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DECARBOXYLATION PRODUCTS OF ECHINOCYSTIC ACID

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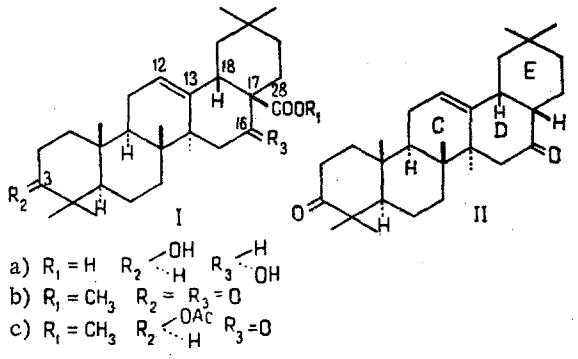
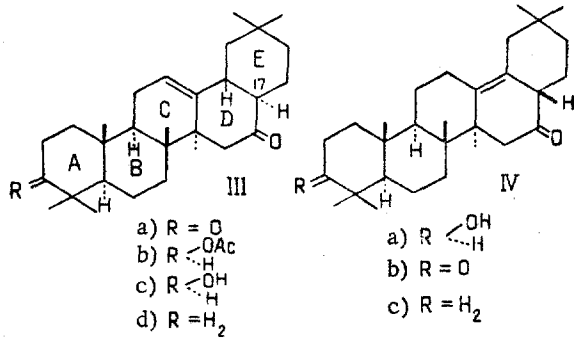
As a result of a study of the structure of echinocystic (3β, 16α-dihydroxyolean-12-en-28-oic) acid (Ia), two isomeric nordiketo compounds have been isolated. The first of them was obtained by the alkaline saponification of the methyl ester of 16-oxooleanonoic acid (Ib) and has been called norechinocystenedione, and the second—isonorechinocystenedione—by the oxidation of echinocystic acid with chromic anhydride [1]. On being boiled with alkali or acid, isonorechinocystenedione is converted into norechinocystenedione [1-3]. Since the isomerization of the isonor compound into norechinocystenedione can be explained by the well-known conversion of cis-α-decalones and many analogous ketones into the trans-forms, isonorechinocystenedione must be regarded [4, 5] as the cis-isomer (II) and norechinocystenedione as the trans-compound (IIIa).

On studying the dispersion of the optical rotation of the acetate of norechinocystenolone, for which formula (IIIb) must be assumed on the basis of considerations due to Bilham and Alves [5], Djerassi showed that the hydrogen at C-17 has the β-configuration and came to the conclusion that the formula of norechinocystenedione must be (II), and that of isonorechinocystenedione (IIIa).





However, we consider that a change in the linkage of the D and E rings, i.e., epimerization at C-17, in the conversion of isonorechinocystenedione into norechinocystenedione is unlikely. If the formation of compound (IIIa) with the trans-linkage of rings D and E were energetically favorable, it would take place even during the oxidation of echinocystic acid; the decarboxylation of β-keto acids takes place through the enolic form [7]. But in such a compound rings C, D, and E form a trans-cis-trans-perhydrophenanthrene system in which the central ring can exist only in the boat form. Even the presence of a double bond, the valence angle of which differs little from 109°, in the 12-13 position in compound (IIIa) does not exert a substantial influence on the shape of ring D. However, its conversion from the chair form into the boat form with weakened bowsprit interactions must increase the energy of the system considerably [8].

The isonorechinocystenedione formed on decarboxylation must have the structure of the more stable isomer (II). Its conversion into the less stable isomer (IIIa) under the action of alkali would contradict the usual ideas.

The change in the molecular rotation in the isomerization of isonorechinocystenedione into norechinocystenedione shows that the isomerization consists in the migration of the double bond from the C-12 to the C-13 (18) position:

Substance	$[M]_D$, deg
Methyl olean-12-ene-3, 16-dion-28-oate (Ib)	+24 [9]
Methyl olean-13 (18)-ene-3, 16-dion-28-oate	−752 [10]
Difference	−776
Isonorechinocystenedione [11]	+364
Norechinocystenedione	−415
Difference	−779

In carrying out an experimental check on a number of previous investigations, we became convinced that norechinocystenolone $C_{29}H_{46}O_2$ is identical with the natural nortriterpene albigenin, the position of the double bond in which has been reliably shown by partial synthesis [11].

For a complete demonstration of the identity of these compounds, we obtained norechinocystenelone by two different methods and prepared its acetate, benzoate, and 2, 4-dinitrophenylhydrazone and the 2, 4-dinitrophenylhydrazone of the acetate, and also norechinocystenedione; their properties did not differ from those of the corresponding derivatives of albigenin.

Substance	deg	Substance	deg
Norechinocystenolene	223–225 $[\alpha]_D$ −113	Albigenin	226–228 $[\alpha]_D$ −114
Norechinocystenolone acetate	210–212 $[\alpha]_D$ −99	Albigenin acetate	211–212 $[\alpha]_D$ −101
Norechinocystenolone benzoate	315–318 $[\alpha]_D$ −72	Albigenin acetate	312–315 $[\alpha]_D$ −72
Norechinocystenolone 2, 4-dinitrophenylhydrazone	262–264	Albigenin 2, 4-dinitrophenylhydrazone	266–268
Norechinocystenolone acetate 2, 4-dinitrophenylhydrazone	255–257	Albigenin acetate 2, 4-dinitrophenylhydrazone	259–260
Norechinocystenedione	201–203 $[\alpha]_D$ −95	Albigenone	200–204 $[\alpha]_D$ −98

The decarboxylation of the methyl ester of 16-oxooleanonoic acid and of the methyl ester of 16-oxo-δ-oleanonoic acid is accompanied by identical changes in the molecular rotation:

Substance	$[M]_D$, deg
Methyl olean-12-ene-3, 16-dion-28-oate	+24 [9]
Isonorechinocystenedione	+364
Difference	+340 [10]
Methyl olean-13 (18)-ene-3, 16-dion-28-oate	−752
Norechinocystenedione	−415
Difference	+337

The similar values of the differences in the molecular rotations confirm the fact that the configuration of the hydrogen at C-17 in norechinocystenedione must be the same as in isonorechinocystenedione, i.e., it is β.

Our proposals concerning the configuration at C-17 agree with Djerassi's results [6]. On the basis of what has been said above, we give the new structure (IVa) for norechinostenolone, making it identical with albigenin and assuming that the configuration of the hydrogen at C-17 will be β; norechinocystenedione must have the corresponding structure (IVb).

In addition to the isomeric nordiones and norechinocystenolone, we have obtained from echinocystic acid norechinocystenone-B in the form of two isomers. One of them was isolated by Bilham [4] and later by Alves [5]. We have called the substance the trans-form. Structure (IIId) has been assigned to it. Molecular rotation calculations that we have performed have shown that this compound is also a derivative of 28-norolean-13(18)-ene:

Substance	$[M]_D$, deg
Methyl olean-12-ene-3, 16-dione-28-oate	+24 [9]
Norechinocystenedione (albigenone)	−415
Difference	−439
Methyl olean-12-ene-3β-ol-16-on-28-oate	−19 [9]

Substance	$[M]_D$, deg
Norechinocystenolone (albigenin)	−469
Difference	−450
Methyl olean-12-ene-16-on-28-oate	−48 [1]
Norechinocystenone-B (transform)	−488 [5]
Difference	−440

Thus, norechinocystenone-B (trans-form) corresponds to structure (Vc).

The NMR spectra of norechinocystenedione and of norechinocystenolone benzoate exhibits signals with $\delta = 5.45$ and $\delta = 5.40$, respectively, which generally correspond to olefinic protons and which we cannot at the moment explain.

The structure of albigenin and albigenic acid has been demonstrated by Barua and Raman [10, 11] by their partial synthesis from echinocystic acid. The interpretation of all the reactions which they performed was based on ideas generally accepted at the present time on the occurrence in such systems of reactions that have been confirmed by the results of many experimental investigations.

Experimental

Melting points are uncorrected. The samples for analysis were dried at 100° C under a residual pressure of 100 mm for 15–20 hr.

Norechinocystenolone (IVa). A. One gram of 3, 28-dihydroxyolean-12-en-16-one diacetate, obtained by Barton's method from primulagenin A, was boiled with 40 ml of a 1% ethanolic solution of caustic potash for 1 hr. The norechinocystenolone was precipitated with water, mp 223–224° C (from methanol), $[\alpha]_D$ −113° (c 0.66; chloroform).

B. A mixture of 650 mg of the acetate of methyl 16-oxooleanolic acid obtained as described by White [1] was boiled for 3.5 hr with 30 ml of a 5% alcoholic solution of caustic potash. The norechinocystenolone was precipitated with water and extracted with ether. The melting point and the specific rotation agreed with literature data [9, 12, 13].

Norechinocystenolone acetate. A mixture of 250 mg of norechinocystenolone, 5 ml of dry pyridine and 5 ml of acetic anhydride was left at room temperature for 24 hr. The reaction mixture was worked up in the usual way. The crystals from methanol had mp 210–212°, $[\alpha]_D$ −99° (c 0.81; chloroform).

Found, %: C 79.31, 79.59; H 10.30, 10.37. Calculated for $C_{31}H_{48}O_3$, %: C 79.44; H 10.32.

Benzoylation of norechinocystenolone. A mixture of 180 mg of norechinocystenolone, 2 ml of pyridine, and 1.5 ml of benzoyl chloride was kept at 80° C for 1 hr and was then poured into cold water. The lower oily layer, on treatment with 60% aqueous alcohol, gave the benzoate with mp 315–318° C (chloroform–methanol), $[\alpha]_D$ −72° (c 0.64; chloroform).

Found, %: C 81.56; H 9.49. Calculated for $C_{36}H_{50}O_3$, %: C 81.46; 9.49.

2, 4-Dinitrophenylhydrazone of norechinocystenolone and its acetate. A solution of 2, 4-dinitrophenylhydrazine in 10 ml of methanol and 0.5 ml of sulfuric acid was added to 100 mg of norechinocystolone in 15 ml of methanol. The 2, 4-dinitrophenylhydrazone was isolated in the form of a precipitate decomposing at 262–264° C (chloroform–methanol).

Found, %: N 9.40. Calculated for $C_{35}H_{50}O_5N_4$, %: N 9.23.

The 2, 4-dinitrophenylhydrazone of norechinocystenolone acetate was obtained similarly; it decomposed at 255–257° C (chloroform–methanol).

Found, %: N 8.78 Calculated for $C_{37}H_{52}O_6N_4$, %: N 8.63.

Isonorechinocystenedione. A solution of 1.3 g of echinocystic acid in 50 ml of acetic acid was treated with 530 mg of sodium dichromate in 35 ml of 80% acetic acid and 5 ml of 10% sulfuric acid. After 30 min, 1 ml of alcohol was added and the mixture was heated to the boil. The reaction product was precipitated with water, filtered off, and dissolved in ether. The ethereal extract was washed with dilute sodium carbonate solution and with water, after which the solvent was distilled off. The residue consisted of isonorechinocystenedione with mp 218–220° C (from methanol), $[\alpha]_D$ +86.5° (c 0.83; chloroform). Literature data: mp 230–233° C, $[\alpha]_D$ +85.7° [1]; mp 210–211° C [14].

Preparation of norechinocystenedione (IVb). A. 0.5 g of isonorechinocystenedione was boiled for 1.5 hr in 50 ml of 95% ethanol containing 0.5 g of caustic potash. The mixture was poured into water and the reaction product was extracted with ether. After the solvent had been driven off, a yellow oil was left from which crystals were obtained with mp 201–203° C (from methanol), $[\alpha]_D$ −95° (c 0.93; chloroform). Literature data: mp 200–203° C, $[\alpha]_D$ −93.2° (dioxane) [2], mp 203–205°, $[\alpha]_D$ 94.2° (dioxane) [3].

B. A solution of 50 mg of sodium dichromate in 10 ml of 80% acetic acid was added to 100 mg of norechinocyste-

nolone in 15 ml of glacial acetic acid. After 30 min, 1 ml of ethanol was added to the mixture and the reaction product was precipitated with water. The precipitate was filtered off, dissolved in benzene, and filtered again through a column containing 10 g of alumina. This gave substance (IVb), $C_{29}H_{44}O_2$, with mp 200–202° C (from methanol).

Summary

1. The structure of norechinocystenolone has been established and it has been shown to be identical with the natural nortriterpene albigenin.

2. The isomerization of isonorechinocystenedione into norechinocystenedione consists in the migration of a double bond from 12–13 position to the 13–18 position.

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