SYNTHESIS OF 13-EPIMANOOL

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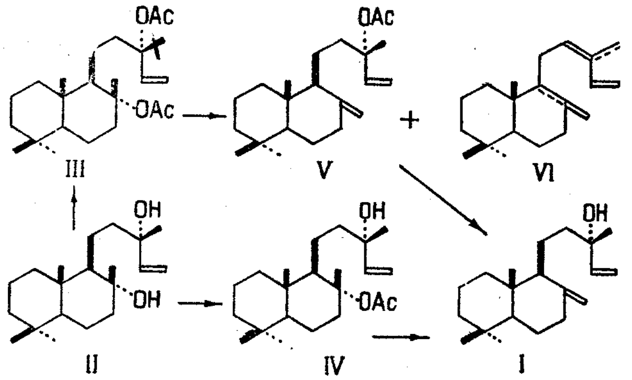
The diterpene alcohol of the labdane group 13-epimanool (I) is the main component of the neutral part of a benzene extract of the roots of Pinus contorta [1]. The structure of the alcohol (I) was established by the production on its hydrochlorination of a trichloride identical with the product formed under the same conditions from manool and also on the basis of spectroscopic data.

For a final identification, it was of interest to effect the synthesis of 13-epimanool (I). The attempt of Barltrop et al. [2] to synthesize compound (I) by the ethynylation of 14, 15-bis-nor-$\Delta^{8(20)}$-labden-13-one with subsequent reduction (after separation of the mixture of epimers) of the 14-dehydro-13-epimanool was unsuccessful.

In the present paper we describe the synthesis of 13-epimanool starting from 13-episclareol (II). The latter was isolated by a published method [3] from Salvia sclarea.

According to the data of Büchi and Biemann [4] and of Ohloff [5], when sclareol diacetate is subjected to pyrolysis the ester group at C_8 is split off considerably more readily than that in the side chain. Since the stereochemistry of 13-episclareol (II) at C_8 is the same as in sclareol and a change in the configuration at the C_{13} asymmetric center should not affect the readiness with which the ester group connected to it is split off pyrolytically, it was to be expected that pyrolysis of episclareol diacetate would take place similarly to the pyrolysis of sclareol diacetate. By pyrolyzing episclareol diacetate (III) we did in fact obtain 13-epimanool acetate (V).



13-Episclareol (II) was acetylated with acetyl chloride in dimethylaniline under the conditions described by Ohloff [5]. In contrast to the case of sclareol, whose diacetate Ohloff obtained in good yield, the esterification of the glycol (II) gave not only the diacetate (III) but also a considerable amount (40%) of the 8-monoacetate (IV). The yield of the latter decreases with an increase in the proportion of acetylating agent, but amounts to 8% even with a two-fold excess of acetyl chloride.

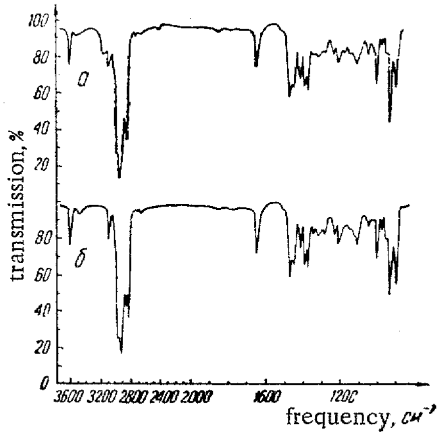
13-Episclareol diacetate (III) was pyrolyzed by distillation in vacuum at 7 mm. Under these conditions, part of it (~ 14%) was recovered unchanged. Under more severe conditions, although substance (III) was completely pyrolyzed, the yield of epimanool acetate (V) fell, since not only was the C_8 acetate group split off but also that at C_{13} with the formation of a large amount (up to 60%) of hydrocarbons (VI).

Saponification of the acetate (V) gave 13-epimanool (I) in the form of a colorless viscous liquid which could not be crystallized. (As is known, Rowe and Scroggins [1] succeeded in crystallizing natural 13-epimanool only after the addition of seeds of crystalline manool, which was not available to us.) However, the physical properties, IR spectrum, and constants of the 3, 5-dinitrobenzoate of the product obtained agree well with the data of the American authors for natural 13-epimanool (I). The IR spectrum of compound (I) is similar to that of the spectrum of manool (figure).

The structure of 13-episclareol monoacetate was established on the basis of the similarity of its IR spectrum to that of sclareol 8-monoacetate [4], and was confirmed by the production of 13-epimanool (I) on its pyrolysis.

Experimental

Acetylation of 13-episclareol (II). With stirring, at a temperature of 5-10°C, 1.1 g (3.1 mole) of acetyl chloride was added to a solution of 1.7 g of (II) (mp 129-130°C, $[\alpha]_D^{20}$ +10.6°) in 5 ml of freshly distilled dimethylaniline. The reaction mixture was stirred for a further 1 hr at the same temperature and was left at 23°C for a day. Then it was diluted with water, ether was added, and this mixture was carefully acidified with cold 5% sulfuric acid. The ethereal layer was separated off, and the aqueous layer was extracted twice with ether. The ethereal extracts were combined and were washed successively with 20% sulfuric acid, water, saturated sodium hydrogen carbonate solution, and water again, and then dried with anhydrous sodium sulfate; the ether was evaporated off in vacuo. The residue (2 g) crystallized. From the results of thin-layer chromatography [neutral alumina of activity grade III; solvent: benzene-ethyl acetate (85:15)], it was found to consist of three components (R_f 0.08, 0.59, and 0.89). It was chromatographed on a column containing 80 g of neutral alumina (activity grade III). A mixture of petroleum ether and benzene (1:1) eluted 1.22 g (57.3%) of 13-episclareol diacetate (III), mp 59.5-60.5°C (from petroleum ether), $[\alpha]_D^{25}$ −14.4° (c 12.7, $CHCl_3$), R_f 0.89; IR spectrum: 928, 996, 1023, 1250, 1371, 1390, 1643, 1727 cm^{-1}. The IR spectrum of substance (III) is similar to that of sclareol diacetate (cf. [4, 5]).



IR spectra of manool (a) (liquid, obtained from sclareol [5]) and 13-epimanool (b) (4% solutions in CCl_4).

Found: C 73.57, 73.36; H 10.42, 10.23. Calculated for $C_{24}H_{40}O_4$, %: C 73.43; H 10.27.

Benzene eluted from the column 0.75 g (39.5%) of 13-episclareol monoacetate (IV), mp 147-148°C (from petroleum ether); $[\alpha]_D^{21}$ −25.3° (c 10.4; $CHCl_3$); R_f 0.59; IR spectrum: 927, 986, 1025, 1370, 1390, 1640, 1723, 3100, 3540, 3620 cm^{-1}. The IR spectrum contained all the frequencies characteristic for sclareol 8-monoacetate (cf. [4]).

Found, %: C 75.51, 75.61; H 10.91, 11.11. Calculated for $C_{20}H_{38}O_3$, %: C 75.38; H 10.92.

Ether and a mixture of ether and methanol (1:1) eluted 30 mg of unchanged 13-episclareol (R_f 0.08).

If the amount of acetyl chloride was increased to 4 moles per mole of substance (II), the yield of the diacetate (III) reached 90% and, correspondingly, the yield of the monoacetate (IV) fell to 8%.

Pyrolysis of 13-episclareol diacetate (III). Five grams of (III) was distilled at 175-190°C (7 mm). The product was chromatographed on 200 g of neutral alumina (activity grade III). Petroleum ether first eluted 1.24 g [23%; the yields are calculated on the amount of (III) that reacted] of a mixture of sclarenes and then 2.28 g (63%) of 13-epimanool acetate (V), bp 148-153°C (0.7 mm); $[\alpha]_D^{20}$ + 33.8° (c 3.7; $CHCl_3$); d_4^{20} 0.9748; n_D^{20} 1.4990, MR_D 100.16; calc. 100.12; IR spectrum: 894, 928, 995, 1020, 1100, 1250, 1370, 1390, 1414, 1642, 1734, 3100 cm^{-1} (cf. [4, 5]).

Found, %: C 79.73, 79.86; H 11.00, 10.92. Calculated for $C_{22}H_{36}O_2$, %: C 79.46; H 10.92.

Benzene eluted 0.69 g of the original diacetate (III) from the column. Under more severe conditions at 220-240°C (40-50 mm), and 5-8 min, substance (III) pyrolyzed completely but under these conditions a considerable amount of sclarenes was obtained and the yield of 13-epimanool acetate (V) did not exceed 40%.

Saponification of 13-epimanool acetate (V). In a flask with a reflux condenser, 2.6 g (V) was boiled for 3.5 hr with a solution of 1.5 g of caustic potash in 17 ml of ethanol and 1 ml of water. The bulk of the ethanol was distilled off under vacuum, and the residue was diluted with water and extracted three times with ether. The ethereal extract was treated in the usual way, and the ether was distilled off under vacuum. This procedure gave 2.1 g (92.5%) of liquid 13-epimanool (I), bp 159-162°C (0.7 mm); $[\alpha]_D^{20}$ + 50.9° (c 2.5; $CHCl_3$). Literature data: mp 36.5-38.5°C; $[\alpha]_D$ +51° [1].

Found, %: C 82.57, 82.41; H 11.44, 11.81. Calculated for $C_{20}H_{34}O$, %: C 82.69; H 11.80.

12-Epimanool 3, 5-dinitrobenzoate. A solution of 560 mg (2 mole) of 3, 5-dinitrobenzoyl chloride in 2.5 ml of dry benzene was added to a cooled solution of epimanool (364 mg) in 2 ml of dry pyridine, and the mixture was left at room temperature for 5 days. The residue obtained after the usual working up crystallized. It was dissolved in the minimum amount of methylene chloride and precipitated with methanol. The precipitation was repeated three times. The yield of 13-epimanool 3, 5-dinitrobenzoate was 270 mg (46%), mp 117.5-119°C (decomp), $[\alpha]_D^{20}$ + 34.1° (c 3, $CHCl_3$). Literature data: mp 116.5-118° (decomp.), $[\alpha]_D^{22}$ +33° [1].

Found, %: C 66.70, 66.59; H 7.33, 7.49; N 5.89, 5.93. Calculated for $C_{27}H_{36}O_6N_2$, %: C 66.92: H 7.49; N 5.78.

Pyrolysis of 13-episclareol monoacetate (IV). 0.2 g (IV) was distilled at 169-173°C (1 mm). According to the results of chromatography on alumina, pyrolysis was only 50% complete.

0.53 g (IV) was heated for 10 min at 225°C (bath temperature) (52 mm) and then the product was distilled at 194°C (10 mm). This yielded 0.4 g (91%) of a liquid product which, from chromatographic and spectroscopic results, was identical with 13-epimanool (I). The 3, 5-dinitrobenzoate with mp 117-119°C (decomp.) obtained from it gave no depression with the 3, 5-dinitrobenzoate of 13-epimanool (I).

Summary

13-Epimanool has been synthesized.

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