PARTIAL SYNTHESIS OF OCTANOR-13β-DAMMARANE

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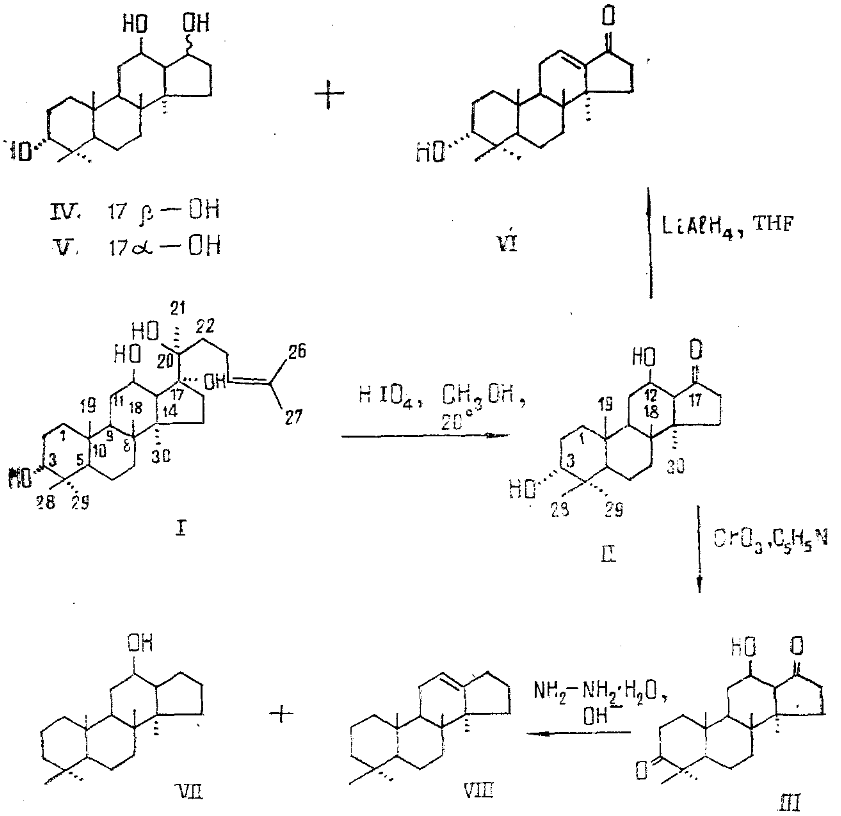
The partial synthesis of octanor-13β-dammarane — one of the basic compounds for calculating the effects of substituents in the ^{13}C NMR spectra of tetracyclic triterpenoids of the dammarane series — has been effected.

One of the most satisfactory methods for the complete assignment of the carbon atoms in the ^{13}C spectra of natural compounds is a comparison of the spectra of related compounds, taking the effects of substituents into account. However, the wide use of these effects requires the existence of a large set of functionally substituted and basic compounds relative to which the substituent effects are calculated. For a number of tetracyclic triterpenoids of the dammarane series such a basic compound may be considered to be octanor-13β-dammarane, which, together with some of its derivatives, is also of interest for structural correlations in the determinations of the structures of unknown triterpenoids by chemical methods.

Within the framework of a study of dammarane triterpenes from Far Eastern species of the genus *Betula* by the ^{13}C NMR spectroscopic method [1, 2], we have performed the partial synthesis of the hydrocarbon (X).



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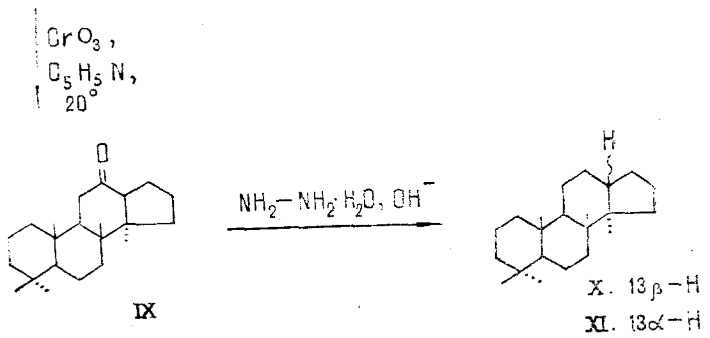


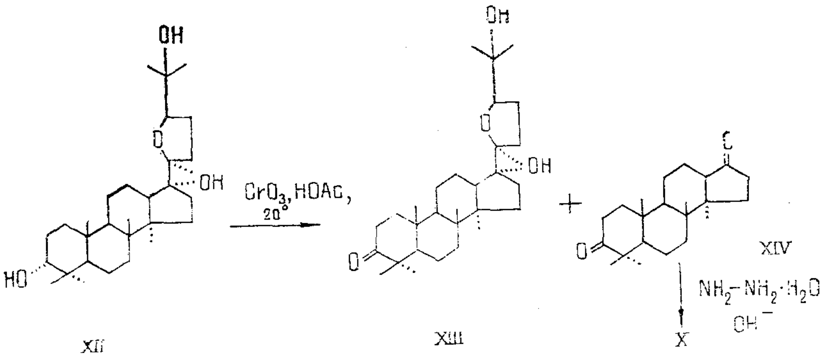
Treatment of the tetraol (I) [3-6] with periodic acid led to the cleavage of the C^{17}—C^{20} bond with the formation of the known dihydroxy ketone (II) [7], which, on oxidation with CrO_3 in C_5H_5N both at room temperature and at a reduced temperature, gave a good yield of the diketol (III), and not the 3,12,17-triketone, as reported previously [7]. Attempts to obtain this triketone by changing the temperature conditions of oxidation and the sequence of the addition of the reactants did not give a satisfactory result. The stability of 12β-OH group in compound (II) to oxidation is apparently connected with the existence of a strong intramolecular hydrogen bond between the 12-hydroxy group and the keto group of the five-membered ring, the presence of which is confirmed by the results of studies by IR and ^1H NMR spectroscopy.

The hydride reduction of compound (II) led to the formation of a mixture of the triols (IV) and (V) epimeric at C^{17} and, which was unexpected, the α,β-unsaturated ketone (VI), obtained previously [4] on severe oxidation of 3α,12β-diacetoxydammarane-25-olfollowed by saponification.

The formation of the hydroxy enone (VI) is probably explained by the fact that a complex of the $LiAlH_4$ molecule with the 12β-OH group of the ketodiol (II) partially blocks the carbonyl group and interferes with its hydride attack, and the subsequent decomposition of the complex when the reaction mixture is worked up leads to the dehydration of the initial β-hydroxy ketone.

The Wolff—Kishner reduction of the diketol (III) gave a mixture of the alcohol (VII) and the unsaturated hydrocarbon (VIII). The ketone (IX) was obtained in good yield from substance (VII) by oxidation with CrO_3 in C_5H_5N. On Wolff—Kishner reduction, the ketone gave a mixture difficult to separate (∿1:1) of the hydrocarbon (X) and (XI) epimeric at C^{13}, the appearance of the cis-hydrocarbon (XI) in the products of the reduction of the ketone (IX) being obviously connected with a considerable epimerization of the initial ketone at C^{13} in the strongly basic medium.

The desired trans hydrocarbon (X) was obtained by dehydrating the side chain of 20(S), 24(R)-epoxydammarane-3α,17α,25-triol (XII) [8].



Oxidation of the latter with CrO_3 in HOAc led to the formation of a mixture of the ketone (XIII) and the diketone (XIV), the Wolff—Kishner reduction of which gave a low yield of only the octanor-13β-dammarane (X). In this case no formation of the cis hydrocarbon (XI) was observed. It is interesting to note that 3β-hydroxyoctanor-13β-dammarane-17-one, which is close in structure to the diketone (XIV), was converted on treatment with bases into the more stable cis form (13α-H) [9].

The trans linkage of rings C and D in (X) was confirmed by the analysis of its ^{13}C NMR spectrum. The signals in the ^{13}C spectrum most sensitive to a change in the stereochemistry of the linkage of rings C and D in (X) and most convenient for determining their position are those of the C^{11}, C^{18}, and C^{30} atoms. The ^{13}C spectrum of (X) shows that the C^{11} and C^{18} signals do not change their position in comparison with the chemical shifts of the corresponding signals in the ^{13}C spectrum of dammar-24-ene-3β-20-diol (X), which shows the transoid linkage of rings C and D in (X). In the case of their cisoid linkage, the C^{11} signal should have been shifted upfield by ∿4.5 ppm through the elimination of the $\gamma_{H^{11},H^{13}}$ interaction [11], and the C^{18} signal downfield by 2-5 ppm through the appearance of two syn-diaxial δ-interactions with C^{16} and C^{17} [11]. The transoid linkage of rings C and D in (X) is also confirmed by the behavior of the C^{30} signal in the ^{13}C spectrum, which shifts upfield by 1.7 ppm in comparison with the C^{30} chemical shift in the spectrum of dammar-24-ene-3β,20-diol, probably as a consequence of the disappearance of the δ-effect of the side chain at C^{17}. A similar δ-effect has been reported previously in the ^{13}C spectra of steroids [12] for an equatorial hydroxy group. With the cisoid linkage of rings C and D, the C^{30} signal in the ^{13}C spectrum of (X) should be shifted downfield by ∿7-9 ppm through the appearance of two additional $\gamma_{H,H}$ interactions [11] with H_a^{15} and H_e^{13}.

EXPERIMENTAL

IR spectra were recorded on a Specord 75 IR spectrophotometer in $CHCl_3$ solution, mass spectra on an LKB 9000 spectrometer at an ionizing voltage of 70 V, and ^1H and ^{13}C NMR spectra on a Bruker HX-90E instrument with working frequencies of 90 MHz for ^1H and 22.63 MHz for ^{13}C at 30°C. Chemical shifts are expressed in the δ scale relative to TMS. The accuracy of measurement amounted to ±0.15 Hz for ^1H and ±1.5 Hz for ^{13}C. The assignment of the signals in the ^{13}C spectrum of compound (X) was made by the method of off-resonance spin decoupling and by a comparison of the calculated ^{13}C spectrum of (X) [11] with the experimental spectrum. Optical rotations were determined on a Perkin-Elmer instrument in a cell 10 cm long. The melting points of the substances were determined on a Boëtius stage. Type KSK SiO_2 was used for chromatography. The individuality of the substances was checked by TLC on SiO_2 in the benzene—ethanol (10:1), hexane—acetone (2:1), and chloroform—ethanol (10:1) systems. The substances were revealed on the chromatograms with a 10% solution of sulfuric acid in methanol.

Oxidation of Dammar-24-ene-3α,12β,17α,20-tetraol (I). A mixture of 320 mg of the tetraol (I), 193 mg of HIO_4, and 30 ml of CH_3OH was stirred at 20°C for 18 h. After the addition of 150 mg of $Ba(OH)_2$, the precipitate was separated off, and the filtrate was evaporated to 1/5 of its original volume and was extracted with ether. After the usual working up of the ethereal extract, the residue was chromatographed on a column of SiO_2. Elution with petroluem ether—acetone (10:1) gave 116 mg (36%) of 3α-12β-dihydroxyoctanordammarane-17-one (II). IR spectrum (ν, cm^{-1}: 1726, 3433, 3552 (independent of the concentration of the solution), 3614. ^1H spectrum (ppm): 0.86 (s, 3 H); 0.92 (s, 3 H); 0.95 (s, 6 H); 1.10 (s, 3 H); 3.28 (broadened singlet, 1 H, OH); 3.42 (t, 1 H, J = 2.2 Hz, H_e^3); 3.87 (sextet, 1 H, $J_{a,a} = J_{a,a} = 10.0$ Hz, $J_{a,e} = 5.3$ Hz, H_a^{12}).

Hydride Reduction of the Dihydroxy Ketone (II). With stirring, a solution of 237 mg of (II) in 6 ml of absolute THF was added dropwise to a suspension of 150 mg of $LiAlH_4$ in 40 ml of absolute THF. The reaction mixture was boiled with stirring for 5 h. Then 0.5 ml of water, 0.5 ml of 15% NaOH, and 1.5 ml of water were added successively. The organic layer was separated off, washed with water, and dried over Na_2SO_4, and the solvent was driven off in vacuum. The residue was chromatographed on a column of SiO_2. Elution with hexane—acetone (50:1) gave 22 mg (90%) of the enone (VI) with mp 220-224°C (hexane) (according to the literature [4]: 224-227°C). IR spectrum (ν, cm^{-1}): 1728, 3415, 3602. ^1H spectrum (ppm); 0.84 (s, 3 H); 0.87 (s, 3 H); 0.98 (s, 6 H); 1.15 (s, 3 H); 3.43 (t, 1 H, J = 2.1 Hz, H_e^3); 6.63 (t, 1 H, J = 3.5 Hz, H^{12}). Washing the column with hexane—acetone (7:1) gave 18 mg (8%) of octanordammaran-3α,12β-17β-triol (IV) with mp 183-185°C, $[\alpha]_D^{23}$ +11.0° (c 0.5; $CHCl_3$). IR spectrum (ν, cm^{-1}): 3426, 3586. ^1H spectrum (ppm): 0.85 (s, 6 H); 0.90 (s, 3 H); 0.94 (s, 3 H); 1.04 (s, 3 H); 3.41 (t, 1 H, J = 2.2 Hz, H_e^3); 3.79 (sextet, 1 H, $J_{a,e} = 5.4$ Hz, $J_{a,a} = J_{a,a} = 10.3$ Hz, H_a^{12}); 4.30 (sextet, 1 H, ΣJ = 21.7 Hz, H_a^{17}).

Elution with hexane—acetone (6:1) gave 43 mg (18% of octanordammarane-3α-12β-17α-triol (V) with mp 178-180°C, $[\alpha]_D^{23}$ −25.6° (c 0.5; $CHCl_3$). IR spectrum (ν, cm^{-1}): 3441, 3597. ^1H spectrum (ppm): 0.84 (s 3 H); 0.89 (s, 3 H); 0.94 (s, 6 H); 1.11 (s, 3 H); 3.40 (t, 1 H,

J = 2.1 Hz, H_e^3); 3.90 (sextet, 1 H, $J_{a,e}$ = 5.1 Hz, $J_{a,a}$ = $J_{a,a}$ = 10.7 Hz, H_a^{12}); 4.43 (sextet, 1 H, ΣJ = 17.5 Hz, H_e^{17}).

Oxidation of the Dihydroxyketone (II). A mixture of 143 mg of (II), 100 g of CrO_3, and 4 ml of C_5H_5N was stirred at 20°C for 48 h and was then diluted with 10 ml of water and extracted with ether (3 × 5 ml). The combined extracts were washed with water and dried over Na_2SO_4, and the solvent was driven off in vacuum. The residue was chromatographed on a column of SiO_2. Elution with a hexane—acetone (15:1) system gave 87 mg (61%) of 12β-hydroxyoctanordammarane-3,17-dione (III) with mp 187-188°C (petroleum ether—acetone). IR spectrum (ν, cm^{-1}): 1696, 1713, 3470 (independent of the concentration of the solution). ^1H spectrum (ppm): 0.94 (s, 3 H); 0.99 (s, 3 H); 1.06 (s, 3 H); 1.10 (s, 3 H); 1.13 (s, 3 H); 3.26 (broad singlet, 1 H, OH); 3.87 (sextet, 1 H, $J_{a,a}$ = $J_{a,a}$ = 10 Hz, $J_{a,e}$ = 4.6 Hz, H_a^{12}).

Wolff—Kishner Reduction of the Hydroxy Diketone (III). A mixture of 78 mg of (III), 5 ml of C_2H_5OH, 5 ml of diethyleneglycol, and 1 ml of 80% hydrazine hydrate was heated in an oil bath at 150-160°C for 4 h. Then 312 mg of KOH was added, the reflux condenser was replaced by a condenser for downward distillation, and the bath temperature was slowly raised to 240°C. After the excess of hydrazine and water had been distilled off, the descending condenser was again replaced by a reflux condenser and the mixture was heated at 230-240°C for another 3 h. Then it was cooled, poured into ice water, and extracted with ether. The combined extracts were dried over Na_2SO_4, and the solvent was driven off in vacuum. The oil so obtained was chromatographed on a column of SiO_2. Washing with the hexane—acetone (100:1) system gave 21 mg (27%) of octanordammar-12-ene (VIII). IR spectrum, (ν, cm^{-1}): 1658. ^1H spectrum (ppm): 0.81 (s, 3 H); 0.85 (s, 9 H); 1.1 (s, 3 H); 5.10 (m, 1 H, ΣJ = 5.6 Hz, H^{12}).

Elution with the hexane—acetone (50:1) system yielded 40 mg (51%) of octanordammarane-12β-ol (VII). IR spectrum (ν, cm^{-1}): 3434, 3602. ^1H spectrum (ppm): 0.82 (s, 6 H); 0.85 (s, 3 H); 0.88 (s, 3 H); 0.97 (s, 3 H); 3.56 (sextet, 1 H, $J_{a,a}$ = $J_{a,a}$ = 10.0 Hz, $J_{a,e}$ = 5.0 Hz, H_a^{12}).

Oxidation of the Alcohol (VII). A mixture of 34 mg of (VII), 35 mg of CrO_3, and 2 ml of C_5H_5N was stirred at 20°C for 12 h. The usual working up led to the isolation of a viscous oil, which was chromatographed on a column of SiO_2. Elution with hexane—acetone (100:1) gave 20 mg (59%) of octanordammarane-12-one (IX). Ir spectrum (ν, cm^{-1}): 1697.

Wolff—Kishner Reduction of the Ketone (IX). A mixture of 20 mg of (IX), 3 ml of C_2H_5OH, 1.2 ml of diethyleneglycol, and 0.3 ml of 80% hydrazine hydrate was treated in a similar manner to the procedure described above. When the SiO_2 column was eluted with hexane—acetone (130:1), 14 mg (70%) of a mixture (≈1:1) of the cis and trans hydrocarbons (XI) and (X) was obtained.

^1H spectrum of octanor-13α-dammarane (XI) (ppm)*: 0.80 (s, 3 H); 0.85 (s, 6 H); 0.96 (s, 3 H); 1.05 (s, 3 H).

Oxidation of 20(S),24(R)-Epoxydammarane-3α,17α,25-triol (XII). A mixture of 50 mg of (XII), 25 mg of CrO_3, 5 ml of glacial HOAc, and 0.5 ml of water was stirred at 20°C for 48 h. The crystals that deposited were separated off and were washed with water, $NaHCO_3$ solution, and water again. The filtrate was extracted with ether. After the usual working up of the ethereal extracts, the resulting residue was combined with the crystals and the mixture was chromatographed on a column of SiO_2. Elution with hexane—acetone (50:1) gave 14 mg (28%) of octanordammarane-3,17-dione (XIV). IR spectrum (ν, cm^{-1}): 1694, 1726. ^1H spectrum (ppm): 0.91 (s, 3 H); 0.96 (s, 3 H); 1.06 (s, 3 H); 1.10 (s, 6 H). Elution with hexane—acetate (13:1) gave 20 mg (40%) of 17α,25-dihydroxy-20(S),24(R)-epoxydammarane-3-one (XIII) with mp 179-182°C (hexane—acetone), $[\alpha]_D^{25}$ +58.4° (c 0.5; $CHCl_3$). IR spectrum (ν, cm^{-1}): 1695, 3432, 3441, 3575, 3601. ^1H spectrum (ppm): 0.94 (s, 3 H); 0.99 (s, 3 H); 1.04 (s, 3 H); 1.08 (s, 3 H); 1.14 (s, 3 H); 1.15 (s, 3 H); 1.22 (s, 3 H); 1.24 (s, 3 H); 3.77 (t, 1 H, J = 6.9 Hz, H^{24}). Mass spectrum (m/z): 474, 456, ($M^+ - H_2O - CH_3$) 397 ($M^+ - 59 - H_2O$), 331 ($M^+ - 143$), 313 ($381 - H_2O$), 143 (100%), 125, 59.

Wolff—Kishner Reduction of the Diketone (XIV). A mixture of 43 mg of (XIV), 5 ml of C_2H_5OH, 2.5 ml of diethyleneglycol, and 0.7 ml of 80% hydrazine hydrate was treated in a similar manner to the procedure described above. Crystallization of the residue from acetone gave 11 mg (26%) octanor-13β-dammarane (X) with mp 78-81°C, $[\alpha]_D^{22}$ +18.6° (c 0.5 $CHCl_3$). ^1H

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*The assignment of the signals was made from the ^1H spectrum of the mixture of (X) and (XI).

spectrum (ppm): 0.78 (s, 3 H); 0.80 (s, 3 H); 0.85 (s, 3 H). ^{13}C spectrum (ppm): 40.8 (C^1), 18.7 (C^2), 42.2 (C^3), 33.5 (C^4), 57.0 (C^5), 18.8 (C^6), 35.7 (C^7), 40.5 (C^8), 51.1 (C^9), 37.6 (C^{10}), 21.4 (C^{11}), 27.8 (C^{12}), 41.6 (C^{13}), 49.0 (C^{14}), 32.1 (C^{15}), 20.9 (C^{16}), 26.7 (C^{17}), 16.2 (C^{18}), 15.6 (C^{19}), 33.5 (C^{28}), 21.6 (C^{29}), 14.8 (C^{30}).

SUMMARY

A partial synthesis of octanor-12β-dammarane — one of the basic compounds for calculating substituent effects in the ^{13}C NMR spectra of tetracyclic triterpenoids of the dammarane series — has been effected from 20(S),24(R)-epoxydammarane-3α,17α,25-triol, isolated from the leaves of *Betula ovalifolia*.

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CATALYTIC REARRANGEMENT OF 1,2-ORTHOACETATES OF α-D-GLUCOSE AND 20(S),24(R)-EPOXYDAMMARANE-3,12β,25-TRIOLS. I.

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The catalytic rearrangement of 20(S),24(R)-epoxydammarane-3,12β,25-triol 3-mono and 3,12-di(α-D-glucose 1,2-orthoacetate)s leads to the formation of the corresponding 12-mono- and 12,25-diglucosides. The anomalous regioselectivity of the catalytic rearrangements of orthoesters of 20(S),24(R)-epoxydammarane-3,12β,25-triols is evidently due to the influence of strong intramolecular hydrogen bonds. Details of the IR, PMR, and ^{13}C NMR spectra, and also the physicochemical constants, of the newly obtained compounds are given.

The catalytic isomerization of 1,2-orthoacetates of sugars and of alcohols of noncarbohydrate nature is a well-known method for the "two-stage" 1,2-transglycosylation of lower and some higher monohydric alcohols [1-7]. This rearrangement has not been studied among orthoesters of polyhydric polycyclic alcohols, containing orthoester and free hydroxy groups in the molecule simultaneously. In order to study the isomerization of such orthoesters and also to obtain analogs of ginseng glycosides, we have performed the synthesis of the (α-D-glucose 1,2-orthoacetates) 20(S),24(R)-epoxydammarane-3α-12β,25-triol (I) and of 20(S),24(R)-epoxydammarane-3β,12β,25-triol (II).

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