white needles after a few minutes. After 3 hours the product was filtered off, washed with water and recrystallised from aqueous ethanol to give acetyl-acetone-quinide (15) m.p. 104-5° (7.90 g., 66 %.). A sample was purified for analysis and then had m.p. 109° (Lit. value[9] m.p. 109).

I.R. (CCl_4 soln.) : 865, 1757, 1810 $cm.^{-1}$ (acetonide, acetate, lactone)

N.M.R. ($CDCl_3$) 5.2 - 5.7 : 3H multiplet (H-C-OR)

7.0 - 7.7 : 4H multiplet ($-CH_2-$)

7.91 : 3H singlet (acetate)

8.5, 8.7 : 6H 2 singlets (acetonide)

Analysis. Found C : 56.25 %. H : 6.29 %.

Calc. for $C_{12}H_{16}O_6$ C : 56.04 %. H : 6.19 %.

Acetone china alcohol[9](16).

Lithium aluminium hydride (4 g.) was refluxed in anhydrous ether (200 ml.) for 3 hours. The white cloudy suspension was poured into a stoppered cylinder and allowed to stand overnight. The resultant liquid was decanted from the solid and poured into a 1 litre conical flask which contained a magnetic stirrer. To the stirred solution was added dropwise over a period of 1 hour a solution of acetyl-acetone-quinide (8 g.) in ether (200ml.). The resulting mixture was brought slowly to reflux during the next 3 hours. The turbid solution was then ice-cooled and water (60 ml.) added carefully. The ether solution was poured off and extracted with water (4 x 50 ml.). The total aqueous extract was then filtered and the clear solution taken to pH 7-8 by the addition of small lumps of solid carbon dioxide. The solution was filtered again, evaporated to dryness under vacuum and the last traces of water removed by azeotroping with benzene and dry methanol. The solid residue was extracted with anhydrous methanol and evaporated under vacuum to give a thick oil which crystallised on scraping with a glass rod. This was re-crystallised from ethyl acetate to give colourless prisms (3.8 g., 56 %.) m.p. 115-7°, $[\alpha]_D$ -50.1°c = 1 in ethanol (Lit. values[9] m.p. 115-7°, $[\alpha]_D$ -51°).

I.R. ($CHCl_3$ soln.) : 3540, 3600 $cm.^{-1}$ (bonded and non-bonded hydroxyls)

Analysis. Found C : 55.24 %. H : 8.10 %.

Calc. for $C_{10}H_{18}O_5$ C : 55.03 %. H : 8.31 %.

3:4-Isopropylidene-3:4:5-trihydroxy-cyclohexanone[7](10b).

Acetone china alcohol (400 mg.) was dissolved in warm acetone (12 ml.). To the stirred solution at 60° was added lead tetra-acetate (900 mg.) in portions over 10 minutes. After stirring for ½ hour at 50° and slow cooling the solution was filtered and evaporated down under vacuum to give a thick syrup. This was dissolved up in ethanol (10 ml.), decolourised with charcoal black and then evaporated to dryness under vacuum. On rubbing this gave a crystalline mass (240 mg., 76 %.) m.p. 75-9°. This was recrystallised from ethyl acetate - petrol ether 60-80° and then had m.p. 78-9°. This preparation had an identical i.r. and n.m.r. to Fischer's preparation[5] m.p. 72 (see 10a). The R_f values of the two preparations were the same in a variety of solvent systems.

Cyanohydrin Reactions on 3:4-Isopropylidene-3:4:5-trihydroxy-cyclohexanone (10). [Hydroxy ketone]

(1)[1] The hydroxy ketone (250 mg.) was shaken with 40 %. sodium bisulphite solution (1 ml.) until it dissolved. Saturated potassium cyanide (1.5 ml.) was added. After 5 minutes at room temperature this was extracted with ether (5 x 5 ml.). The ether extract was dried over sodium sulphate and evaporated to dryness to give only starting material (204 mg., 82 %.). The material was one spot on t.l.c. and had an i.r. identical with that of the starting material.

(2)[12] The hydroxy ketone (200 mg.) in ethanol (4 ml.) and acetic acid (1.6 ml.) was treated with potassium cyanide (1.5 g.) added at 0° during $\frac{1}{4}$ hour. The reaction was stirred for $\frac{1}{2}$ hour at 0° and then for 2 hours at room temperature. The reaction was worked up by pouring it onto water (20 ml.) and extracting this with ethyl acetate (4 x 20 ml.). The material recovered was one spot on t.l.c. and had the same R_f as the starting material and an identical i.r. (191 mg., 95 %.).

(3)[13] The hydroxy ketone (250 mg.) was dissolved in absolute ethanol (25 ml.) and to this was added water (10 ml.) containing potassium acetate (200 mg.) and potassium cyanide (130 mg.). The solution which was stirred continuously went bright green at once and darkened rapidly to a deep brown colour after about an hour. After 20 hours t.l.c. showed only very polar material to be present. The solvent was therefore removed under vacuum and a dark brown gum obtained. Extraction of this with ethyl acetate (3 x 25 ml.) produced a little pink oil (4 mg.) which was a mixture of several spots on t.l.c.. The gum was further extracted with methanol to give a thick tar (208 mg.) which was not identified.

(4)[14] The hydroxy ketone (250 mg.) was dissolved in acetone cyanohydrin(1 ml.) and stirred for 2 hours at room temperature. T.l.c. of the crude reaction mixture showed only starting material and this was recovered by the addition of a little ethanol, followed by removal of the solvent under reduced pressure. (235 mg., 94 %.)

(5)[15] The hydroxy ketone (200 mg.) was stirred in acetone cyanohydrin (0.6 ml.) for $2\frac{1}{2}$ hours at 60°. After this time the acetone cyanohydrin was removed under vacuum by co-distillation with ethanol and the resultant product was run on a 0.8 mm., 20 x 20 cm. plate using 5 %. methanol in chloroform as solvent. Three bands resulted. The least polar was starting ketone (135 mg., 67 %.). The other two bands were aromatic as judged by their i.r. spectra and neither showed any nitrile bands in the i.r.. The lowest band on the plate was blue in colour (R_f - 0.05, 4 mg.) and the middle band (R_f - 0.1, 11 mg.) pink.

(6) The hydroxy ketone (200 mg.) was dissolved in dimethyl-formamide (2 ml.), acetone cyanohydrin (0.2 ml.) added and the reaction stirred for 24 hours at room temperature. After this time the solvent was removed under high vacuum and the product run on a preparative scale t.l.c. plate (0.8 mm., 20 x 20 cm.). From this was recovered pure starting ketone (166 mg., 83 %.), a little very polar material (6 mg.) which did not move on the plate and a small amount of material which ran very readily (R_f - 0.95, 3 mg.).

(7)[16] The hydroxy ketone (100 mg.) was stirred with acetone cyanohydrin (0.3 ml.) and triethylamine (2 ml.) for 5 hours. The product was plated and the starting material recovered (75 mg., 75 %.). Some very polar material was also present.

(8) The hydroxy ketone (200 mg.) was stirred in absolute ethanol (2 ml.) and acetone cyanohydrin (1 ml.) for 2 hours at room temperature. Removal of the solvents under vacuum and scraping the resulting oil with petrol ether 60-80° produced pure ketone (175 mg., 82 %.).

(9)[16] The hydroxy ketone (100 mg.) in ethanol (5 ml.), acetone cyanohydrin (0.3 ml.) and triethylamine (0.3 ml.) was stirred for 24 hours at room temperature. T.l.c. of the product, after removal of the solvent, gave three bands (5 % methanol in chloroform). Band one (R_f - 0.1, 52 mg.) showed both nitrile and ketone absorption (1715, 2280 $cm.^{-1}$) in the i.r.. Band two (R_f - 0.25, 14 mg.) showed marked absorption in the u.v. (e = 2,200, λ_{max} = 212 mu.) and carbonyl absorption (1660 $cm.^{-1}$) in the i.r.. Band three was pure hydroxy ketone (35 mg., 35 %.)

Cyanohydrin Reactions on 3-Acetyl-4:5-isopropylidene-3:4:5-trihydroxy-cyclohexanone (14). [Acetyl ketone]

(1)[1] The acetyl ketone (200 mg.) was treated, as described above, with sodium bisulphite and potassium cyanide. Only starting material was recovered (170 mg., 85%.). This had the correct R_f and i.r..

(2)[12] The acetyl ketone (100 mg.) was dissolved in ethanol (2 ml.) and glacial acetic acid (0.8 ml.) and solid potassium cyanide (0.35g.) added at 0° over $\frac{1}{4}$ hour. The reaction was then carried out as for the hydroxy ketone. The material recovered was pure starting material (84 mg., 84%.) as judged by t.l.c. and i.r. but it smelled slightly of acetic acid.

(3)[13] The acetyl ketone (100 mg.) was dissolved in absolute ethanol (10 ml.) and to this was added with stirring potassium acetate (80 mg.) and potassium cyanide (50 mg.) in water (4 ml.). On addition of the aqueous solution the reaction mixture went yellow and then darkened to brown. Some polymeric material began to precipitate after about 2 hours. T.l.c. showed only very polar species to be present after 24 hours.

(4)[14] The acetyl ketone (100 mg.) was stirred in acetone cyanohydrin (0.3 ml.) for 2-3 hours at room temperature. Removal of the solvent and preparative scale t.l.c. produced only recovered starting material (84 mg., 84 %.).

(5)[15] The acetyl ketone (100 mg.) was stirred in acetone cyanohydrin (0.3 ml.) for 3 hours at 60°. The starting material (79 mg., 79%.) was recovered by t.l.c..

(6) The acetyl ketone (100 mg.) was stirred overnight at room temperature in acetone cyanohydrin (0.3 ml.) and dimethyl-formamide (1 ml.). The starting material (81 mg., 81 %.) was recovered by t.l.c..

(7)[16] The acetyl ketone (100 mg.) was stirred with acetone cyanohydrin (0.3 ml.) and triethylamine (2 ml.) for 5 hours at room temperature. After removal of the solvent preparative t.l.c. produced an array of about a dozen spots, one of which was the hydroxy ketone. A little starting material also appeared to be present.

(8) The acetyl ketone (90 mg.) was stirred with acetone cyanohydrin (0.3 ml.) and absolute ethanol (1 ml.) for six hours at room temperature. The starting material (72 mg., 80 %.) was recovered by t.l.c..

(9)[16] The acetyl ketone (100 mg.) was stirred for 24 hours at room temperature in ethanol (5 ml.), acetone cyanohydrin (0.3 ml.) and triethylamine (0.3 ml.). T.l.c. of the product produced a series of bands and the products were not identified.

The reaction of lithium acetylide - ethylenediamine with 3:4-isopropylidene-3:4:5-trihydroxy-cyclohexanone.

Lithium acetylide - ethylenediamine (500 mg.) was placed in a reaction vessel under argon cover[17] and dry benzene (10 ml.) added. The stirred suspension was then brought to 35° and the hydroxy ketone (10) [1 g.] in dry benzene added dropwise over a period of 15 minutes. The temperature was maintained for a further $1\frac{3}{4}$ hours and the reaction mixture then allowed to come to room temperature.

Water (5 ml.) was added dropwise and the benzene layer, which had been pale green and cloudy, became clear and colourless. The aqueous layer darkened rapidly from pale orange to brown. The benzene layer was separated and the aqueous layer extracted with more benzene (3 x 20 ml.). The aqueous layer was then extracted in turn with ether (3 x 20 ml.), chloroform (3 x 20 ml.) and ethyl acetate (3 x 20 ml.). The extracts were dried over sodium sulphate and evaporated to dryness under vacuum. No material was recovered from these extracts, and t.l.c. of the aqueous layer showed only very polar material to be present. After constant extraction of the aqueous layer with ethyl acetate for a week a few mgs. of greenish tar were obtained.

The use of ammonium chloride solution in place of water in the work-up did not alter the result of the reaction.

When the above reaction was repeated using 3-acetyl-4:5-isopropylidene-3:4:5-trihydroxy-cyclohexanone the same result was obtained

Attempted formation of the pyrrolidine enamine of 3:4-isopropylidene-3:4:5-trihydroxy-cyclohexanone.

(1) The hydroxy ketone (10) [1 g.] was dissolved in benzene(50 ml.). Pyrrolidine (1.3 ml.) was added and the mixture refluxed for 2-3 hours[19] in a Dene and Stark apparatus. The benzene and excess pyrrolidine were distilled off under vacuum and distillation of the tarry residue gave the product (0.74 g.) b.p. 115 / 0.1 mm., m.p. 145-7°. This was identified as N-(p-hydroxyphenyl)-pyrrolidine from its i.r., u.v. and analysis, and by acetylation. No other product would distil from the tarry residue.(Lit.[20] m.p. 147°)

I.R. (nujol mull) : 830, 1520, 1600, 3350 (1:4-disustituted phenol).

U.V. (ethanol) λ_{max} : 251 (e = 11500), 322 (e = 2000).

Analysis. Found C : 73.28 %. H : 7.86 %. N : 8.74%.

Calc. for $C_{10}H_{13}NO$. C : 73.59 %. H : 8.03 %. N : 8.58%.

(2) The hydroxy ketone (0.5 g.) was stirred at room temperature for five days in benzene (20 ml.) in the presence of pyrrolidine (0.7ml.) and potassium carbonate (1 g.)[22]. The reaction was filtered and then worked up as above to give an identical product (0.41 g.)

Attempted formation of the pyrrolidine enamine of 3-Acetyl-4:5-isopropylidene-3:4:5-trihydroxy-cyclohexanone.

The acetyl ketone (14) [0.5 g.] was dissolved in benzene (50ml.) and refluxed for five hours with pyrrolidine (0.6 ml.) in a Dene and Stark apparatus. Working up as described above yielded the same product as before (0.37 g.).

N-(p-acetoxyphenyl)-pyrrolidine

N-(p-hydroxyphenyl)-pyrrolidine (100 mg.), obtained above, was left overnight in a mixture of pyridine (2.5 ml.) and acetic anhydride (2.5 ml.). The solvent was removed under vacuum and the product distilled to give a pale yellow oil which crystallised on cooling (106 mg., 84 %.) b.p. 135 / 0.7 mm., m.p. 75-8°. The i.r. u.v. and n.m.r. were consonant with the structure assigned to the compound. (Lit.[21] m.p. 80°).

I.R. (nujol mull) : 840, 910, 1510, 1600, 1750 $cm.^{-1}$ (aromatic acetate)

U.V. (ethanol) λ_{max} : 313 (e = 16000), 259 (e = 2500)

N.M.R. ($CDCl_3$)

2.97 - 3.58	:	4H A_2B_2 quartet (aromatic)
6.76	:	4H triplet ($-CH_2-N=$)
7.79	:	3H singlet (acetate)
7.9 - 8.2	:	4H multiplet ($-CH_2-$)

Analysis. Found C : 69.91 %. H : 7.24 %. N : 7.12 %.

Calc. for $C_{12}H_{15}O_2N$ C : 70.22 %. H : 7.37 %. N : 6.82 %.

1-Triacetyl-quinide[4](31).

Quinic acid (10 g.) was refluxed for 3 minutes in acetic anhydride (70 ml.). This was allowed to cool and pyridine (20 ml.) added. Next day the acetylation mixture was removed under vacuum and the product recrystallised from aqueous methanol to give colourless prisms (12.9 g., 68 %.) m.p. 131. A sample recrystallised twice from the above solvent had m.p. 133-4°, $[\alpha]_D$ -13.5° in acetone c = 2 (Lit. values[4] m.p. 134-5°, $[\alpha]_D$ -13.6).

I.R. (CCl_4 soln.) : 1758, 1819 $cm.^{-1}$(acetate, lactone).

N.M.R. ($CDCl_3$) 4.5 - 5.2 : 3H multiplet (H-C-OR)

6.7 - 7.6 : 4H multiplet ($-CH_2-$)

7.85- 8.0 : 9H 3 singlets (acetates)

Analysis. Found C : 52.25 %. H : 5.31 %.

Calc. for $C_{13}H_{17}O_8$ C : 52.00 %. H : 5.37 %.

Quinamide[4](32).

1-Triacetyl-quinide (3.2 g.) was dissolved in absolute methanol (25 ml.) and this saturated with ammonia. After 3 days the solvent was removed under vacuum and the resulting thick oil crystallised from ethyl acetate - methanol to give quinamide as white prisms (1.8 g., 88%.) m.p. 147-150°,$[\alpha]_D$ -47.2° in methanol c = 1 (Lit. values[4] m.p. 150°, $[\alpha]_D$ -49.1°)

I.R. (KBr disc) : 1562, 1660, 1674, 3174, 3290, 3450 $cm.^{-1}$ (amide).

Analysis. Found C : 44.27 %. H : 6.91 %. N : 7.66 %.

Calc. for $C_7H_{13}O_5N$ C : 43.97 %. H : 6.85 %. N : 7.33 %.

Tetra-acetyl-quinamide[5](28).

Quinamide (1 g.) was shaken for 12 hours in a mixture of pyridine (2 ml.) and acetic anhydride (2 ml.). After this time crystallisation was completed by the addition of ether (25 ml.). The product was white needles (1.05 g., 56 %.) m.p. 186-8°, $[\alpha]_D$ -29.1° (Lit. values[5] m.p. 188°, $[\alpha]_D$ -28.5°).

I.R. (KBr disc) : 1590, 1662, 1681, 1700, 1741, 3300, 3400, 3430, 3480, 3590 $cm.^{-1}$ (acetate, amide).

N.M.R. ($CDCl_3$) 3.1 : 1H broad (amide H)

4.2 - 5.1 : 3H multiplet (H-C-OR)

6.25 : 1H singlet exchanges D_2O (-OH)

7.4 - 7.8 : 4H multiplet ($-CH_2-$)

7.8 - 8.0 : 12H 4 singlets (acetates)

Analysis. Found C : 49.43 %. H : 6.16 %. N : 4.20 %.

Calc. for $C_{15}H_{21}O_9N$ C : 50.13 %. H : 5.89 %. N : 3.90 %.

4:5-Isopropylidene-quinamide[24](34).

Acetone-quinide (2 g.) was dissolved in absolute ethanol (50 ml.) and the solution saturated with ammonia gas at 0°. The reaction flask was sealed and left for three days. The ethanol was removed under vacuum and the resultant oil crystallised from ethyl acetate (10 ml.) to which had been added one drop of methanol. The product was the hydrate of the amide m.p. 120-2°. After drying for two days in vacuum the colourless needles had m.p. 141° (1.52 g., 70 %.), $[\alpha]_D$ -49.1° in ethanol c = 1 (Lit. values[24] m.p. 141°, $[\alpha]_D$ -50.9°).

I.R. (KCl disc) : 845, 909, 1569, 1655, 1685, 3390, 3410 $cm.^{-1}$

N.M.R. (pyridine)

5.2 - 5.5	: 3H	multiplet (H-C-OR)
5.1 - 5.3	: 2H	mult. exchanges D_2O (-OH)
7.25 - 7.7	: 4H	multiplet ($-CH_2-$)
8.47, 8.63	: 3H, 3H	2 singlets (acetonide)

Analysis. Found C : 52.13 %. H : 7.29 %. N : 6.06 %.

Calc. for $C_{10}H_{17}O_5N$ C : 51.94 %. H : 7.41 %. N : 6.06 %.

3-Acetyl-4:5-isopropylidene-quinamide[5](27).

Acetone-quinamide (1g.) was dissolved in pyridine (5 ml.) and acetic anhydride (5 ml.). This was left overnight and the solvent then removed at the lowest possible temperature under vacuum. The resultant oily solid was crystallised from methanol to give acetyl-acetone-quinamide (0.62 g., 53 %.) as colourless prisms m.p. 188-90° (Lit. value[5] 190°).

I.R. (KCl disc) : 845, 856, 888, 1598, 1669, 1680, 1739, 3225, 3304, 3339, 3461 $cm.^{-1}$ (acetonide, acetate, amide).

N.M.R. (pyridine) 5.1 : 1H broad (-O<u>H</u> exchanges with D_2O)

5.1 - 5.7 : 3H multiplet (<u>H</u>-C-OR)

7.2 - 7.7 : 4H multiplet (-C<u>H</u>$_2$-)

8.05 : 3H singlet (acetate)

8.40, 8.63 : 3H, 3H singlets (acetonide)

Analysis. Found C : 52.74 %. H : 6.81 %. N : 5.11%.

Calc. for $C_{12}H_{19}O_6N$ C : 52.73 %. H : 7.01 %. N : 5.12%.

Acetic Anhydride Dehydration of Acetone-quinamide.

Acetone-quinamide (200 mg.) was refluxed in acetic anhydride (2 ml.) for 2 hours. The solvent was removed under high vacuum at ca. 30° and the resultant oil run on two 20 x 20 cm.,0.8 mm. t.l.c. plates using 4 %. methanol in chloroform as eluent. Three bands resulted (R_f - 0.3, 0.5, 0.7).

Band I (27 mg., R_f - 0.3) was an amide from it's i.r. spectrum which also showed acetate peaks. It was not further investigated.

Band II (94 mg., R_f - 0.5) was also an amide acetate and was not further investigated.

Band III (36 mg., R_f - 0.7) was tentatively identified as 1-acetyl-4:5-isopropylidene-quinide (15) by its i.r. and t.l.c. properties.

1:3-Diacetyl-4:5-isopropylidene-quinic acid nitrile[5](29).

Acetyl-acetone-quinamide (200 mg.) was refluxed for 2 hours in acetic anhydride (2 ml.). The acetic anhydride was removed at 30° under high vacuum and the resultant oil subjected to t.l.c. on two 20 x 20 cm., 0.8 mm. plates. Three bands resulted when these plates were run in 2 %. methanol in chloroform (R_f - 0.1, 0.25, 0.5).

Band I (23 mg., R_f - 0.1) was identified as recovered starting material from it's i.r. and t.l.c. properties.

Band II (104 mg., R_f - 0.25) showed i.r. absorption bands for acetonide, acetate and amide. N.m.r. showed this compound to be 1:3-diacetyl-4:5-isopropylidene-quinamide (35).

N.M.R. ($CDCl_3$) 3.8 : 2H broad (amide $\underline{NH}_2$)

5.4 - 6.1 : 3H multiplet ($\underline{H}$-C-OR)

7.1 - 7.8 : 4H multiplet (-$C\underline{H}_2$-)

7.87 - 8.1 : 6H 2 singlets (acetates)

8.48,8.64 : 3H, 3H singlets (acetonide)

Band III (38 mg., R_f - 0.5) was the required nitrile (29) b.p. 125° / 0.5 mm..

I.R. (nujol mull) : 850, 870, 895, 1740 $cm.^{-1}$ (acetonide, acetate).

N.M.R. ($CDCl_3$) 5.5 - 6.0 : 3H multiplet (H-C-OR)

7.3 - 7.7 : 4H multiplet ($-CH_2-$)

7.82 : 6H singlet (acetates)

8.47, 8.61 : 3H, 3H singlets (acetonide)

Analysis. Found C : 55.11 %. H : 6.36 %. N : 4.62 %.
C : 57.97 %. H : 6.19 %. N : 4.63 %.

Calc. for $C_{14}H_{19}O_6N$ C : 56.56 %. H : 6.44 %. N : 4.71 %.

Tetra-acetyl-quinic acid nitrile[5] (28).

Tetra-acetyl quinamide (200 mg.) was refluxed in acetic anhydride (2 ml.) for 2 hours and the products recovered by removal of the solvent at 30° under high vacuum and t.l.c. of the residue. T.l.c. was carried out on two 20 x 20 cm., 0.8 mm. plates with 100 %. chloroform as the eluent. Three bands resulted (R_f - 0.2, 0.3, 0.6).

Band I (115 mg., R_f - 0.2) was identified by n.m.r. and i.r. as a penta-acetyl-quinamide (36). Thin-layer t.l.c. showed that this band was contaminated with a little starting material.

Band II (54 mg., R_f - 0.3) was tentatively identified by i.r. of the crude product. This was sublimed (155° / 0.5 mm.) to give white needles, m.p. 162-3°. The identification of this compound as tetra-acetyl-quinic acid nitrile was confirmed by n.m.r. and analysis. (Lit.[5] m.p. 161-2°)

I.R. (nujol mull) : 1745 $cm.^{-1}$ (acetate).

N.M.R. ($CDCl_3$) 4.5 - 4.8 : 3H multiplet (H-C-OR)

7.4 - 7.7 : 4H multiplet ($-CH_2-$)

7.85 - 7.96 : 12H 4 singlets (acetates)

Analysis. Found C : 52.28 %. H : 5.21 %. N : 4.03 %.

Calc. for $C_{15}H_{19}O_8N$ C : 52.78 %. H : 5.61 %. N : 4.10 %.

Band III (30 mg., R_f - 0.6) was tentatively identified as an aromatic acetate from it's i.r.. The n.m.r. spectrum was exceedingly simple and suggested that this compound was hydroquinone diacetate. The compound was recrystallised from ethanol and then had m.p. 120-3°. Comparison with an authentic specimen of hydroquinone diacetate, m.p. 124°, showed the two to have identical i.r. and n.m.r. spectra. The melting-point of the authentic sample was not noticeably depressed on admixture with the unknown material.

N.M.R. ($CDCl_3$) 2.75 : 4H singlet (aromatic)

7.58 : 6H singlet (acetates)

Ditosyl acetone china alcohol[9] (38).

Acetone china alcohol (120 mg.) was dissolved in dry pyridine (0.5 ml.) and the solution cooled in ice. Tosyl chloride (300 mg.) in dry pyridine (0.75 ml.) was added slowly and with shaking. The reaction was set aside overnight and the next day water (10 ml.) added and the mixture then extracted with chloroform (3 x 20 ml.). The chloroform extract was washed with saturated sodium carbonate (25 ml.), dilute hydrochloric acid (25 ml.) and water (25 ml.). The extract was then dried over sodium sulphate and evaporated to dryness to give a colourless oil. This was crystallised from ether - petrol ether 60-80°, to which had been added a few drops of chloroform, to give white needles (190 mg., 64%.) m.p. 134-5°, $[\alpha]_D$ -82°in chloroform c = 2 (Lit. values[9] m.p. 135-7°, $[\alpha]_D$ -84°).

I.R. (nujol mull) : 1170, 1350, 1600 (sulphonate, aromatic).

N.M.R. ($CDCl_3$)

2.1 - 2.7	:	8H 2 superimposed A_2B_2 quartets (aromatic)
5.1 - 6.0	:	3H multiplet (H-C-OR)
6.2	:	2H singlet ($-CH_2-OTs$)
7.57	:	6H singlet (methyl of tosyl gps.)
7.8 - 8.4	:	4H multiplet ($-CH_2-$)
8.76,8.81	:	6H 2 singlets (acetonide)

China alcohol trityl ether[1] (40).

Acetone china alcohol (1.8 g.) was dissolved in water (5 ml.) and Amberlite IR-120 (2 ml.) added. This was heated on a steam-bath for 3 hours, filtered and evaporated to dryness under vacuum. The last traces of water were removed by azeotroping with benzene. The product, china alcohol (39) [1.45 g.] showed no carbonyl absorption in the i.r..

The crude pentol was dissolved in dry benzene (40 ml.) and trityl chloride (3.0 g.) added. The reaction mixture was heated on a steam-bath for $\frac{1}{2}$ hour, stoppered and allowed to stand overnight at room temperature. The solvent was removed under vacuum and the resultant semi-crystalline mass dissolved in chloroform (25 ml.), washed with potassium bisulphate solution, sodium bicarbonate solution and water (25 ml. of each), and then dried over sodium sulphate. The dried solution was evaporated down to 5 ml. and plated on 5 one metre, 0.8 mm. t.l.c. plates. These were run with 100 %. benzene and gave two bands (R_f - o.1 and 0.6). The upper band was trityl alcohol and the lower a mixture of the trityl ethers of china alcohol (40 and 41). This latter band was extracted, re-plated and re-run with 3.5 % methanol in chloroform to give two main bands (R_f - 0.5 and 0.15).

The more polar band was china-alcohol mono-trityl ether (4o) [1.54 g., 45 %.] and had m.p. 143-5°, and i.r. and n.m.r. in

agreement with this structure (Lit. value[1] m.p. 142-5°). The compound was recrystallised for analysis from iso-propanol and n.m.r. of the analytical sample showed iso-propanol in the lattice.

I.R. (KBr disc) : 708, 1496, 1602, 3350 $cm.^{-1}$ (aromatics and bonded hydroxyl).

Analysis. Found C : 72.85 %. H : 7.33%.

Calc. for $C_{26}H_{28}O_5$ (C_3H_8O) C : 72.47 %. H : 7.55 %.

The less polar band was dityrityl china alcohol (41) [450 mg., 8%.] and had the correct i.r. and n.m.r. for this product, m.p. 175-7° (Lit. value[1] 173-5°).

I.R. (nujol mull) : 710, 1595, 3450 $cm.^{-1}$ (aromatics and bonded hydroxyl).

N.M.R. ($CDCl_3$)

2.5 - 2.8	:	30H broadened singlet (aromatic)
5.9 - 6.7	:	3H multiplet (H-C-OR)
6.6	:	1H singlet exchanges D_2O (-OH)
6.85	:	1H singlet exchanges D_2O (-OH)
7.15	:	1H singlet exchanges D_2O (-OH)
7.1 - 7.4	:	2H quartet(-CH_2-OTr)
8.2 - 8.5	:	4H multiplet (-CH_2-)

Triacetyl china alcohol trityl ether[1](42).

China alcohol trityl ether (400 mg.) was dissolved in pyridine (3 ml.) and acetic anhydride (1.5 ml.) added with cooling. This solution was allowed to stand for 3 days at room temperature and then added dropwise to a stirred ice-cold solution of sodium bicarbonate (1N). Stirring was continued for 2 hours and the resultant white-pale yellow powder recovered by filtration. This was washed with water and dried overnight in vacuo. The product (460 mg.,94 %.) was one spot by t.l.c. and had m.p. 189-90° and $[\alpha]_D$ -50° in benzene c = 2 (Lit. values[1] m.p. 189°, $[\alpha]_D$ -50.5°). An analytical sample was recrystallised from iso-propanol as white needles.

I.R. (CCl_4 soln.) : 1491, 1751, 3490, 3610 $cm.^{-1}$ (aromatic, acetate, bonded and non-bonded hydroxyls)

N.M.R. ($CDCl_3$)

2.5 - 2.8	:	15H multiplet (trityl)
4.5 - 5.2	:	3H multiplet (H-C-OR)
6.9 - 7.0	:	2H singlet ($-CH_2-OR$)
7.8 - 8.2	:	9H 3 singlets (acetate)
8.0 - 8.5	:	4H multiplet ($-CH_2-$)
7.2	:	1H exchanges with D_2O (-OH)

Analysis. Found C : 70.09 %. H : 6.09 %.

Calc. for $C_{32}H_{34}O_8$ C : 70.31 %. H : 6.27 %.

3:4:5-Triacetoxy-cyclohexanone[1](8).

Triacetyl china alcohol trityl ether (330 mg.) was dissolved in warm glacial acetic acid (3.5 ml.) and water (0.7 ml.) added. The solution was then heated on the steam-bath for 1 hour and water (17 ml.) added. The solution was then allowed to cool and the triphenyl carbinol which precipitated was filtered off. The solution was evaporated under vacuum to give a colourless oil [43] (140 mg.). The i.r. of this oil showed that it was no longer aromatic.

This oil was shaken with lead tetra-acetate in benzene (20ml.) for 1 hour. The benzene solution was filtered and shaken with ice-water (5 ml.) added. The benzene layer was separated, filtered, dried over sodium sulphate and evaporated to dryness at 40° under vacuum. The oily product, 3:4:5-triacetoxy-cyclohexanone (96 mg., 58 %.), had the expected i.r. and n.m.r..

I.R. (CCl_4 soln.)	: 1736, 1759 $cm.^{-1}$	(ketone, acetate)
N.M.R. ($CDCl_3$)	4.5 - 4.7	: 3H multiplet (H-C-OR)
	7.2 - 7.4	: 4H multiplet ($-CH_2-$)
	7.89 - 7.95	: 9H 3 singlets (acetates)

References.

(1) R.Grewe and E.Vangermain, Ber., 98, 104, (1965).

(2) R.Grewe and H.Haendler, Ann., 658, 113, (1962).

(3) F.A.H.Rice and A.Johnson, J. Amer. Chem. Soc., 78, 428, (1956).

(4) G.Zemplen, I.Döry and Z.Mészáros, Magyar Kémiai Folyóirat, 61, 113, (1955).

(5) H.O.L.Fischer and Gerda Dangschat, Ber., 65, 1009, (1932).

(6) H.O.L.Fischer, Ber., 54, 775, (1921).

(7) G.Zemplen, L.Mester and I.Döry, Hung. Chim. Acta, 4, 151, (1954).

(8) K.Josephson, Ber., 61, 911, (1928).

(9) R.Grewe and Eliz. Nolte, Ann., 575, 1, (1951).

(10) R.Grewe, A.Bokranz and H-W.Herberg, Ber., 88, 1367, (1955).

(11) D.Cornthwaite and E.Haslam, J.Chem. Soc., 3008, (1965).

(12) W.J.Adams, D.K.Patel, V.Petrow and I.A.Stuart-Webb, J. Chem. Soc., 1825, (1954).

(13) H.L.Herzog, M.J.Gentles, H.M.Marshall and E.B.Hershberg, J. Amer. Chem. Soc., 82, 3691, (1960).

(14) A.Ercoli and P.de Ruggieri, J. Amer. Chem. Soc., 75, 650, (1953).

(15) P.de Ruggieri and C.Ferrari, J. Amer. Chem. Soc., 81, 5725, (1959).

(16) R.Gardi, P.P.Castelli, R.Gandolfi and A.Ercoli, Gazz. Chim. Ital., 91, 1250, (1961).

(17) O.F.Beumel Jr. and R.F.Harris, J. Org. Chem., 29, 1872, (1964).

(18) J.Szmuszkovicz, Advan. in Org. Chem., Vol.IV, pg. 79, (Interscience Publishers, New York and London, 1963 : Editors - R.A.Raphael, E.C.Taylor and H.Wynberg)

(19) G.Stork, A.Brizzolara, H.Landesman, J.Szmuszkovicz and R.Terrell, J. Amer. Chem. Soc., 85, 207, (1963).

(20) Chem. Abs., 62, 11789d, (1965) , [Gevaert Photo-Producten N.V., Belg. pat. 619,971].

(21) Chem. Abs., 47, 4330e, (1953) , [O.Wichterle and M.Vavruska, Chem. Listy, 46, 237, (1952)].

(22) C.Mannich and H.Davidsen, Ber., 69, 2106, (1936).

(23) G.Knöpfer, Archiv der Pharm., 245, 78, (1907).

Geraniol and Nerol.

Geraniol (1) and nerol (2) are isomeric monoterpenoid primary alcohols with the formula $C_{10}H_{18}O$. They are of wide occurrence in nature and have been isolated from many of the oils used in perfumery.

Geraniol (1) was first isolated by Jacobsen[1] from Palmarosa oil and is itself a colourless oil, b.p. 229-30°,[2] with a rose-like odour. It can be oxidised to give the aldehyde, citral a[3] (3), and geranic acid (4), and it forms a tetra-bromide,[4] m.p. 70-1°. Oxidation of geraniol with alcoholic potassium hydroxide yields[5] the alcohol (5) which indicates the position of the double bonds. This and similar evidence[2] established the gross structure beyond doubt.

Nerol (2) was first isolated from neroli oil[2] and is an oil, b.p. 225-6°, similar to geraniol in most respects but having a rather different smell with a better tone. Oxidation of nerol gives an aldehyde similar to that obtained above but differing in the stereochemistry of one double bond[4,6] (citral b , 6). It forms a different tetra-bromide, m.p. 116-8°, from geraniol.

From the evidence above it was possible to infer that geraniol and nerol were cis-trans isomers. It was Zeitschel[7] who observed that the rate of cyclisation of the alcohols to α-terpineol (7) was faster in the case of nerol and concluded that nerol must therefore be the cis isomer. Recently Greenlee and Wiley[8] reduced geraniol and nerol to the corresponding dimethyl-octadienes (8a and 8b) and assigned these in agreement with Zeitschel's formulae. Valenzuela and Cori[9] repeated Zeitschel's work on a quantitative basis and showed that the rate of cyclisation was 18 x faster in the case of nerol, thus further strengthening the case for the assignment of the alcohols.

An x-ray analysis of geranylamine hydrochloride (9) was carried out by Jeffrey[10] and this showed that the double bond was trans in this compound. Extrapolation of this result to geraniol itself is however somewhat doubtful. The distance found by Jeffrey for the C5 - C6 bond is very short(1.44 Å) and he explains this as being due to hyperconjugation of the hydrogen atoms attached to this bond.

Rummens applied[11] the concept of rehybridisation[12] to the case of the double bond in question in geraniol and concluded from the small differences in the C=C stretching frequencies

in the i.r. of geraniol and nerol and their acetates that the alcohols had been wrongly assigned. He backed his assertion with the evidence of boiling points, g.l.c. retention times and refractive indices.

The recent synthesis of geraniol (1) and nerol (2) by Burrell et al.[13] has however removed almost all doubt. The ketone (10) was reacted with methoxy-acetylene to give the acetylenic ether (11). This was isomerised with acid to give the unsaturated methyl ester (12). This was a mixture of the cis (12a) and trans (12b) isomers and these were assigned on the basis of the position of the C3-methyl band in the n.m.r.. Lithium aluminium hydride reduction of the esters furnished the respective alcohols : geraniol from the trans ester.

Geraniol and nerol are believed[14] to be formed from mevalonate in vivo. Mevalonic acid (13) first undergoes three consecutive phosphorylations to give the pyrophosphate (14). This in turn decarboxylates to give Δ^3-isopentenyl pyrophosphate (15) which may be isomerised to 3:3-dimethyl pyrophosphate (16). Coupling of one unit of each of the unsaturated pyrophosphates leads to geranyl pyrophosphate (17) and this in turn furnishes the monoterpenes. The addition of another unit gives farnesyl pyrophosphate (18) which gives the

sesquiterpenes directly or the triterpenes by coupling two farnesyl units. The addition of two geranyl units gives the diterpenes. The coupling of further units leads to the carotenoids and polyisoprenoids.

References.

(1) O.Jacobsen, Ann., 157, 232, (1871).

(2) J.L.Simonsen, The Terpenes Vol. 1 , pg. 40 et seq. [Cambridge University Press, 2nd. Edn., 1947].

(3) F.W.Semmler, Ber., 23, 2965, (1890) and 24, 201, (1891).

(4) H. v.Soden and W.Treff, Ber., 39, 906, (1906).

(5) F.Tieman, Ber., 31, 2991, (1898).

(6) H. v.Soden and W.Treff, Ber., 37, 1094, (1904).

(7) O.Zeitschel, Ber., 39, 1780, (1906).

(8) K.W.Greenlee and V.G.Wiley, J. Org. Chem., 27, 2304, (1962).

(9) P.Valenzuela and O.Cori, Tet. Lets., 3089, (1967).

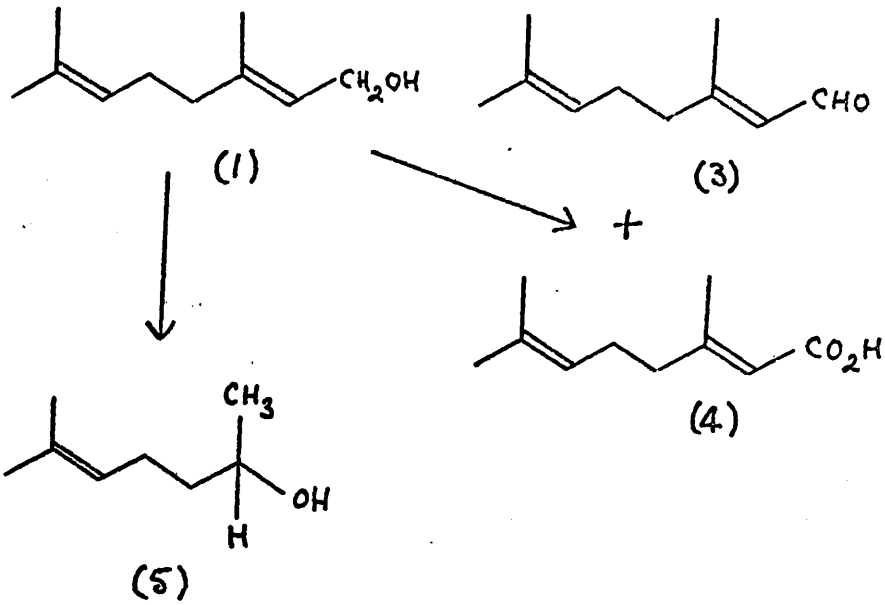
(10) G.A.Jeffrey, Proc. Royal Soc., A183, 388, (1945).

(11) F.H.A.Rummens, Rec. trav. chim., 84, 1003, (1965).

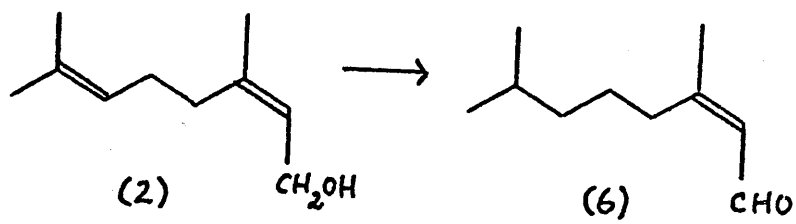
(12) F.H.A.Rummens, Rec. trav. chim., 84, 5, (1965).

(13) J.W.K.Burrell, R.F.Garwood, L.M.Jackman, E.Oskay and B.C.L.Weedon, J. Chem. Soc. (C), 2144, (1966).

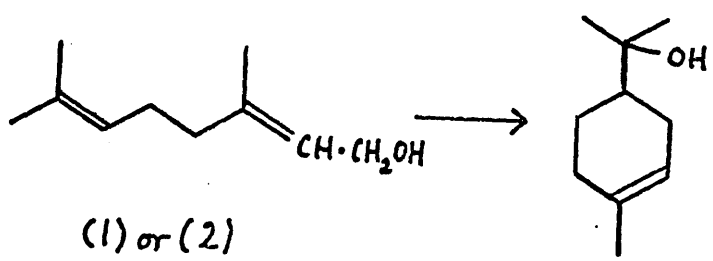
(14) J.D.Bu'Lock, The Biosynthesis of Natural Products, Chap.4, [McGraw Hill, London, 1965].



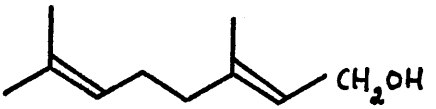
(1) (3) (4) (5)



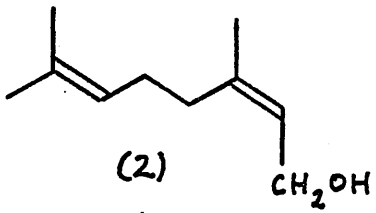
(2) (6)



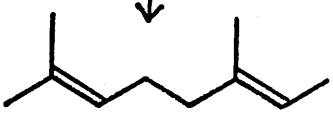
(1) or (2) (7)



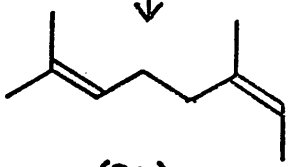
(1)



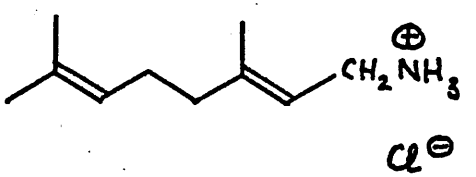
(2)



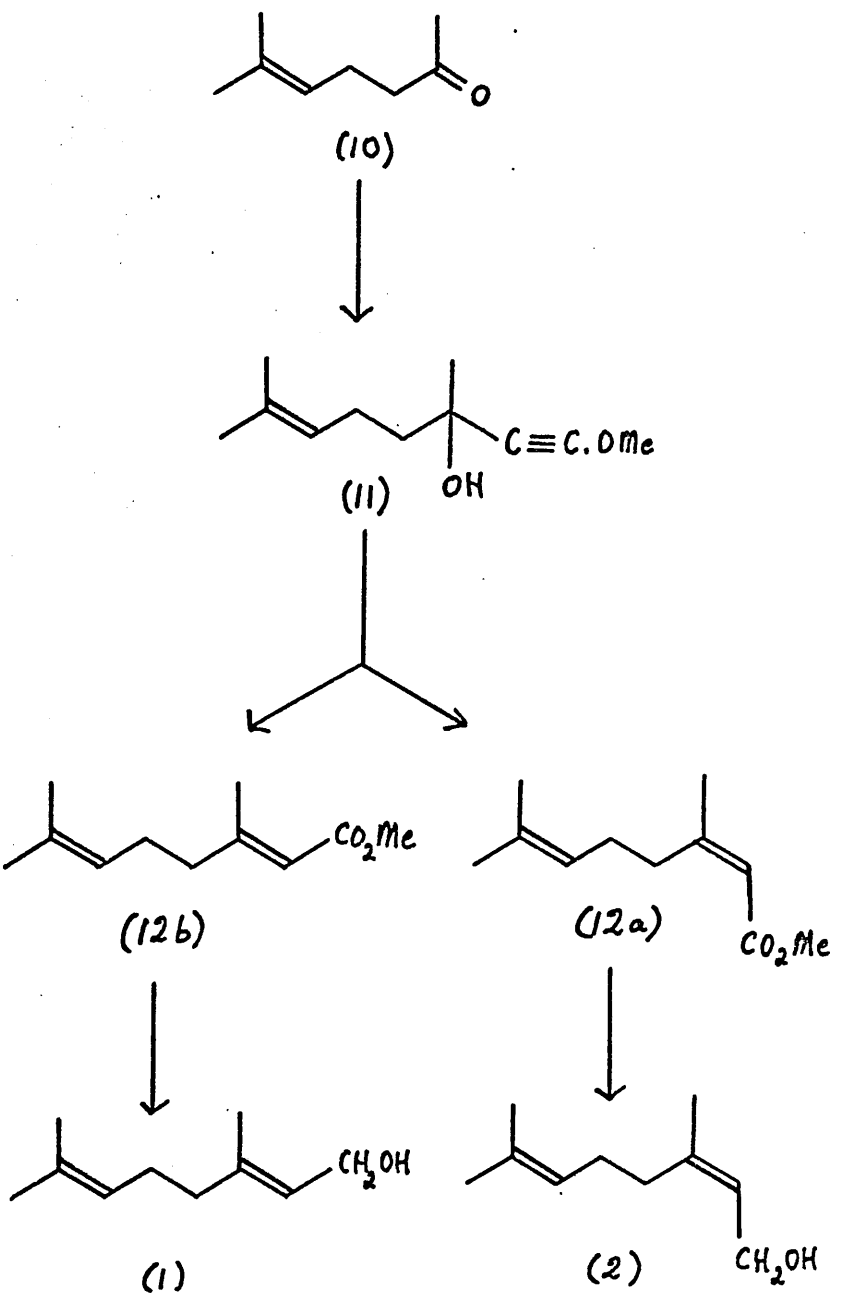
(8a)

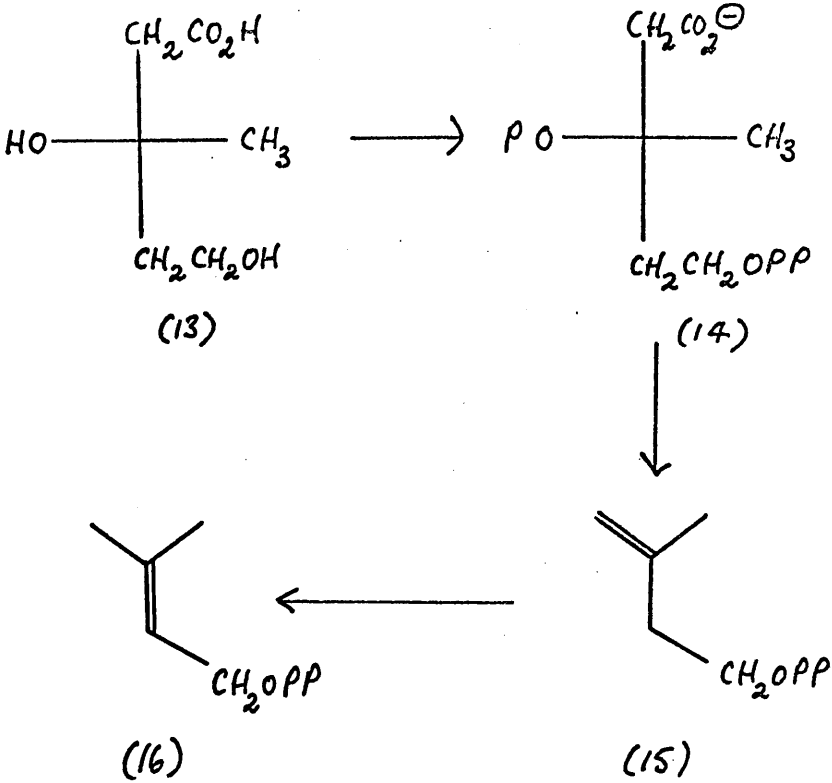


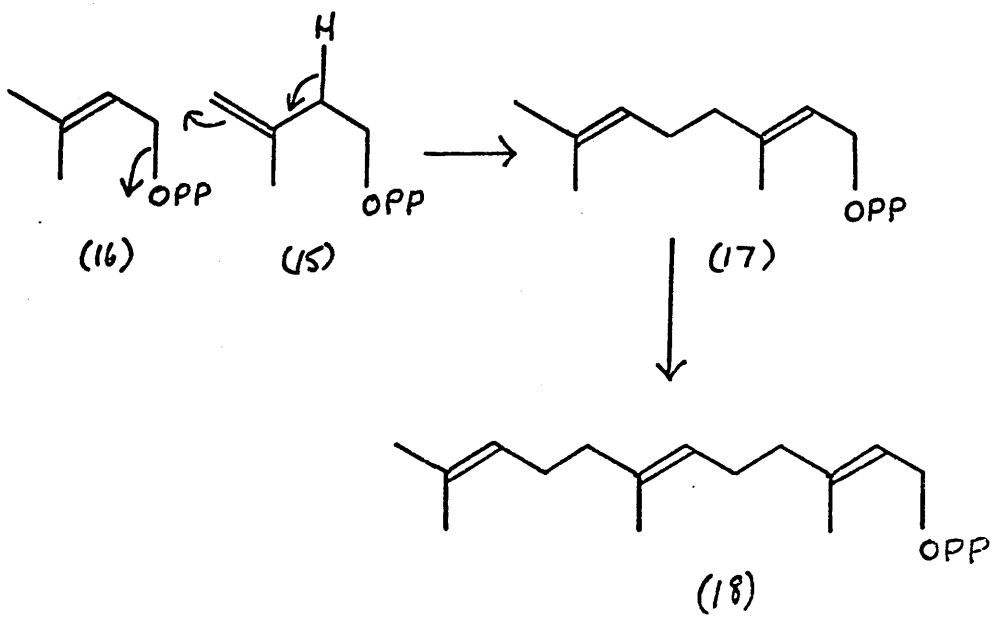
(8b)



(9)


O
(10)
C≡C.OMe
OH
(11)
CO2Me
(12b)
CO2Me
(12a)
CH2OH
(1)
CH2OH
(2)


CH2CO2H
HO
CH3
CH2CH2OH
(13)
CH2CO2⊖
PO
CH3
CH2CH2OPP
(14)
CH2OPP
(15)
CH2OPP
(16)


H
OPP
OPP
(16)
(15)
OPP
(17)
OPP
(18)

1 × C_{10} unit	⟶	monoterpenes.
1 × C_{15} unit	⟶	sesquiterpenes.
2 × C_{10} unit	⟶	diterpenes.
2 × C_{15} unit	⟶	triterpenes.
2 × C_{20} unit	⟶	carotenoids.
n × C_5	⟶	polyisoprenoids.

Discussion.

The importance of geraniol (1) and nerol (2) in the biosynthesis of natural products made it appear worthwhile to prepare an x-ray derivative of these alcohols in order to establish their configurations unambiguously. The configurations of these alcohols are critical in the elucidation of the biosynthetic steps which lead to the terpenoids in general and the highly important steroids in particular.

The assignment of the trans structure to geraniol (1) was first made by Zeitschel[1] on the grounds of the apparently faster rate of cyclisation of nerol to α-terpineol (3). This reaction was carried out with sulphuric acid and a number of transformations might take place in this medium before cyclisation occurred. It is therefore difficult to be sure that the rate of cyclisation observed is in fact that of the alcohol and not of some other species, which has resulted from the prior isomerisation of the alcohol and which may or may not retain the original configuration about the double bond in question. Further quantitative work by Valenzuela and Cori[2] has shown that the rate constant for the cyclisation to α-terpineol is 18 x greater for nerol than geraniol. A similar difference in rate was observed by these authors for

the pyrophosphates of the alcohols. There is thus no doubt that the rate of conversion of nerol to α-terpineol is faster than that of geraniol, but it is difficult to assess how much evidence this constitutes for the assignment of the alcohols, particularly as Valenzuela and Cori[2] found other terpenoid products in their experiments.

The work of Greenlee and Wiley[3] showed that reduction of the two alcohols led to different dimethyl-octadienes (4a and 4b). Their assignment of these octadienes in agreement with that of Zeitschel was however based on the boiling points of the two isomers. Rummens[4] has since claimed that these isomers were assigned the wrong way round as evidenced by Greenlee and Wiley's own boiling points.

Rummens[4] used the boiling points, densities, refractive indices and retention times on g.l.c. as evidence for geraniol being the cis isomer. He then examined small differences in the i.r. absorptions of the alcohols and their acetates and stated that these were in agreement with those predicted on the assumption that geraniol was the cis isomer.

An x-ray analysis of geranylamine hydrochloride (5), carried out by Jeffrey[5], showed that this compound had the trans configuration. There is however some doubt as to whether the

configuration of the allyl group is retained in the preparation of the amine from the alcohol.

The recent synthesis of geraniol and nerol by Burrell et al.[6] appears to prove the configuration of the two alcohols. However, close examination of their work leaves some slight doubt. The ketone (6) was reacted with methoxy-acetylene to give the ether (7) and this was then isomerised to a mixture of the cis and trans esters (8a and 8b). These esters were separated by chromatography and then reduced to the alcohols. The assignment of the esters was made on the basis of the position in the n.m.r. of the C3-methyl group. This assignment is absolutely critical and the differences involved in the n.m.r. are very small. In addition the reference compounds used to formulate the rule that a cis methyl group occurs at higher field include the methyl esters derived from nerol and geraniol.[7]

It thus seemed reasonable to us to eliminate all doubt by an unambiguous x-ray study.

The first work carried out was the preparation of the known geranyl 3:5-dinitrobenzoate (9) according to the method of Peyron.[8] The derivative obtained was as that of Peyron and hence it was concluded that the sample used was indeed geraniol.

The most obvious derivative to make was the p-iodobenzoate

and this was made by reacting the alcohol with p-iodobenzoyl chloride in pyridine. T.l.c. of the product gave pure geranyl p-iodobenzoate (10) and neryl p-iodobenzoate (11) from the respective alcohols. These compounds were however liquids and no method of crystallising them was found.

Geranyl p-bromobenzoate (12) and neryl p-bromobenzoate (13) were then prepared as above and these also proved to be liquids.

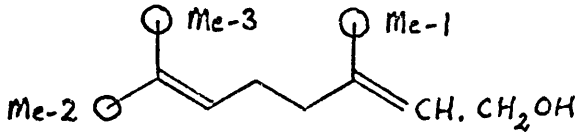
At this point the literature was searched for any known derivative which might be made with the incorporation of a heavy atom. The esters of the alcohols were found to be liquids almost without exception. The p-(p-nitrophenylazo)-benzoates[9] had been prepared and were crystalline solids ; geranyl ester (14) m.p. 107-9° and neryl ester (15) m.p. 90-1°. It was thus decided to try to obtain the corresponding bromo-derivatives.

p-Bromoaniline (16) was oxidised with ammonium persulphate to give p-bromo-nitrosobenzene (17) as described by Ingold.[10] The nitroso-compound was then coupled with p-aminobenzoic acid (18) in glacial acetic acid to give p-(p-bromophenylazo)-benzoic acid (19). The acid (19) was treated with thionyl chloride and sodium carbonate to give the acid chloride (20). The method used for these last steps was as described by Aspon et al.[11] for the

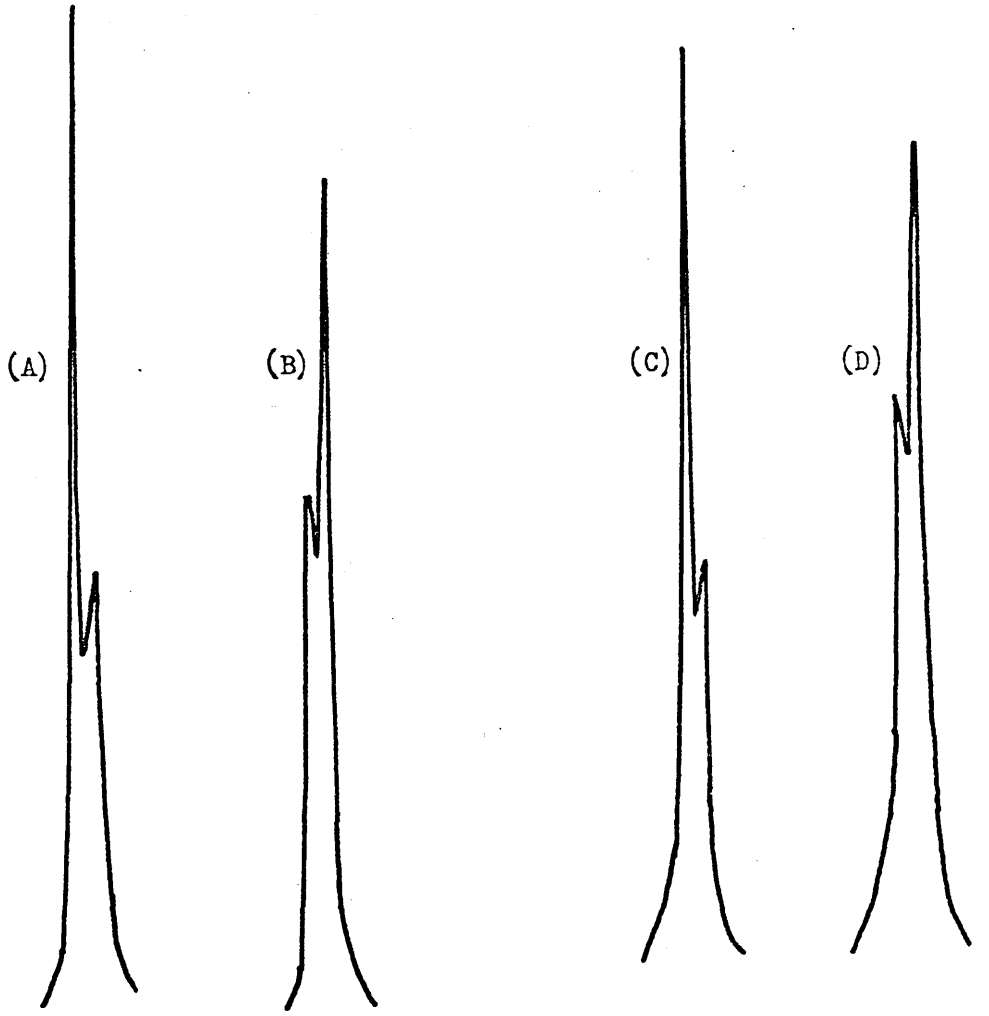
unsubstituted p-phenyl-azobenzoic acid.

The acid chloride (20) was reacted with geraniol and nerol in pyridine to give the esters as lustrous red plates after chromatography and recrystallisation of the crude product; geranyl ester (21) m.p. 89-90° and neryl ester (22) m.p. 77-9°. The geranyl ester was recrystallised several times and submitted for x-ray analysis as plates (from aqueous ethanol). The neryl ester was recrystallised several times from aqueous ethanol and finally allowed to crystallise slowly from a large volume of acetone. When crystallised in this way it had m.p. 57-9°, but showed an identical n.m.r. to the higher-melting modification. The crystals so obtained were large triclinic needles and they were submitted for x-ray analysis in this form.

As a check against isomerisation it was decided to make the derivatives of α-terpineol (3), citronellol (23) and linalool (26). The ester (24) of α-terpineol was prepared in very poor yield and the citronellyl ester (25) in good yield. When the reaction was carried out on linalool a number of bands were obtained and it was impossible to be certain which was the required ester. Examination of the n.m.r. spectra of the various esters ruled out any possibility of isomerisation.



	$-CH_2-CH_2-$	Me-1	Me-2	Me-3
Geranyl 3:5-dinitrobenzoate	(7.85) 7.90	8.20	8.32	8.39
Geranyl p-iodobenzoate	(7.87) 7.93	8.23	8.32	8.40
Geranyl p-bromobenzoate	(7.88) 7.92	8.24	8.33	8.40
Geranyl p-(p-bromophenylazo)-benzoate	(7.85) 7.91	8.21	8.32	8.39
Neryl p-iodobenzoate	7.84 (7.90)	8.21	8.34	8.41
Neryl p-bromobenzoate	7.84 (7.89)	8.22	8.33	8.40
Neryl p-(p-bromophenylazo)-benzoate	7.82 (7.87)	8.20	8.33	8.40
Geraniol	(7.92) 7.98	8.35	8.34	8.40
Nerol	7.89 (7.95)	8.27	8.34	8.40



(A) Neryl p-bromobenzoate

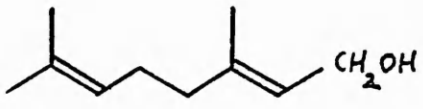
(B) Geranyl p-bromobenzoate

(C) Neryl p-(p-bromophenylazo)-benzoate

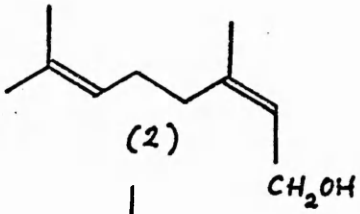
(D) Geranyl p-(p-bromophenylazo)-benzoate

Examination of the n.m.r. spectra of the geranyl esters (9, 10, 12 and 21) and the neryl esters (11, 13 and 22) revealed no real difference in the position of the C3-methyl group absorption. Such a difference was found for the alcohols themselves by Bates and Gale[12] who also found different values for each of the terminal methyl groups. The values reported by them for the two terminal methyl groups were borne out by those found by us for the esters.

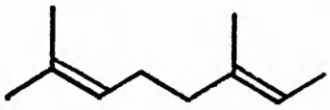
An obvious difference in the n.m.r. spectra of the esters of geraniol and nerol did however exist in the shape of the peak due to the four protons on the saturated carbon atoms in the centre of the molecule. In every derivative prepared these protons appeared as two overlapping singlets. When the derivative was of geraniol the more intense of the bands appeared at higher field, but in the neryl esters the more intense band appeared at lower field. In every case the intensity difference between the two singlets was greater if the ester was a neryl one (see table and diagram). When the spectra of the alcohols were run the same differences in the intensities were found to be present.



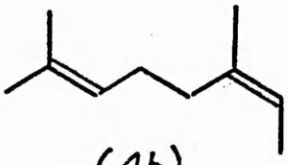
(1)



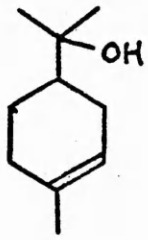
(2)



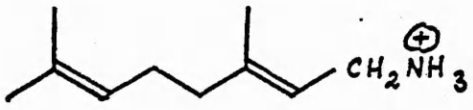
(4a)



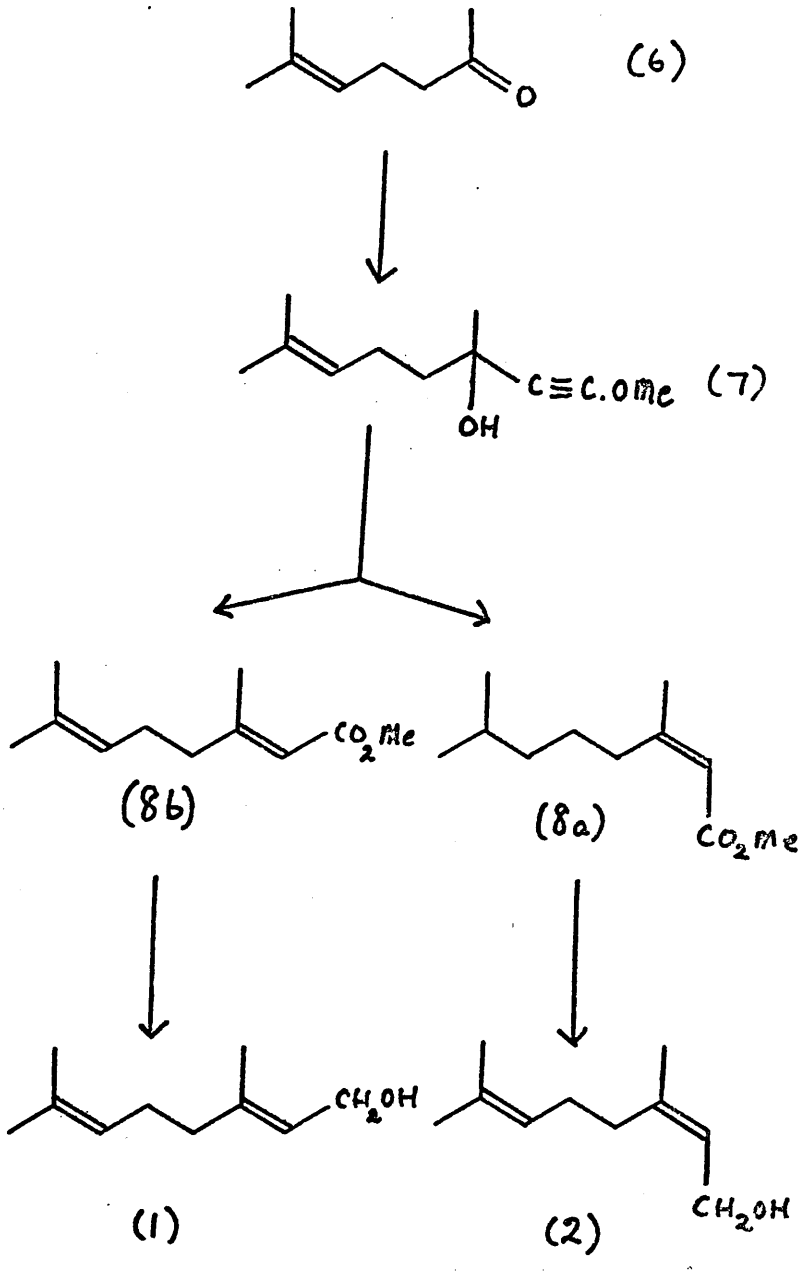
(4b)



(3)



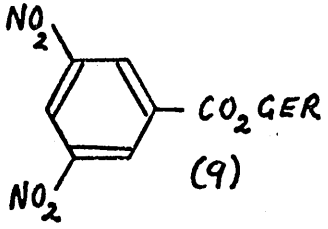
(5)


O
(6)
C≡C.OMe
OH
(7)
CO2Me
(8b)
(8a)
CO2Me
CH2OH
(1)
(2)
CH2OH

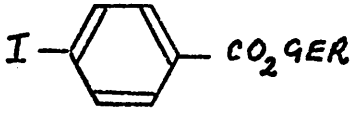
$$RCOCl + R'OH \longrightarrow RCO_2R'$$

GER = GERANYL

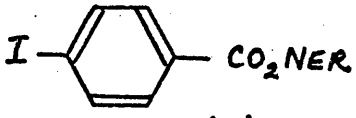
NER = NERYL



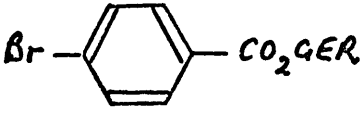
(9)



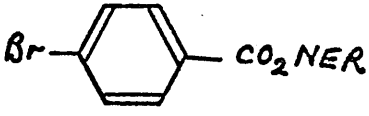
(10)



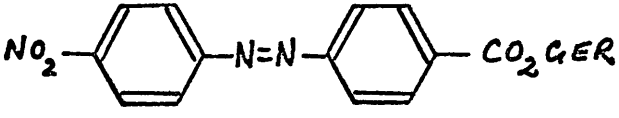
(11)



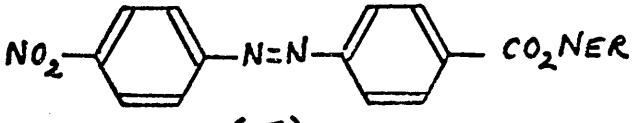
(12)



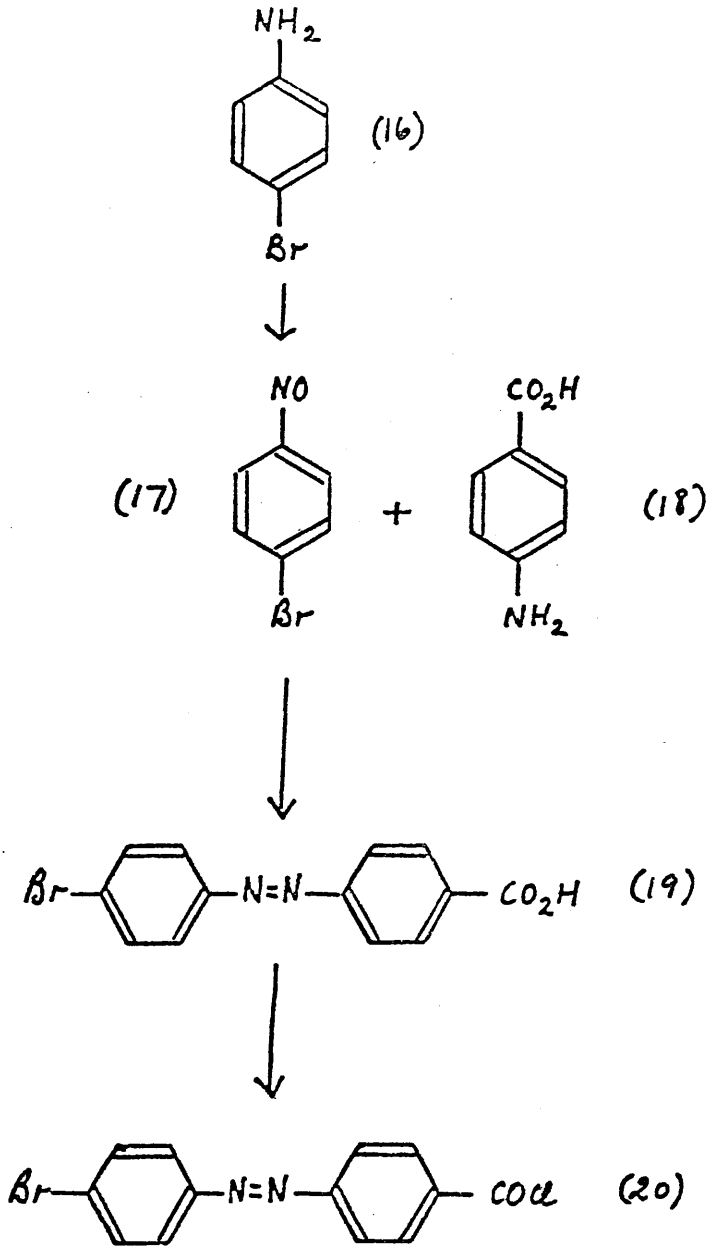
(13)

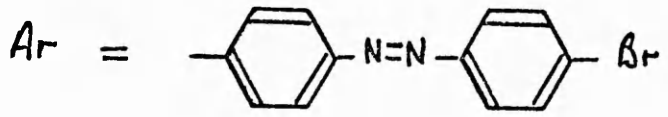


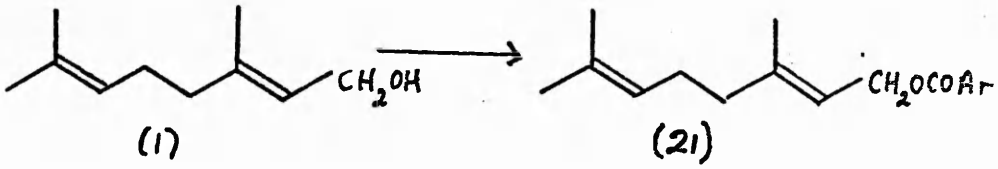
(14)



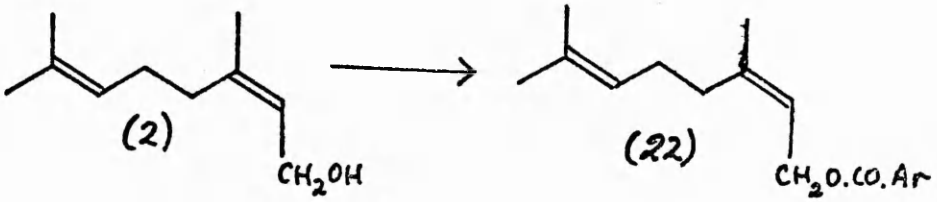
(15)

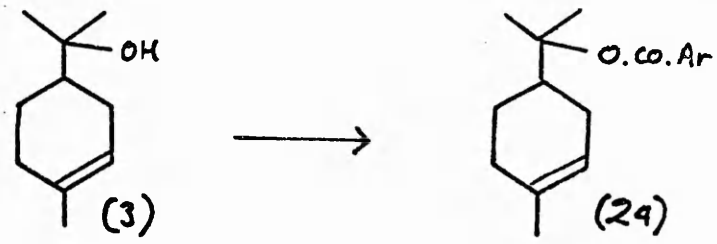

NH2
Br
(16)
NO
Br
(17)
+
CO2H
NH2
(18)
Br
N=N
CO2H
(19)
Br
N=N
COCl
(20)

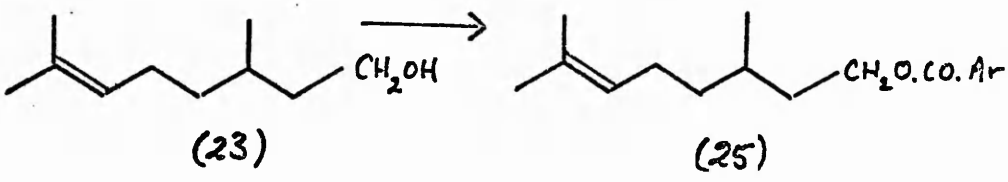

Ar =
N=N
Br

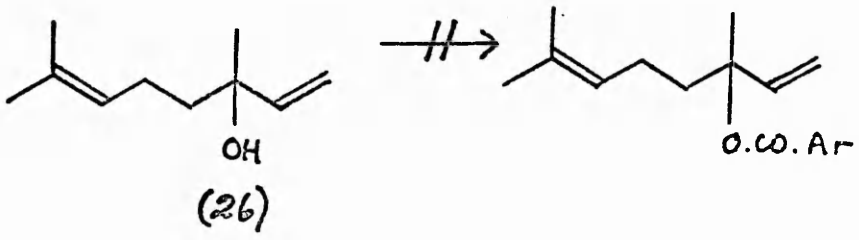

CH2OH
CH2OCOAr

(1) (21)


(2)
CH2OH
(22)
CH2O.CO.Ar


OH
(3)
O.CO.Ar
(24)


CH2OH
(23)
CH2O.CO.Ar
(25)


OH
(26)
O.CO.Ar

Experimental.

Notes as for this section of Part 1.

Geranyl 3:5-dinitrobenzoate[8] (9).

Dicyclohexyl-carbodiimide (206 mg.) was dissolved in dichloroethane (3 ml.) and this added to a solution of geraniol (154 mg.) in dichloroethane (5 ml.). The solution rose in temperature to about 30° due to reaction. After about 4 hours at room temperature with intermittent shaking the by-product (urea) was filtered off.

The solution was washed with 2½% acetic acid (10 ml.), water (10 ml.), filtered and then washed with bicarbonate (10 ml.). The solution was washed to neutrality, dried over magnesium sulphate and evaporated to dryness under vacuum to give a colourless oil (350 mg., quantitative). After recrystallisation from dilute acetone and aqueous methanol white needles m.p. 62-3° were obtained (Lit.[8] m.p. 63°). The i.r. and n.m.r. were in agreement with the structure.

I.R. (nujol mull) : 720, 940, 1615, 1660, 1705 $cm.^{-1}$ (aromatic ester)

N.M.R. ($CDCl_3$)

0.78	: 3H singlet (aromatic)
4.35-4.6	: 1H triplet ($\underline{H}$-C=C)
4.9	: 1H multiplet ($\underline{H}$-C=C)
4.95, 5.08	: 2H 2 singlets (-$C\underline{H}_2$-OR)
7.85, 7.90	: 4H 2 singlets (-$C\underline{H}_2$-$C\underline{H}_2$-)
8.20, 8.32, 8.39	: 9H 3 singlets ($C\underline{H}_3$-C=C)

Geranyl p-iodobenzoate (10).

p-Iodobenzoyl chloride (268 mg.) was dissolved in dry pyridine (2 ml.) and geraniol (154 mg.) added with ice-cooling. The reaction was left at room temperature for two days. One drop of water was added and after ½ hour the mixture was poured onto an ice-water mixture (100 ml.) and allowed to stand for a further hour. It was then extracted with ethyl acetate (3 x 50 ml.) and the extract dried over magnesium sulphate and taken to dryness in vacuo. The oily residue was taken up in chloroform (5 ml.) containing a few drops of methanol and painted onto a thick-layer t.l.c. plate (1 m. x 20 cm. x 0.8 mm.). The plate was run in chloroform (100 %.) and after drying the bands developed with an iodine spray. The ester appeared as a non-polar band (R_f- 0.8) and two other bands (R_f - 0.35 and 0.4) were observed. The upper of these was identified as unreacted geraniol.

The ester band was scraped off and extracted with warm ethyl acetate (100 ml.). The extract was taken to dryness on the rotary evaporator (10 mm.), dissolved in chloroform (20 ml.), dried over magnesium sulphate and once more evaporated to dryness in vacuo. The resulting pale-yellow oil (237 mg., 61 %.) was geranyl p-iodobenzoate which was distilled for analysis (b.p. 150 / 0.3 mm.).

I.R. (liquid film) : 770, 920, 1585, 1715 $cm.^{-1}$ (aromatic ester)

N.M.R. ($CDCl_3$) 2.21 : 4H singlet (aromatic)

4.4 - 4.6 : 1H distorted triplet ($\underline{H}$-C=C)

4.9 : 1H multiplet ($\underline{H}$-C=C)

5.10, 5.21 : 2H 2 singlets (-$C\underline{H}_2$-OR)

7.87, 7.93 : 4H 2 singlets (-$C\underline{H}_2$-$C\underline{H}_2$-)

8.22, 8.33, 8.40 : 9H 3 singlets ($C\underline{H}_3$-C=C)

Analysis. Found C : 53.09 %. H : 5.47 %.

$C_{17}H_{21}O_2I$ requires C : 53.25 %. H : 5.55 %.

Neryl p-iodobenzoate (11).

p-Iodobenzoyl chloride (268 mg.) was dissolved in dry pyridine (2 ml.) and nerol (154 mg.) added with ice-cooling. The reaction was then worked up as for the geranyl ester. The product isolated, a pale-yellow oil, (245 mg., 64%.) was neryl p-iodobenzoate. The i.r. spectrum was identical to that of the geranyl ester. The compound was distilled for analysis, (b.p. 140° / 0.1 mm.).

I.R. (liquid film) : 770, 920, 1585, 1715 $cm.^{-1}$ (aromatic ester)

N.M.R. ($CDCl_3$) 2.21 : 4H singlet (aromatic)

4.4 - 4.6 : 1H distorted triplet ($\underline{H}$-C=C)

4.9 : 1H multiplet ($\underline{H}$-C=C)

5.15, 5.27 : 2H 2 singlets (-$C\underline{H}_2$-OR)

7.84, 7.90 : 4H 2 singlets ($-C\underline{H}_2-C\underline{H}_2-$)

8.22, 8.34, 8.40 : 9H 3 singlets ($C\underline{H}_3-C=C$)

Analysis. Found C : 53.10 %. H : 5.68 %.

$C_{17}H_{21}O_2I$ requires C : 53.25 %. H : 5.55 %.

Geranyl p-bromobenzoate (12).

p-Bromobenzoyl chloride (220 mg.) was dissolved in dry pyridine (2 ml.) and geraniol (154 mg.) added with ice-cooling. The reaction was worked up as above. The product was a pale-yellow oil (201 mg., 59 %.) and had an i.r. very similar to that of the p-iodo ester. Geranyl p-bromobenzoate was distilled for analysis (b.p. 130° / 0.1 mm.).

I.R. (liquid film) : 770, 910, 1585, 1715 $cm.^{-1}$ (aromatic ester)

N.M.R. ($CDCl_3$) 2.0 - 2.4 : 4H A_2B_2 system (aromatic)

4.45 - 4.65 : 1H distorted triplet ($\underline{H}-C=C$)

4.90 : 1H multiplet ($\underline{H}-C=C$)

5.10, 5.23 : 2H 2 singlets ($-C\underline{H}_2-OR$)

7.86, 7.93 : 4H 2 singlets ($-C\underline{H}_2-C\underline{H}_2-$)

8.24, 8.33, 8.40 : 9H 3 singlets ($C\underline{H}_3-C=C$)

Analysis. Found C : 60.40 %. H : 6.13 %.

$C_{17}H_{21}O_2Br$ requires C : 60.54 %. H : 6.28 %.

Neryl p-bromobenzoate (13).

p-Bromobenzoyl chloride (220 mg.) was dissolved in dry pyridine (2 ml.) and nerol (154 mg.) added with ice-cooling. The reaction was worked up in the usual way. The product, neryl p-bromobenzoate (208 mg., 62 %.), was a pale-yellow oil and was distilled for analysis (b.p. 125° / 0.1 mm.).

I.R. (liquid film) : 770, 910, 1585, 1715 $cm.^{-1}$ (aromatic ester)

N.M.R. ($CDCl_3$) 2.0 - 2.42 : 4H A_2B_2 system (aromatic)

4.4 - 4.65 : 1H distorted triplet ($\underline{H}$-C=C)

4.9 : 1H multiplet ($\underline{H}$-C=C)

5.15, 5.28 : 2H 2 singlets (-$C\underline{H}_2$-OR)

7.84, 7.89 : 4H 2 singlets (-$C\underline{H}_2$-$C\underline{H}_2$-)

8.22, 8.33, 8.40 : 9H 3 singlets ($C\underline{H}_3$-C=C)

Analysis. Found C : 60.49 %. H : 6.25 %.

$C_{17}H_{21}O_2Br$ requires C : 60.54 %. H : 6.28 %.

p-(p-Bromophenylazo)-benzoic acid (19).

p-Bromo-nitrosobenzene[10] (981 mg.) was added to a cold solution of p-aminobenzoic acid (685 mg.) in glacial acetic acid[11] (10 ml.). This was shaken until total solution was obtained. Precipitation of the product began rapidly and on occasion commenced before total solution was obtained. The reaction was allowed to stand overnight and the product then filtered off. It was washed with a little acetic acid and then with water. This furnished almost pure p-(p-bromophenylazo)-benzoic acid as bronze needles (1.37 g., 82 %.). This could be recrystallised from tetrahydrofuran to give blood-red needles, m.p. 338°.

I.R. (KBr disc) : 710, 834, 878, 1578, 1609, 1687 $cm.^{-1}$

(C-Br, 1:4 disub., N=N, aromatic, acid)

Analysis. Found C : 50.97 %. H : 3.15 %. N : 9.23 %.

$C_{13}H_9O_2N_2Br$ requires C : 51.17 %. H : 2.97 %. N : 9.18 %.

p-(p-Bromophenylazo)-benzoyl chloride (20).

Raw p-(p-bromophenylazo)-benzoic acid (303 mg.) was ground up in a mortar with anhydrous sodium carbonate (400 mg.). This was refluxed[11] in freshly distilled thionyl chloride (5 ml.) for 1½ hours. The thionyl chloride was then removed in vacuo and the residue extracted with petrol ether 80-100° (25 ml.). The extract was filtered and concentrated until crystallisation began. The pure acid chloride crystallised as pink needles (320 mg., quantitative) m.p. 144-5 °

I.R. (nujol mull) : 720, 1580, 1600, 1740, 1760 $cm.^{-1}$

(C-Br, N=N, aromatic, -COCl)

Analysis. Found C : 48.23 %. H : 2.79 %. N : 8.43 %.

$C_{13}H_8ON_2BrCl$ requires C : 48.24 %. H : 2.49 %. N : 8.66 %.

Geranyl p-(p-bromophenylazo)-benzoate (21).

p-(p-Bromophenylazo)-benzoyl chloride (161 mg.) was suspended in dry pyridine (2 ml.) and geraniol (75 mg.) added with ice-cooling. The reaction and work-up were then carried out as described for geranyl p-iodobenzoate. The red solid obtained was recrystallised from aqueous acetone to give lustrous red plates (137 mg., 62 %.) m.p. 89-90°.

I.R. (CCl_4 soln.) : 869, 1609, 1726 (aromatic ester)

N.M.R. ($CDCl_3$) 1.7 - 2.7 : 8H complex (aromatics)

4.35 - 4.65 : 1H distorted triplet ($\underline{H}$-C=C)

4.85 : 1H multiplet ($\underline{H}$-C=C)

5.05, 5.17 : 2H 2 singlets (-$C\underline{H}_2$-OR)

7.85, 7.91 : 4H 2 singlets (-$C\underline{H}_2$-$C\underline{H}_2$-)

8.21, 8.32, 8.39 : 9H 3 singlets (CH_3-C=C)

Analysis. Found C : 62.82%. H : 5.49 %. N : 6.14 %.

$C_{23}H_{25}O_2N_2Br$ requires 62.58%. H : 5.71 %. N : 6.34 %.

Neryl p-(p-bromophenylazo)-benzoate (22).

p-(p-Bromophenylazo)-benzoyl chloride (161 mg.) was suspended in dry pyridine (2 ml.) and nerol (75 mg.) added with ice-cooling. The reaction was then carried through as before. The product was recrystallised from aqueous ethanol to give lustrous red plates m.p. 77-9° (182 mg., 83 %.). When crystallised slowly from acetone large orange triclinic needles were obtained m.p. 57-9°.

I.R. (CCl_4 soln.) : 870, 1610, 1726 $cm.^{-1}$ (aromatic ester)

N.M.R. ($CDCl_3$) 1.7 - 2.7 : 8H complex (aromatic)

4.35 - 4.7 : 1H distorted triplet ($\underline{H}$-C=C)

4.85 : 1H multiplet ($\underline{H}$-C=C)

5.09, 5.21 : 2H 2 singlets (-$C\underline{H}_2$-OR)

7.82, 7.87 : 4H 2 singlets (-$C\underline{H}_2$-$C\underline{H}_2$-)

8.20, 8.33, 8.40 : 9H 3 singlets (CH_3-C=C)

Analysis. Found C : 62.38 %. H : 6.00 %. N : 6.50%.

$C_{23}H_{25}O_2N_2Br$ requires C : 62.58 %. H : 5.71 %. N : 6.34%.

α-Terpineol p-(p-bromophenylazo)-benzoate (24).

p-(p-Bromophenylazo)-benzoyl chloride (220 mg.) was suspended in dry pyridine (2 ml.) and a solution of α-terpineol (104 mg.) added with ice-cooling. The reaction was then carried out as usual. The product crystallised from aqueous ethanol as dull red needles (26 mg., 9%.) m.p. 127-9°.

I.R. (nujol mull) : 880, 1610, 1725 $cm.^{-1}$ (aromatic ester)

N.M.R. ($CDCl_3$) 1.76 - 2.73 : 8H complex (aromatics)

4.60 : 1H multiplet (H-C=C)

7.95 - 8.05 : 6H multiplet ($-CH_2-$)

8.40 : 9H singlet (methyls)

Analysis. Found C : 62.38 %. H : 6.00 %. N : 6.15%.

$C_{23}H_{25}O_2N_2BrCl$ requires C : 62.58 %. H : 5.71 %. N : 6.34%.

Citronellyl p-(p-bromophenylazo)-benzoate (25).

p-(p-Bromophenylazo)-benzoyl chloride (107 mg.) was suspended in dry pyridine (2 ml.) and citronellol (51 mg.) added with ice-cooling. The reaction was carried out as usual and the product crystallised from aqueous acetone to give lustrous red plates (60 mg., 41 %.) m.p. 60-1°.

I.R. (CCl_4 soln.) : 869, 1610, 1727 $cm.^{-1}$ (aromatic ester)

N.M.R. ($CDCl_3$) 1.7 - 2.7 : 8H complex (aromatic)

4.9 : 1H multiplet ($\underline{H}$-C=C)

5.60 : 2H distorted triplet (-$C\underline{H}_2$-OR)

8.33, 8.40 : 6H 2 singlets ($C\underline{H}_3$-C=C)

7.8 - 8.9 : 9H broad band ($C\underline{H}_3$-R, -$C\underline{H}_2$-)

Analysis. Found C : 62.50 %. H : 6.25 %. N : 6.32 %.

$C_{23}H_{27}O_2N_2Br$ requires C : 62.30 %. H : 6.13 %. N : 6.29 %.

References.

(1) O.Zeitschel, Ber., 39, 1780, (1906).

(2) P.Valenzuela and O.Cori, Tet. Lets., 3089, (1967).

(3) K.W.Greenlee and V.G.Wiley, J. Org. Chem., 27, 2304, (1962).

(4) F.H.A.Rummens, Rec. trav. chim., 84, 1003, (1965).

(5) G.A.Jeffrey, Proc. Royal Soc., A183, 388, (1945).

(6) J.W.K.Burrell, R.F.Garwood, L.M.Jackman, E.Oskay and B.C.L.Weedon, J. Chem. Soc. (C), 2144, (1966).

(7) L.M.Jackman and R.H.Wiley, J. Chem. Soc., 2881 and 2886, (1960).

(8) L.Peyron, Bull. Soc. chim. France, 613, (1960).

(9) E.Hecker, Ber., 88, 1666, (1955).

(10) C.K.Ingold, J. Chem. Soc., 125, 87, (1924).

(11) H.D.Aspon, Org. Syntheses Vol 25, pg. 86, and G.H.Coleman, G.Nichols, C.M.McCloskey and H.D.Aspon, pg. 87, [John Wiley & Sons, New York, 1945, Editor - W.E.Bachmann].

(12) R.B.Bates and D.M.Gale, J. Amer. Chem. Soc., 82, 5749, (1960).