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Terpenes. IX.[1] The Conversion of Sclareol to Manool

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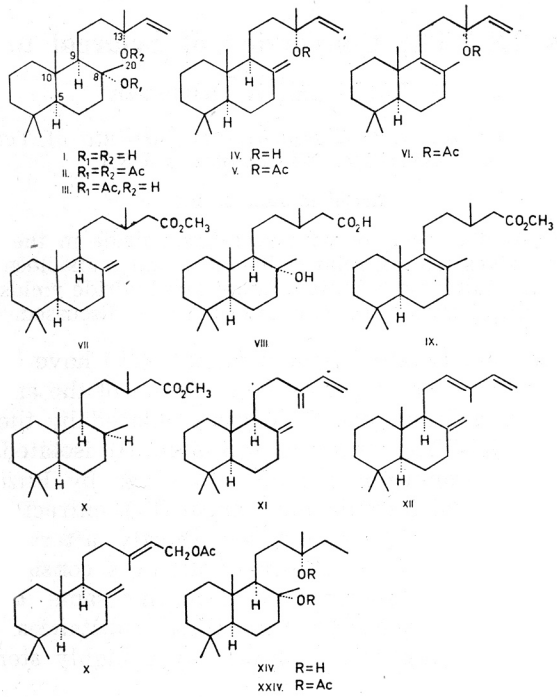
Acetylation of sclareol with acetic anhydride in the presence of pyridine gives mainly sclareoldiacetate and manoolacetate. Reduction of the latter with lithium aluminum hydride yields manool. The stereochemistry of the two diterpenes is discussed.

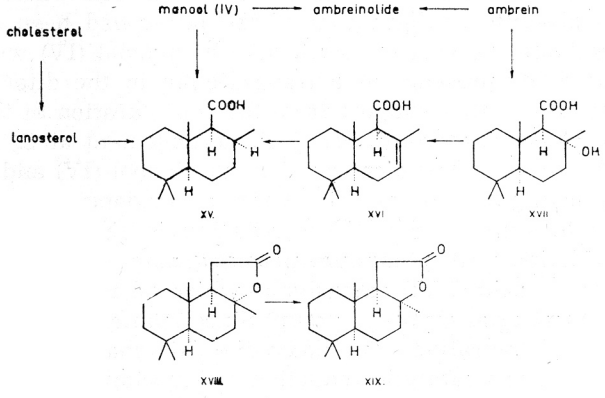
In recent years both sclareol (I) and manool (IV) have become the major sources for the commercial preparation of perfumes of the ambergris type and the highly expensive ambrein has thus been replaced by these more readily available plant materials. The structure of sclareol (I), isolated from the leaves of *Salvia sclarea,* was determined many years ago by Ruzicka and Janot[2], while the correct structual formula for manool (IV), extracted from the wood oil of *Dacrydium biforme,* was established shortly afterwards by Hosking and Brandt[3]. Since these pioneering investigations a considerable number of natural products have been shown to contain this same bicyclic diterpene skeleton and it has been suggested[4] that these substances are synthesized *in vivo* from a common aliphatic precursor by a highly stereospecific cyclization process.

Manool (IV) and sclareol (I) on treatment with hydrogen chloride yield the same trichlorocompound[3] and if one assumes that these changes do not involve the $\Delta^{8,9}$-olefin the two diterpenes must have identical configurations at C_5, C_9 and C_{10}. Their absolute configurations have been established in the following manner. The conversion of both manool (IV) and lanosterol to the same degradation product (XV)[5] proves that the C_{10} methyl group is β in both compounds because lanosterol had been correlated with cholesterol by synthesis[6] and the absolute configuration of the latter had been ascertained by a variety of methods. An earlier correlation[7] of manool (IV) with abietic acid had demonstrated the presence of a trans-decalin in the diterpenes and this assignment received further support from the configuration of the degradation product XV. Evidence concerning the steric arrangement at C_9 in manool (IV) was provided by three independent studies. (a) Manool (IV) and ambrein must have the same configurations at this center as evidenced by the conversion of manool (IV) to ambreinolide.[8] The hydroxyacid (XVII)[9], obtainable from ambrein by oxidation with potassium permanganate, on dehydration yielded the β,γ-unsaturated acid (XVI) exclusively, which on reduction was converted to XV with an equatorial carboxyl group. Since epimerization of the carboxyl group during the dehydration is unlikely, the side chain of manool (IV) must be equatorial. *(b)* If the catalytic reduction of IX available by dehydration of

labdanolic acid[10] (VIII) does indeed occur at the α-face of the molecule, as the molecular model indicates, the dihydroacid X must have an α-hydrogen at C_9. Compound X was shown to be identical with dihydrocativic acid which had been correlated with manool (IV) previously by Zeiss and Grant.[11]



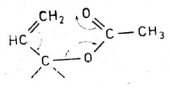
(c) Optical rotation studies led Klyne[12] to suggest the presence of an equatorial side chain at C_9 of these diterpenes. Evidence concerning the configuration of the hydroxyl group at C_8 in sclareol (I) is based on the acid catalyzed isomerization of the *trans*-γ-lactone (XVIII), prepared from sclareol (I), to the more stable *cis*-γ-lactone (XIX).[13] The hydroxyl group at C_8 in I is thus equatorial



These experimental facts leave little doubt that the configurations in the nuclear portion of sclareol and manool are as shown in I and IV. The remaining stereochemical problem is to ascertain the configurations at C_{13} in the aliphatic chain of the two diterpenes. It must be stated here that the formation of an identical trichloroderivative from I and IV does not necessarily demand identical configurations at C_{13} because one of the conversions might have proceeded with inversion to give the most stable halide.

The steric problem at hand could be settled by either *(a)* a conversion of one natural product to the other or *(b)* by a degradation of the two to an aliphatic compound which still contains the asymmetric center originally present at C_{13}. We have chosen the first approach and we would now like to report a conversion of sclareol (I) to manool (IV).

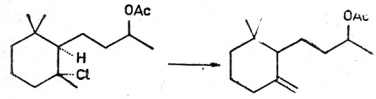
Formally, the conversion of I to IV involves merely a dehydration, but if one considers the problem more carefully it is realized that the double bond to be generated has to be in the unstable exocyclic position while the sensitive tertiary allylic alcohol grouping in the side chain should remain unaffected. It is therefore necessary *(a)*, to effect the dehydration by a process in which the products formed are controlled by reaction rates rather than thermodynamic stability and *(b)*, to avoid an allylic rearrangement. Our initial experiments were concerned with acetate pyrolyses because we had assumed that this reaction would satisfy both requirements. We had previously reported that the pyrolyses of both patchouliacetate[14] and maaliacetate[15] lead mainly to the corresponding olefins with terminal methylene groups and Bailey[16] has shown that this process generally produces the least substituted olefin. Encouraged by these previous findings we had hoped that sclareol-diacetate (II) could be converted to manoolacetate (V) by selective pyrolytic deacetylation. In fact, pyrolysis of II at 250—300° led to a mixture of a hydrocarbon (XI) and an acetate, $C_{22}H_{38}O_2$. Virtually the same products were formed when manoolacetate (V), prepared by acetylation of manool (IV), was subjected to the same conditions. The formation of these products can be rationalized with ease if one assumes that the allylic acetate system present in the side chain undergoes two competing reactions. *(a)* Elimination of acetic acid can lead to either XI or XII or a mixture of the two and both the ultraviolet absorption spectrum (λ_{max} 228 mμ, ε 12000) as well as the infrared spectrum of the triene are in agreement with this postulate. *(b)* Allylic rearrangement of V, presumably through a six atom transition state (A) could result in the formation of the rearranged



acetate (XIII): The structure of XIII is based on its infrared spectrum which has bands at 1665 cm^{-1} (trisubstituted double bond); 1740 cm^{-1} (acetate); 3100, 1643, 888 cm^{-1} (terminal methylene), but no bands associated with vinyl groups.

We next turned to a study of E_2 type elimination reactions. Conformational considerations led us to suppose that dehydration of methylcarbinols with equatorial hydroxyls should lead to exocylic olefins because coplanarity

for antiparallel elimination is best obtained with a hydrogen from the methyl group. Experimental support for this argument was already available at the outset of our study. The base catalyzed dehydrohalogenation of XX, for example, was shown to give more than 60% of the isomer XXI containing the exocyclic double bond.[17] While our work was in progress two papers



XX XXI

appeared, one describing the dehydration of 3α-methylcholestanol[18] by means of phosphorous oxychloride in pyridine solution and the other, the dehydration of labdanolic acid[10] (VIII) by the same method. In both instances high yields of the exocyclic methylene isomers were reported.

Exploratory experiments on the dehydration of sclareol (I) with either phosphorous oxychloride or thionyl chloride in pyridine resulted in the formation of high percentages of water soluble materials which we assumed to be pyridinium salts of the rearranged primary allylic halides. The desired dehydration was eventually effected as follows. Sclareol (I) (1 part) on heating under reflux with acetic anhydride (10 parts) in the presence of pyridine (3.6 parts) was converted to a mixture of a diacetate (II), m. p. 79—80°, a liquid acetate ($C_{22}H_{38}O_2$), and a triene containing two conjugated double bonds. The ratio of these compounds varies with the duration of the treatment. After a reaction time of two hours the main product was the diacetate (II); after five hours the mixture consisted of 43% of the diacetate (II), 36% of the acetates (V+VI) and 3% of the hydrocarbons (XI+XII), while after ten hours only the acetates (V+VI) and the hydrocarbons (XI+XII) were isolable. Acetylation of sclareol (I) (1 part) with acetic anhydride (4 parts) in pyridine (10 parts) at reflux temperature for two hours gave 35% of the same diacetate (II) and 29% of a monoacetate ($C_{22}H_{38}O_3$), m. p. 121—122°, which had infrared bands at 3600 cm^{-1} (hydroxyl); 1726, 1250, 1020 cm^{-1} (acetyl group) and 3080, 1640, 990, 921 cm^{-1} (vinyl group). The band at 1726 cm^{-1} was attributed to the C_8 acetoxygroup because manoolacetate (V) and linalylacetate (XXIII) exhibit absorption at 1737 cm^{-1}, whereas sclareoldiacetate (II) (see below) has bands at both positions. This sclareolmonoacetate accordingly was formulated as III and the large difference in optical rotation between III and I as compared to the small differences between V and IV is in agreement with this assignment.

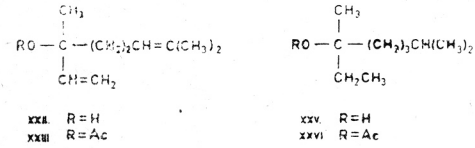
The infrared spectrum of the diacetate had bands at 1737, 1726, 1250, 1020 cm^{-1} (acetates); 3080, 1642, 990 and 921 cm^{-1} (vinyl group) in harmony with structure II which was confirmed by basic hydrolysis to sclareol (I).

The infrared spectrum of the acetate mixture was practically identical with the spectrum of manoolacetate (V), the only difference between the two were the slightly lower intensities of the methylene bands at 3020, 1640 and 887 cm^{-1} in the synthetic sample. The specific rotation of this acetate from sclareol $[\alpha]_D^{25}$ + 30.2° was somewhat higher than that of authentic manoolacetate (V), $[\alpha]_D^{25}$ + 24.5. Both facts are best explained by the assumption that the acetate

represents a mixture of manoolacetate (V) and a small amount of an isomeric substance with a $\Delta^{8,9}$ double bond (VI). This suggestion received strong support from the work of Cocker and Halsall[10] who have shown that the $\Delta^{8,9}$-isomer of anhydromethyllabdanolate (IX) has $[\alpha]_D^{25}$ + 64° whereby the corresponding $\Delta^{8,20}$-isomer (VII) has $[\alpha]_D^{25}$ + 27°. Finally, the acetate (V) was converted to the corresponding carbinol by reduction with lithium aluminum hydride. After purification by chromatography over silica gel a crystalline substance, m. p. 48—50°, was obtained which was identical with manool (IV) as evidenced by comparison of infrared spectra, optical rotations, melting points and mixed melting point. This conversion proves that sclareol (I) and manool (IV) have the same cnfigurations not only at C_{10}, C_5 and C_9 but also at C_{13} and furthermore confirms the equatorial configuration of the hydroxyl group at C_8 in sclareol (I).

We have attempted to determine the configuration of the two diterpenes at C_{13} by comparison of optical rotations of some derivatives with the corresponding compounds of the linalool series. The absolute configuration of linalool has recently been investigated by Prelog[19] and it seems certain that (-) linalool has the (S)-configuration. The pertinent molecular rotation data are listed in Table I.

Comparisons A and C seem to indicate that sclareol (I) has the same absolute configuration at C_{13} as (S) - (-) - linalool (XXII). The figures in section B, unfortunately, cannot be used for a correlation because the change in rotation between II and XXIV is within the limits of experimental error. The



XXII R=H
XXIII R=Ac

XXV R=H
XXVI R=Ac

figures of section D seem to indicate opposite configurations in manool (IV) and (S) - (-) - linalool (XXII). It must be pointed out though that the optical correlations between these two diterpenes and linalool (XXII) are somewhat unreliable because the changes in rotations due to the asymmetric carbon atom in the side chain are all very small while the rotatory contributions of the nuclear asymmetric centers are relatively large. Our conversion of sclareol (I) to manool (IV) clearly established identical configurations at C_{13} in the two natural products and on the basis of the optical comparisons listed in sections A and C of Table I we are inclined to believe that these diterpenes have (S)-configuration at C_{13}. It is of interest to mention here that the linalool recently isolated from *Salvia sclarea* has the (S) -(—)-configuration.[22]

EXPERIMENTAL

Melting points are corrected. Optical rotations were determined in chloroform in a 1 dm. tube. The accuracy of the readings is ± 0.02°. Infra red spectra were determined in 10% solution (carbon tetrachloride or carbon disulfide) with a Perkin Elmer recording spectrophotomer, Model 21C.

TABLE I

A. Sclareol (I) → Dihydrosclareol (XIV)
—9.0° 0.0° Δ = + 9.0°

(S) - (-) - Linalool (XXII) → (R) - (-)Tetrahydrolinalool (XXV)
—22.6° [20] —0.87° [21] Δ = +21.7°

B. Sclareol diacetate (II) → Dihydrosclareol diacetate (XXIV)
—106.8° —108.9° Δ = —2.1°

(S-(—)-Linalylacetate (XXIII) → (R)-(—)-Tetrahydrolinalyl-acetate (XXVI)
—13.0° [20] —5.4° [21] Δ + 7.6°

C. Sclareol monoacetate (III) → Sclareol diacetate (II)
—124° —106.8° Δ = +17.2°

D. Manool (IV) → Manool acetate (V)
+94.0° +81.3° Δ = —12.7°

Linalool (XXII) → Linalylacetate (XXIII)
—22.6° [20] —13.0° [21] Δ + 9.4°

Acetylation of Sclareol (I)

Ten grams of I (recrystallized from petroleum ether, m. p. 102—103.5°) were refluxed with a mixture of 100 ml. acetic anhydride and 36 ml. pyridine for 5 hours. After cooling, the mixture was evaporated under reduced pressure. The residue was digested with saturated sodium bicarbonate solution, extracted with ether, and the ethereal extracts were washed with bicarbonate and then with water. After drying, the solvent was evaporated and the residue (11.6 g. brown oil) was then chromatographed on 200 g. alumina (neutral, act. II). Fraction 1 (eluted with pet. ether) contained 0.30 g. of an oil, presumably a mixture of XI and XII; ultraviolet absorption maximum at 228 mμ, ε 13400 and no hydroxyl or ester band in the infrared. Fraction 2—7: 3.87 g. colorless oil, n_D^{25} 1.4990, $[\alpha]_D^{25}$ + 30.2° (α + 0,78°, c 2.58). Infrared spectrum same as of manool acetate (see below) except a slightly lower baseline and lower intensity of the bands at 3080, 1640 and 887 cm^{-1}. Yield 36% (calculated for manool acetate). Fraction 11—20 (eluted with pet. ether/benzene 1:1): 5.56 g. (43.5%) sclareoldiacetate (II), m. p. 76—79°. For analysis a sample was recrystallized from pet. ether as needles, m. p. 79—80°, $[\alpha]_D^{25}$ — 27.2° (α — 0.64°, c 2.34). Principal infrared bands: Ester groups 1737 (shoulder), 1726, 1250, 1020; vinyl group 3080, 1642, 990, 921; methyl group 1388, 1366 cm^{-1}.

Anal. Calcd. for $C_{24}H_{40}O_4$; C, 73.43; H, 10.27; CH_3CO, 22.05.
Found: C, 73.17; H, 10.43; CH_3CO, 21.83.

Acetylation of Manool (IV)

Under exactly the same conditions IV (3.50 g.) was acetylated with acetic anhydride (21 ml.) and pyridine (7.7 ml.). On chromatography 2.80 g. (70%) of manool acetate (V) was obtained from the crude product. For analysis a sample was distilled at 0.4 mm. (bath. temp. 150°): colorless oil, n_D^{25} 1,4980, $[\alpha]_D^{25}$ +24.5° (α+0·62°, c 2.52). Principal infrared bands: Ester group 1737, 1250, 1020; exocyclic methylene group 3080, 1640, 887; vinyl group 990, 921; methyl group 1388 and 1366 cm^{-1}.

Anal. Calcd. for $C_{22}H_{36}O_2$: C, 79.46; H, 10.92.
Found: C, 79,68; H, 11.19.

Reconversion of Manool Acetate (V) *to Manool* (IV)

To a solution of 300 mg. of V in 10 ml. absolute ether was added 2.5 ml. of a saturated solution of lithium aluminum hydride in ether. After heating under reflux for 2 hours, a small amount of water was added and the etheral solution decanted from the lithium aluminate. After washing with more ether, the combined solutions were dried and evaporated. After distillation of the residue at 0.25 mm. (bath temp. 150—160°) 212 mg. (81%) of a colorless oil was obtained which crystallized on seeding. Recrystallized from pet. ether at —15°: m. p. 51—53°, undepressed on mixing with IV.

Lithium Aluminum Hydride Reduction of the Liquid Product Obtained by Acetylation of Sclareol

Fractions 2—7 (3.87 g.) of the acetylation product of I was dissolved in 25 ml. of ether and slowly added to 336 mg. of lithium aluminum hydride in 25 ml. of ether. The reaction mixture was heated under reflux for 2 hours and 45 minutes and worked up as described above. The product, 3.225 g. (95%) colorless oil could not be crystallized and was therefore chromatographed on 240 g. of silica gel. The first 25 fractions (pet. ether with increasing benzene content) contained only approximately 350 mg., whereas pure benzene (fr. 26—40) eluted 2.84 g. Fractions 27—36 crystallized partially on seeding with manool. Fr. 29—35 were combined (1.80 g.), dissolved in 4 ml. pet. ether and kept at —15° for several days. The total yield of crystalline material was 680 mg. (20%), m. p. 48—50°, undepressed

on mixing with manool (IV). The infrared spectrum was identical in all respects with that of authentic IV. $[\alpha]_D^{25}$ + 33.4° (α + 0.88°, c 2.63). Optical rotation of IV in chloroform: $[\alpha]_D^{25}$ + 32.4° (α + 0.90, c 2.77).

Reconversion of Sclareol Diacetate (II) *to Sclareol* (I)

Sclareol diacetate (600 mg.) was heated to reflux with a solution of 500 mg. potassium hydroxide in 1 ml. of water and 10 ml. of methanol for 3 hours. After standing over night at room temperature the mixture was poured into 50 ml. of water and extracted with ether. After drying and evaporating the solvent, the residue (497 mg.) was recrystallized from pet. ether; 358 mg. (76%), m. p. 102—103.5°, undepressed on mixing with I.

Sclareol Monoacetate (III)

A solution of 2.5 g. of sclareol (I) in 25 ml. of pyridine and 10 ml. of acetic anhydride was refluxed for 2 hours. The reaction was worked up as in the previous experiments. Chromatography on 50 g. alumina (neutral, act. III) and elution with pet. ether gave 1.12 g. (35%) of the diacetate (II) followed by 0.813 g. of an oil, which crystallized on treatment with a few drops of pet. ether. After recrystallization from this solvent, m. p. 121—122°. $[\alpha]_D^{25}$ —35.4° (α — 0.82°, c 2.35). Principal infrared bands: Hydroxyl group 3600 (broad); ester group 1726, 1250, 1020; vinyl group 3080, 1642, 990, 921; methyl group 1388 and 1366 cm^{-1}.

Dihydrosclareol Diacetate (XXIV)

Sclareol diacetate (II), 0.80 g., was hydrogenated on 0.30 g. palladium - charcoal (10% Pd) in 30 ml. of ethyl acetate. 1.12 mole equivalents of hydrogen was taken up within 25 min. The filtrate was evaporated to dryness and gave 0.74 g. of a crystalline residue, 0.70 g. of which was chromatographed on 50 g. silica gel. Pet. ether-ether (30 : 1) eluted 133 mg. of a colorless oil, followed by 536 mg. of crystalline material, eluted with pet. ether-ether (9 : 1). After recrystallization from petroleum ether, it melted at 87—88° $[\alpha]_D^{25}$ —27.7° (α — 0.628°, c 2.26). Principal infrared bands: 2920, 1725, 1465, 1385, 1366, 1250, 1040 and 940 cm^{-1}.

Anal. Calcd. for $C_{24}H_{42}O_4$: C, 73.05; H, 10.73.
Found: C, 73.11; H, 10.69.

Dihydrosclareol (XIV)[23]

Two and one half grams of sclareol (I) was hydrogenated on 1 g. palladium - charcoal (10% Pd) in 80 ml. of ethanol. The filtrate was evaporated and the residue recrystallized twice from ethyl acetate. 1.667 g. needles of m. p. 115—116. $[\alpha]_D^{27}$ + 2.62° (α + 0.118°, c 4.50 in ethanol). $[\alpha]_D^{27}$ 0.0° (α = 0.0°, c 2.69 in chloroform). Principal infrared bands: 3400, 1465, 1385, 1366 and 936 cm^{-1}.

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IZVOD

Terpeni IX. Prevođenje sklareola u manool

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Acetiliranjem sklareola s anhidridom octene kiseline dobiju se kao glavni produkti sklareoldiacetat i manoolacetat. Reakcijom manoolacetata s litijskim aluminijskim hidridom dobije se manool. Prevođenjem sklareola u manool utvrđena je identičnost konfiguracije na C_{13} atomu u ova dva prirodna spoja. Na temelju usporedbe optičkih svojstava autori pretpostavljaju, da oba diterpena imaju (S)-konfiguraciju na C_{13} atomu.

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