SYNTHESIS OF MANOYL OXIDE AND 13-EPIMANOYL OXIDE

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The reaction of sclareol (I) with acetic anhydride [1] or with a mixture of acetic anhydride and acetic acid [2] has given 13-epimanoyl oxide (III) containing, according to Hodges and Reed, 2% of manoyl oxide (II) [3, 4].

Since compounds (I) and (III) have different configurations at C_{13} [4–6], it could be concluded that the formation of 13-epimanoyl oxide in the dehydration of sclareol takes place stereospecifically as an intramolecular S_N2 substitution at C_{13}. In this case, 13-episclareol (IV) should give manoyl oxide (II). It was of interest to study the reaction of 13-episclareol with acetic anhydride and hence to study the mechanism of the dehydration of sclareol to 13-epimanoyl oxide.

When a solution of 13-episclareol (IV) in acetic anhydride was boiled, 13-epimanoyl oxide (III) was obtained, and with a higher yield than from sclareol. Thus, the dehydration of the glycol (IV) takes place with retention of the configuration at the C_{13} asymmetric center, i.e., by a S_N1 mechanism.

Composition of the Products Obtained in the Dehydration of Sclareol and 13-Episclareol with Acetic Anhydride

Experiment No.	Substance	Weight, g	Heating period, hr	Yield of saponified product, g	Composition of the reaction products, %					
					Sclarene	13-epimanoyl oxide (III)	Manoyl oxide (II)	Manool or 13-epimanool	Labda-8(20), 13-dien-15-ol	Initial glycol
1	Sclareol	5	1	4.46	6.05	3.34	8.4	53.8	7.85	19.3
2		2.5	2	2.16	32.9	4.08	6.25	24.6	28.3	–
3		2.5	4	2.26	50.1	4.55	6.25	15.5	20	–
4	13-Episclareol	5	1	4.47	6.3	5.05	2.74	53.5	6.85	22.4

In view of the fact that the change in the configuration of sclareol (I) at C_{13} does not affect the ease of elimination of the hydroxyl group at this center [7], the dehydration of compound (I) to form (III) must also take place by a S_N1 mechanism and, consequently, the interaction of (I) and (IV) with acetic anhydride must give a mixture of manoyl oxide (II) and 13-epimanoyl oxide (III) (their epimers at C_8 cannot be formed since the β side of the molecules of sclareol and 13-episclareol are screened).

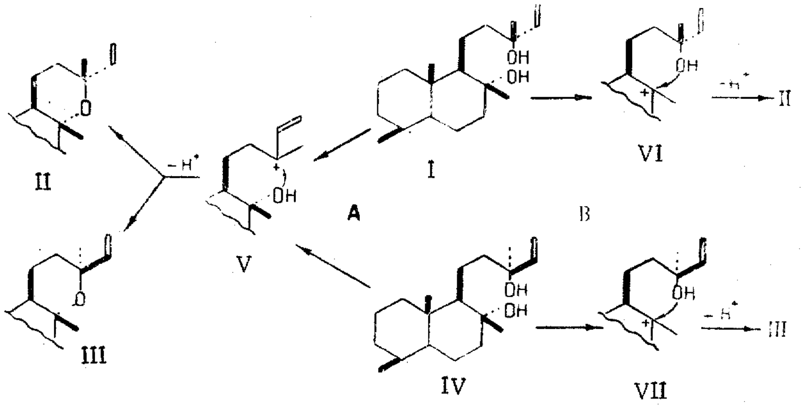
In actual fact, by chromatographing the oxide fractions obtained from the glycols (I) and (IV) in a thin layer of silica gel impregnated with silver nitrate [8], we found that they consisted of two components.

When these fractions were chromatographed on columns with the same adsorbent [9], crystalline 13-epimanoyl oxide (III) was eluted first, and then manoyl oxide (II). The order of elution of the epimeric oxides corresponds to the configuration established for them [4–6]. The equatorial vinyl group of manoyl oxide is less screened than the axial group in 13-epimanoyl oxide, and the complex formed by it with the silver ions must be more stable, i.e., manoyl oxide must be absorbed on silica gel containing silver more strongly than 13-epimanoyl oxide, which agrees with the experimental results.

The table shows the composition of the products obtained by the reactions of sclareol and 13-episclareol with acetic anhydride. It can be seen from this that an increase in the time of the reaction has little influence on the yield of the oxide fraction, although it markedly affects the quantitative composition of the other components [the yield of manool and of labda-8 (20), 13-dien-15-ol fall and the amount of sclarene increases correspondingly (experiments nos. 1-3)].

In the oxide fraction formed from sclareol (I), manoyl oxide (II) predominates, and in that from 13-episclareol (IV) 13-epimanoyl oxide (III) predominates, i.e., the epimer with the same configuration at C_{13} as that in the initial glycol. This can be explained by the fact that the dehydration of the substances (I) and (IV) to a mixture of (II) and (III) by a S_N1 mechanism takes place by two possible routes in parallel. If the dehydration of (I) and (IV) takes place by scheme A through one and the same cation (V), then, apparently, as is normal when the reaction takes place by a

S_N1 mechanism, a mixture of both epimers, manoyl oxide and 12-epimanoyl oxide, is obtained. If, however, the reaction takes place by scheme B, only the epimer with the same configuration at C_{13} as that in the initial glycol is formed, since the attack of the cations (VI) and (VIII) at C_8 is possible only from the α side of the molecule (the β side being screened).



In Dacrydium colensoi, manoyl oxide (II) is found together with manool [10], which is possibly its biogenetic precursor. The biogenetic conversion of manool into manoyl oxide probably takes place through a cation of type (VI).

The figures in the table show that the yield of the oxide fraction does not exceed 11.7%, and the yield of manoyl oxide (from the reaction with sclareol) amounts to only 6–8% (experiments nos. 1–3). Nevertheless, the yield of manoyl oxide in this case is several times greater than when it is synthesized from sclareol in nine stages [11, 12].

When sclareol (I) and 13-episclareol (IV) are boiled with acetic anhydride for a short time, manool and 13-epimanool, respectively, are obtained in good yield (51% taking the recovered glycol into account), while under these conditions only a very small amount of sclarene is formed (experiments nos. 1 and 4) (cf. [2, 13]).

Thus, the treatment of sclareol or 13-episclareol with acetic anhydride is a convenient method for the synthesis of manoyl oxide or 13-epimanoyl oxide, and also of manool or 13-epimanool.

Experimental

Reaction of sclareol (I) and 13-episclareol (IV) with acetic anhydride (general procedure). 1 g of the glycol was dissolved in 4 ml of freshly-distilled acetic acid, and the solution was boiled under reflux at 160° C in the absence of moisture for a predetermined time. The reaction mixture was cooled to 25° C, mixed with a fivefold amount of water, and left to stand for 3 hr. Then the product was extracted with ether. The ethereal extract was washed with water, 5% caustic soda solution, and water again, and was dried with anhydrous sodium sulphate, after which the ether was distilled off.

The resulting product was saponified by boiling for 3.5 hr with an excess of a 10% ethanolic solution of caustic potash. The bulk of the alcohol was evaporated off under vacuum, and the residue was treated with water and extracted several times with ether. The combined ethereal extracts were washed with water and dried with anhydrous sodium sulfate. The ether was distilled off and the product was chromatographed on alumina [activity grade III; ratio of substance to adsorbent (1 : 45)]. The composition of the eluted fraction was checked by thin-layer chromatography on alumina.

Petroleum ether (bp 40°–65° C) first eluted sclarene and then the oxide; a mixture of petroleum ether and benzene (97 : 3) eluted manool (or 13-epimanool); benzene eluted labda-8(20), 13-dien-15-ol; and ether eluted the unchanged glycol.

From the results of thin-layer chromatography on silica gel impregnated with silver nitrate [8] [solvent: petroleum ether–benzene (1 : 1); spots revealed with 2% potassium permanganate], the oxide fractions consisted of two components (R_f 0.25 and 0.52). When chromatographed in a thin layer of alumina, the latter were not separated.

The oxide fraction was chromatographed on a silica gel column containing silver nitrate [9] (ratio of substance to adsorbent 1 : 30). Mixtures of petroleum ether and benzene (90 : 10 and 85 : 15) eluted 13-epimanoyl oxide (III) with mp 100.5°–101.5° C (from acetone), $[\alpha]^{25}$ +43.3° (c 3; chloroform). Its IR spectrum was identical with that of an authentic sample of 13-epimanoyl oxide that we had obtained previously [1].

A mixture of petroleum ether and benzene (4 : 1) eluted manoyl oxide (II), bp 143° – 146° C (0.45 mm), mp 25°–26.5° C; $[\alpha]_D^{24}$ + 18.3° (c 7.4; alcohol), d_4^{24} 0.9821; n_D^{24} 1.5094; MR_D 88.38; calc. 89.14.

Found, %: C 82.22, 82.31; H 11.69, 11.67. Calculated for $C_{20}H_{34}O$, %: C 82.69; H 11.80.

The IR spectrum of (II) was identical with that given for manoyl oxide in the literature [11, 14].

The manool, 13-epimanool and labda-8(20), 13-dien-15-ol were identified by a comparison (chromatographic and spectroscopic) with authentic samples of these compounds.

The IR spectra were taken in carbon tetrachloride in a UR-10 spectrophotometer.

Summary

1. The reaction of sclareol and 13-episclareol with acetic anhydride has been studied. In addition to other products, manoyl oxide and 13-epimanoyl oxide are formed.

2. A mechanism for the dehydration of sclareol and 13-episclareol by acetic anhydride with the formation in each case of a mixture of manoyl oxide and 13-epimanoyl oxide has been proposed.

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