CYCLIZATION AND REARRANGEMENT OF DITERPENOIDS.

II. CYCLIZATION OF cis-LABDA-8,13-DIEN-15-OL BY THE COMPLEX OF TITANIUM TETRACHLORIDE WITH N-METHYLANILINE

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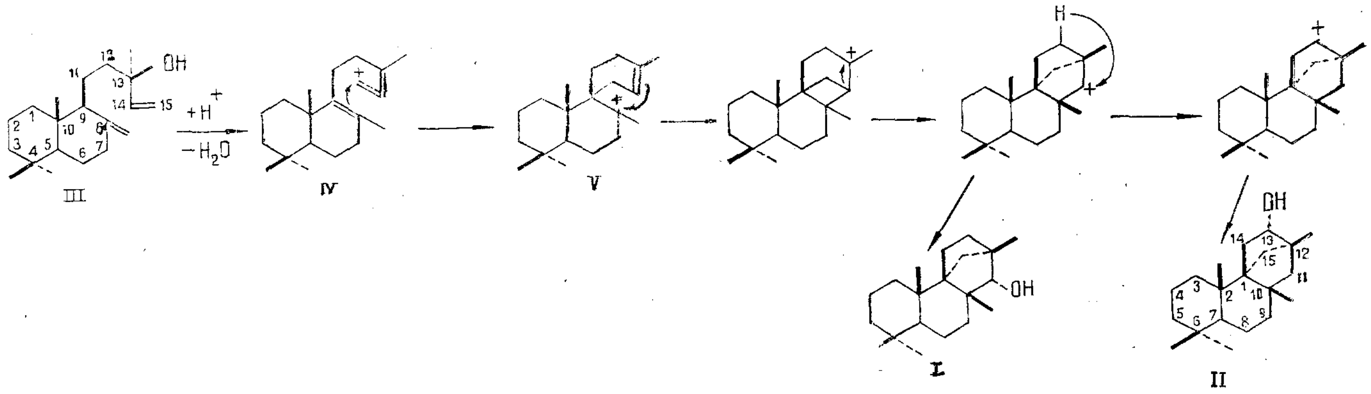
It has been shown that the product of the reaction of cis-labda-8,13-dien-15-ol (I) with the complex of $TiCl_4$ (II) and $PhNHCH_3$ (III) is (1R,2R,7S,10S,12S,13S)-13-chloro-2,6,6,10,12-pentamethyltetracyclo[10.2.1.$0^{1,10}$.$0^{2,7}$]eicosane (IV), the formation of which gives information on the transformation of labdane diterpenoids into tetracycloeicosane derivatives. The reduction of (IV) with $LiAH_4 \cdot CoCl_2$ gave the corresponding hydrocarbon. It has been shown that (IV) is formed by the reaction of 13-hydroxy-2,6,6,10,12-pentamethyltetracyclo[10.2.1.$0^{1,10}$.$0^{2,7}$]eicosane with $SOCl_2$ and $ZnCl_2$. The characteristics of its IR, mass and NMR spectra are given.

It has been shown previously [1] that the reaction of a number of labdane diterpenoids (manool, sclareole, manoyl oxides, acetates of the isometric labda-8,13-dien-15-ols etc.) with acids gives, in addition to other products, 11- and 13-hydroxy derivatives of (1R,2S,7S,10S,12S)-2,6,6,10,12-pentamethyltetracyclo[10.2.1.$0^{1,10}$.$0^{2,7}$]eicosane (I and II) with a new carbon skeleton. We suggested the pathway shown in Fig. 1 (for the case of manool (III)) for their formation.

In order to confirm this we have studied the reaction of 6-labda-8,13-dien-15-ol (VI) with the titanium tetrachloride—N-methylaniline complex.



Scheme 1.

It is known [2] that nerol (VII), on reacting with this complex, gives terpenyl chloride (VIII). By analogy, we expected the formation from the alcohol (VI) of the tricyclic chloride (IX), the solvolysis of which could pass through the carbocation (V) to substances with the same carbon skeleton as the alcohols (I) and (II), thus confirming the proposed mechanism of their formation.

The initial dienol (VI) was synthesized from Δ^8-isomanool (X) [3]. The latter was converted as described previously [4] into a mixture of the acetates (XI) and (XII) giving on saponification with alkali a mixture of the alcohols (VI) and (XIII) which were separated by chromatography on a column of silica gel. Their structure and stereochemistries were shown

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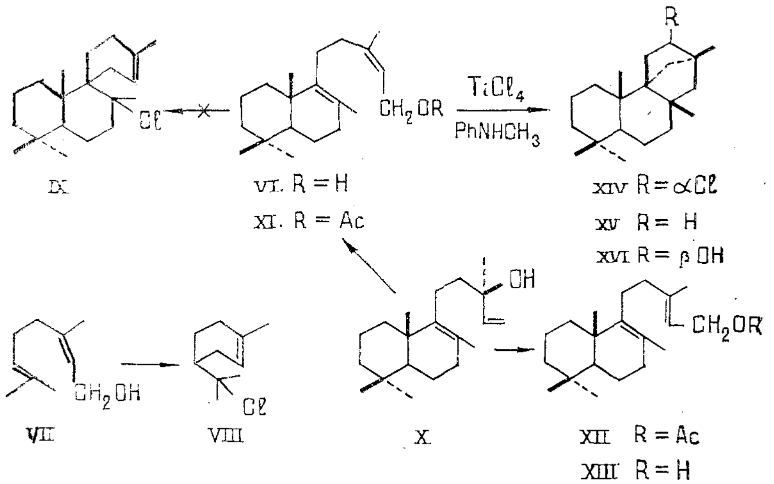
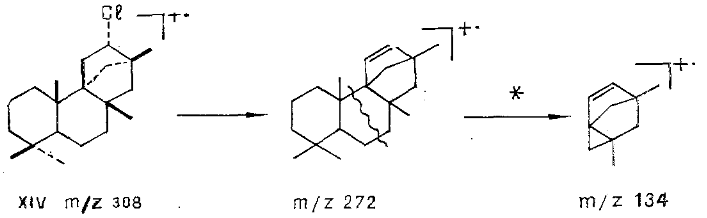


by spectral means. As was to be expected, the isomer (VI) was eluted from the column first and its methyl group at C_{13} resonated in a weaker field than that in the trans isomer (XIII) [5].

When the alcohol (VI) was cyclized with the titanium tetrachloride–N-methylaniline complex, both under the conditions used by Itoh et al. [2] and that at a considerable lower temperature (–70°C), the predominating reaction product (yield ~60%) was (1R,2S,7S,10S,12S,13S)-13-chloro-2,6,6,10,12-pentamethyltetracyclo[10.1.1.$0^{1,10}$.$0^{2,7}$]eicosane (XIV), and not its tricyclic isomer (IX). The structure of the chloride (XIV) followed from its spectral characteristics. Its IR spectra had maxima at 695, 1030, and 1273 cm^{-1}, which are characteristic for a carbon–chlorine bond, and in the PMR spectrum there were the signals of five methyl groups at quaternary carbon atoms and the signal of a proton attached to a carbon bearing a chlorine atom at 3.62 ppm. The muliplet nature of the latter signal showed that the chlorine could not be present at C_{11}. The mass spectrum of the substance under investigation also agreed with the structure (XIV), one of the main and most informative directions of fragmentation of which under the action of electron impact, confirmed by the presence of the metastable ion with m/z 66, is shown in Scheme 2.



Scheme 2.

The structure of compound (XIV) was shown definitively on the basis of its chemical transformations. Thus, it was obtained by the reaction of the alcohol (II) with thionyl chloride and zinc chloride [6]. The alcohol (II) did not react with triphenylphosphine and carbon tetrachloride [7], and with thionyl chloride in dimethylformamide [8] gave only a small yield (~14%) of product (XIV). When the chloride (XIV) was reduced with lithium tetrahydroaluminate in the presence of cobalt chloride [9], the known hydrocarbon (XV) [1] was formed. It must be mentioned that substance (XIV) was fairly inert. Thus, it did not react with lithium tetrahydroaluminate on boiling in tetrahydrofuran [10], with sodium tetrahydroborate in dimethyl sulfoxide [11], or with magnesium.

The chloride (XIV) apparently had the exo configuration, since it was formed on the chlorination both of the alcohol (II) and of its epimer (XVI), i.e., the replacement of their hydroxy groups by chlorine under the action of thionyl chloride and zinc chloride took place by a monomolecular mechanism and, as is known [12], the attack of bornane carbocations by small nucleophiles takes place from the exo side.

Thus, in the reaction of the dienol (VI) with the titanium tetrachloride—N-methylaniline complex the expected product (IX) was not obtained, since in this case the cyclization process proceeded further. Nevertheless, the formation of the tetracyclic chloride (XIV), having the same carbon skeleton as the alcohols (I) and (II), confirms the suggested scheme of the formation of the latter (scheme 1) and, in particular, the fact that the mesomeric allyl carbocation (IV) with the cis configuration at the C_{14}—C_{15} bond took part in the initial stage of cyclization, since it is known that the configuration of the double bond of the allyl alcohols does not change on reaction with the complex of titanium tetrachloride and N-methylaniline [2].

EXPERIMENTAL

The melting points of the substances were determined on a heated Boetius stage. The IR spectra were taken in CCl_4 on a Specord 74 IR spectrophotometer and PMR spectra in CCL_4 on a Telsa BS 467 (60 MHz) instrument with DMS as internal standard, the signals being given on the δ scale. Mass spectra were taken on an MKh 1320 spectrometer with a glass system for the introduction of the sample into the ion source at an ionizing energy of 70 eV. GLC analysis was performed on a Tsvet-106 instrument with a flame-ionization detector. Silica gel L 40/100μ was used for chromatography. Solutions of the substances in organic solvents were dried with anhydrous sodium sulfate. The petroleum used had bp 40-70°C.

Synthesis of cis and trans-Labda-8,13-dien-15-ols (VI) and (XIII). A mixture of the acetates (XI) and (XII) was obtained as described previously [4] from Δ^8-isomanool (X) [3]. A solution of 1.28 g of the mixture of acetates of (XI) and (XII) in 1 ml of ethanol was treated with 3 ml of a 10% ethanolic solution of KOH and the mixture was kept at room temperature for 3.5 h and was then diluted with 15 ml of water and extracted with ether (3 × 20 ml). The extract was washed successively with 10% H_2SO_4, water, saturated $NaHCO_3$ solution, and water again, and it was dried, filtered, and evaporated in vacuum. This gave 1.03 g (92.1%) of a mixture of the alcohols (VI) and (XIII) containing 32% of the cis isomer (VI) and 68% of the trans isomer (XIII) (GLC results; glass column, 1 m × 3.5 mm, filled with 5% of SE-30 on Chromaton N-AW-DMCS; temperature programmed from 180 to 220°C at a rate of heating of 3 deg/min; carrier gas helium (45 ml/min); temperature of the evaporator 230°C).

The reaction product was chromatographed on a column containing 25 g of silica gel. A mixture of petroleum ether and ethyl acetate (19:1) eluted 104.2 mg of the alcohol (VI) in the form of a colored viscous liquid, $[\alpha]_D^{22}$ + 48° (c 7.1; $CHCl_3$). IR spectrum (cm^{-1}): 975, 3475 (weak band), 3615 (OH), 1655 ($>C=C<_H$). PMR spectrum (ppm): 0.82 (s, 3 H, C_{10}—CH_3); 0.85 (s, 3 H), 0.90 (s, 3 H) [$C_4(CH_3)_2$]; 1.55 (s, 3H, C_8—CH_3); 2.95 (br. s, 1 H, OH); 3.97 (d, 2 H, J = 7 Hz, C_{15}—CH_2); 5.25 (t, 1 H, j = 7 Hz, C_{14}—H). The same solvent then eluted 642 mg of a mixture of the alcohols (VI) and (XIII), followed by 243.5 mg of the alcohol (XIII) in the form of a colorless viscous liquid, $[\alpha]_D^{22}$ + 36.5° (c 5.4; $CHCl_3$). IR spectrum (cm^{-1}): 1120, 3365 (very strong band), 3600 (w.) (OH), 1655 ($>C=C<_H$). PMR spectrum (ppm): 0.83 (s, 2 H, C_{10}—CH_3); 0.89 (s, 3 H, 0.94 (s, 3 H), [$C_4(CH_3)_2$]; 1.55 (s, 3 H, C_8—C_3); 1.67 (s, 3 H, C_{13}—CH_3); 2.8 (br.s, 1 H, OH); 3.97 (d, 2 H, J = 7 Hz, C_{15}—CH_2); 5.33 (t, 1 H, J - 7 Hz, C_{14}—H).

Production of the Chloride (XIV). From the Alcohol (VI) [2]. A. At 0°C with stirring, a cooled solution of 170 mg (∿0.9 mmole) of $TiCl_4$ in 2 ml of CH_2Cl_2 was added to a solution of 96.3 mg (0.9 mmole) of $PhNHCH_3$ in 2 ml of CH_2Cl_2. The mixture was cooled to –25°C, a solution of 170 mg (∿0.6 mmole) of the alcohol (VI) in 2.5 ml of CH_2Cl_2 was added to it, the mixture was stirred for another 1 h at the same temperature and was then diluted with 10 ml of water and extracted with ether. The extract was washed with water (2 × 10 ml), with 1 N HCL (5 ml), with water (2 × 5 ml), with saturated $NaHCO_3$ solution (10 ml), and with water (2 × 10 ml) and was dried and filtered and the ether was distilled off. The residue (160 mg) was chromatographed on a column containing 5 g of SiO_2. Petroleum ether eluted 50 mg of a mixture of hydrocarbons and the chloride (XIV), and the 76 mg of the chloride (XIV) with mp 104-105°C (from CH_3CN), $[\alpha]_C^{23}$ + 60.6° (c 1.7; $CHCl_3$). Found, %: C 77.87; H 10.97; Cl 11.00. $C_{20}H_{33}Cl$. Calculated, %: C 77.76; H 10.77; Cl 11.47. IR spectrum (cm^{-1}): 695, 1030, 1273 (Cl). PMR spectrum (ppm): singlets of 3 H each at 0.80, 0.85, 0.88, 1.04, 1.06 (CH_3 groups at quaternary carbon atoms); 3.62 (m, 1 H, C_{13}—H). Mass spectrum (m/z, intensity, %): 308

(M^+, 63), 293 (29), 272 (17), 265 (6), 257 (14), 245 (15), 224 (14), 191 (57), 177 (52), 163 (29), 157 (23), 149 (23), 134 (100), 121 (69), 107 (57), 95 (66), 81 (66), 69 (77), 55 (77), 41 (89).

A mixture of petroleum ether and ethyl acetate eluted from the column 30 mg of a mixture of four substances which were not investigated further. The first fraction (50 mg) was rechromatographed on a column containing 2.2 g of SiO_2, and another 17 mg of the chloride (XIV) was obtained. Its total yield was ∿56%.

B. With stirring, a solution of 72 mg of the alcohol (VI) in 1.2 ml of CH_2Cl2 was added to a solution of the complex obtained as described above from 0.45 mg of $PhNHCH_3$ and 0.75 mg of $TiCl_4$ in 1 ml of CH_2Cl_2 and cooled to −70°C. The mixture was stirred at the same temperature for another 1.5 h and was then worked up as described in paragraph A, and the product (70 mg) was chromatographed on a column containing 2.5 g of SiO_2. This gave 35.1 mg (47%) of the chloride (XIV) with mp 104-105°C (from CH_3N).

From the Alcohol (II). A solution of 595.8 mg of the alcohol (II) in 616 ml of dry dioxane cooled to 5°C was treated with 787.6 mg of SiO_2 and 33.7 mg of $ZnCl_2$ [6]. The mixture was kept at room temperature for 14 h and was then diluted with 25 ml of water and extracted with ether (3 × 20 ml). The extract was washed with water (2 × 15 ml), with saturated sodium bicarbonate solution (15 ml), and with water (2 × 20 ml), was dried and filtered, and the solvent was distilled off. The residue (628 mg) was chromatographed on a column containing 10 g of SiO_2. Petroleum ether eluted 592 mg of the chloride (XIV) with mp 105-106.5°C, identical with the product obtained in paragraph A.

From the Alcohol (XVI). A solution of 87 mg of the alcohol (XVI) in 1 ml of dioxane cooled to 5°C was treated with 115 mg of $SOCL_2$ and 5 mg of $ZnCl_2$. The mixture was kept at room temperature for 2.5 h and was worked up as described above. The product (79 mg) was chromatographed on a column containing 3 g of SiO_2. This gave 71 mg (76.7%) of the chloride (XIV) mp 105-106°C (from CH_3CN), identical with the products of the chlorination of the alcohol (II).

Reduction of the Chloride (XIV). A solution of the chloride (XIV) in 1.5 ml of dry THF was treated with 85 mg of $SOCl_2$ and then with a solution of 200 mg of $LiAlH_4$ in 5 ml of THF [9]. The mixture was boiled under reflux for 1.5 h, the excess of hydride was decomposed with ethyl acetate, and the mixture was acidified with 10% H_2SO_4 (15 ml) and extracted with ether (2 × 10 ml), and the extract was washed with water (2 × 15 ml), $NaHCO_3$ solution (15 ml), and water (2 × 15 ml) and was dried and filtered and the solvent was distilled off. The residue (79.1 mg) was chromatographed on a column containing 8 g of SiO_2. Petroleum ether eluted 57 mg of the hydrocarbon (XV) with mp 72-73.5°C (from CH_2OH), identical with a sample of this material obtained previously [1], 11.4 mg of a mixture of the initial compound and the hydrocarbon (XV), and 8.1 mg of the chloride (XIV).

SUMMARY

It has been established that the main products of the reaction of cis-labda-8,13-dien-15-ol with the complex of titanium tetrachloride and N-methylaniline is (1R,2S,7S,10S,12S,13S)-chloro-2,6,6,10,12-pentamethyltetracyclo[10.2.1.$0^{1,10}$.$10^{2,7}$]eicosane, the formation of which throws light on the mechanism of the cyclization of labdan diterpenoids to derivatives of tetracyclo[10.2.1.$0^{1,10}$.$0^{2,7}$]eicosane.

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HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY OF THE PHYTOECDYSTEROIDS OF *Melandrium nutans*

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With the aid of high-performance liquid chromatography, six phytoecdysteroids have been detected in the butanolic fraction of extractive substances from the epigeal part of *Melandrium nutans* L. Preparative separation has yielded ecdysterone and polypodine B.

The overwhelming majority of ecdysteroids — polyhydroxylated steroids of natural origin fulfilling the role of insect molting hormones — contain in their molecule a carbonyl group and α,β-unsaturation which give a characteristic absorption maximum in the UV spectrum. On the basis of these properties, Nigg et al. [1], using high-performance liquid chromatography (HPLC), separated a number of ecdysteroids: α-ecdysterone and its 5α isomer, 20-hydroxyecdysone and its 5α isomer, 26-hydroxyecdysone, and 22-deoxyecdysone, and also some of their synthetic analogues.

Later [2] HPLC was used for the analysis of a mixture of ecdysterone and inokosterone from *Achyranthes fauriei*. Separation was performed on a Permaphase ODS reversed-phase column using aqueous methanol as the mobile phase. Furthermore, using standard samples of ecdysterone and inokosterone, the optimum conditions for separation and then the percentages of the individual components in the plant extract were determined.

Using HPLC, Dinan et al. [3] found conditions for the differential determination of 3-dehydroecdysone, 20-hydroxy-3-dehydroecdysone, 3-epiecdysone, ecdysone, 20-hydroxy-3-epiecdysone, 2-deoxyecdysone, etc..

The selective effect of stationary and mobile phases has also been studied with several ecdysteroids as examples [4].

We have used HPLC on reversed-phase columns for the separation of a complex mixture of ecdysteroids from the plant *Melandrium nutans* L. (*Silene nutans* L. family Caryophyllaceae). First, on an analytical liquid chromatograph, we selected the conditions for separating the individual ecdysteroids isolated from the fairly well-studied plants *Rhaponticum integrifolium* C. Winkl. [5] and *Silene brahuica* Boiss [6].

Below we give the experimental results for the retention times of some ecdysteroids isolated from the plants mentioned. The substances that we extracted differ from one another by the nature and number of their oxygen-containing functions. The capacity factors of the ecdysteroids (column 25 × 0.46 cm, Zorbax C-8, eluent: 20% isopropanol; rate of flow 1 ml/min):

Integristerone	1.06
Sileneoside	1.10
Ecdysterone	2.67
2-Deoxyecdysone	2.85

In a methanolic extract of *M. nutans* with the aid of analytical HPLC we detected at least six phytoecdysteroids. Two compounds predominated: the universal molting hormone ecdysterone, which is widely distributed in animal and plant organisms, and polypodine B. The retention time of one of the other four phytoecdysteroids, according to our observations,

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