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NONENZYMATIC STEREOSPECIFIC CYCLIZATION OF ISOPRENOIDS

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The cyclization of 1,5-dienes under the action of acids may be regarded as a model for studying the chemical regularities of the biosynthesis of cyclic isoprenoids from acyclic ones. The features of the structural direction of this reaction have been clarified to a considerable extent; however, its stereochemistry and mechanism have so far been studied very little. The spatial course of cyclization has been investigated most rigorously using the example of a 2,6,10-triene—apofarnesylic acid—and it has been shown that the reaction proceeds nonstereospecifically, with formation only of derivatives of the trans-decalin series, irrespective of the configuration of the 6,7-double bond in the initial acyclic molecule (⌒1). Similar nonstereospecificity was also observed in a number of other 2,6,10-trienes containing a carboxyl group conjugated with the 10,11-double bond. From these data it was concluded (⌒2) that, in general, a stereospecific course of isoprenoid cyclization can be ensured only with the participation of enzymes. However, cyclization of geranylacetone (⌒3) under the action of acids proceeds stereospecifically, and, depending on the cis or trans configuration of the 6,7-double bond, hexahydrochromene derivatives with cis or trans ring fusion are formed. This allowed us to suppose that the stereospecific course of nonenzymatic cyclization of isoprenoids is feasible provided that an effective nucleophilic center is present in the molecule. The purpose of the present work was to determine whether stereospecific formation of a decalin system is possible in the acid cyclization of a 2,6,10-triene that does not contain an electron-accepting group conjugated with the 10,11-double bond.

As a model, individual stereoisomers of farnesylacetone (I) were selected: cis-6,7-trans-10,11 (Ia) and trans-6,7-trans-10,11 (Ib). The reaction was carried out under conditions previously developed by us for the structurally selective and stereospecific cyclization of geranylacetone. As was shown by gas–liquid chromatography, cyclization of Ia and Ib proceeds with structural ambiguity, giving a mixture of products. Figure 1 presents typical chromatograms of reaction mixtures obtained by cyclization under identical conditions of trans-6,7-farnesylacetone (curve A) and cis-6,7-farnesylacetone (curve B). The mixture can be separated into a number of narrower fractions only by chromatography on neutral SiO_2. Thus, on chromatographing the cyclization product of cis-6,7-farnesylacetone (Ia) (curve B), two main zones can be isolated (together amounting to 90% of the weight of the initial mixture) with R_f 0.6 and 0.1 (curves V, G). The fractions with R_f 0.6 were studied in greatest detail; from them, by purification through the semicarbazones of the corresponding oxo ketones, individual products (IIa and IIb) were isolated. The structure of IIa and IIb as tricyclic unsaturated oxides was demonstrated by the reactions shown in the scheme, and also by the data of IR and NMR spectra.

It turned out that the IR, NMR, and mass spectra of IIb and of an authentic sclareol oxide obtained by oxidation of natural sclareol coincide completely. They are also identical according to gas-liquid chromatography on two phases and according to R_f on alumina and silica gel. From this it follows unambiguously that the tricyclic oxide obtained upon cyclization of trans-6,7-trans-10,11-farnesylacetone is racemic sclareol oxide with trans-anti-trans ring fusion, as shown in formula IIb.

The isomeric oxide obtained from the cis-6,7-isomer of farnesylacetone (Ia) differs appreciably from IIb according to TLC data (the relative retention volume of IIa with respect to IIb is 1.05 on Apiezon M and 1.12 on neopentyl glycol adipate). The IR and, especially, NMR and mass spectra of these two products differ sharply from one another. Since the starting ketones Ia and Ib differed only in the configuration at the 6,7-double bond, it could be assumed that the isomeric tricyclic products obtained from them upon cyclization, having one and the same skeleton, would also differ only in configuration at the 5,10 bond, i.e.,

[reaction scheme with compounds Ib, IIb, IIIb, Ia, IIa, IIIa, hydrogenation product, and stereochemical annotations]

stereochemistry of the fusion of rings A/B*. Since the trans fusion of rings A/B for isomer IIb has been proved, cis fusion of these rings should be assigned to IIa. Analysis of the NMR spectra confirms this assumption.

In interpreting the NMR spectra (Fig. 2), we assume that in the general case the chemical shift of the angular methyl group at C_{10} lies in the region of the strongest fields, which is consistent with literature data on the NMR spectra of di- and triterpenes (4,5). On the other hand, it is known that the transition from a trans fusion of rings A/B to a cis fusion leads to a shift of the signal of the angular methyl group into the region of weaker fields by 0.1-0.13 ppm (6,7). In our case the chemical shift for the angular CH_3 group at C_{10} for oxide IIb, which has a trans fusion of rings A/B, is 0.76 ppm. The chemical shift of the protons of the angular methyl group at C_{10} for oxide IIa is 0.875 ppm. The observed difference $\delta_{10-\mathrm{CH3,\ IIa}} - \delta_{10-\mathrm{CH3,\ IIb}} = 0.115$ ppm, which corresponds to the assumption of the presence of a cis fusion of rings A/B in oxide IIa. Analysis of the mass spectra of IIa and IIb also confirms the presence of a cis-decalin system in isomer IIa, of which a more detailed account will be given later.

* The trans fusion of rings B/C in isomer IIa, as in IIb, follows from the data

obtained by us on the stereochemistry of formation of the hexahydrochromene system upon cyclization of geranylacetone.

In accordance with these data, for IIa as well one may assume a cis-syn-trans or cis-anti-trans stereochemistry of ring fusion. The cis-syn-trans configuration represented in formula IIa seems to us more probable on the basis of the generally accepted hypothesis concerning the regularities of stereospecific cyclization of isoprenoids (1). It has already been pointed out that, in addition to IIa (or IIb), upon cyclization of Ia (or Ib) a number of other products are also formed. Their nature has not yet been established, but they all differ sharply from II (a and b) either according to GLC data or in their behavior during chromatography on silica gel (see Fig. 1). The relative amount of the individual products depends on the conditions under which the cyclization is carried out (see Table 1).

It is essential to note that, although the yield of products IIa and IIb varies greatly depending on the reaction conditions, the stereospecificity of their formation is completely retained, and the admixture of IIa in IIb and of IIb in IIa does not exceed 3-5% (relative).

Fig. 1. Chromatograms obtained on Apiezon M (10% on Chromosorb W, 200°, 60 ml/min He). A —cyclization of Ib, —cyclization of Ia (see No. 7 in Table 1), —zone with R_f 0.6, —zone with R_f 0.1 (on silica gel)

Fig. 2. NMR spectra of IIa and IIb (60 MHz, CCl_4)

The stereospecific formation of trans-decalin derivatives (IIb) upon cyclization of trans-6,7-farnesylacetone (Ib) and of cis-decalin derivatives (IIa) upon cyclization of cis-6,7-farnesylacetone (Ia) is the first example of a nonenzymatic stereospecific cyclization of isoprenoids. These data may be regarded as chemical substantiation of the principal postulates of Ruzicka (8). The result obtained also confirms the correctness of our assumption that the 10,11-double bond, not deactivated by conjugation with the carboxyl group, possesses sufficient nucleophilicity to ensure stereospecific forma-

formation of a bicyclic system. Apparently, this conclusion is also applicable to the cyclization of other isoprenoids containing only isolated double bonds.

Experimental Part

The starting ketones Ia and Ib were obtained by the described procedure (9). All experiments to select the optimal conditions for obtaining II (a or b) were carried out according to the standard procedure: to a solution of the ketone in nitropropane, with vigorous stirring, at −70°, a solution of sulfuric acid in a minimal amount of nitropropane was added.

Table 1

No. of exp.	Amount of H_2SO_4, in moles per mole of I	Amount of $C_3H_7NO_2$, in ml per 1 g of I	Time, min	Content of oxide II (a or b), % upon cyclization* Ia	Content of oxide II (a or b), % upon cyclization* Ib
1	10 : 1	300 : 1	30	17	23
2	3 : 1	100 : 1	360	–	17
3	5 : 1	100 : 1	120	–	22
4	10 : 1	100 : 1	10	24	34
5	40 : 1	100 : 1	10	36	41
6	5 : 1	10 : 1	10	28	30
7	40 : 1	10 : 1	10	42	45

* Calculated from gas-liquid chromatography data, taking into account the results of separation on silica gel.

Samples were periodically withdrawn into a test tube cooled to −70°, and after the usual work-up were analyzed by chromatography (Table 1, Nos. 1-6). For the preparative preparation of oxides IIa or IIb a somewhat different procedure was used (experiment No. 7): to a solution of 4 ml of acid in 4 ml of nitropropane cooled to −70°, with stirring, a cooled solution of 0.5 g of ketone in 1 ml of nitropropane was added at such a rate that the temperature did not exceed −65°. The mixture was kept at this temperature for 5-10 min and poured into a stirred mixture of ice water and petroleum ether. After the usual work-up, 0.4-0.45 g of a mixture was obtained (see chromatograms in Fig. 1), which was separated by chromatography on neutral KSK silica gel on 24 × 21 cm plates (layer thickness 2 mm) in the benzene-ethyl acetate system (20 : 1). To develop the chromatogram, a control plate, 24 × 3 cm, was simultaneously set up and then placed in iodine vapor. In this way, from 1.4 g of the cyclization product of Ia or Ib, 0.55 g of a fraction with R_f 0.6 and 0.65 g of a fraction with R_f 0.1 were obtained (Fig. 1 shows chromatograms of these fractions for Ia).

From the fractions with R_f 0.6, by the usual method, in a yield of about 50%, the semicarbazones of the oxoketones were obtained, which were purified by crystallization from aqueous methanol. The semicarbazone of the oxide obtained from Ia (IIIa) had m.p. 189-190°. Found, %: C 67.11; 66.92; H 10.83; 10.56. $C_{19}H_{35}O_2N_3$. Calculated, %: C 67.61; H 10.45. The semicarbazone of the oxide obtained from Ib (IIIb) had m.p. 171-172°. Found, %: N 12.51, 12.52. Calculated, %: N 12.45. For the hydrolysis of IIIa and IIIb, they were stirred with a mixture of 5 N sulfuric acid and petroleum ether for 2 hours. After the usual work-up, IIa was obtained: Found, %: C 82.41; H 11.61. $C_{18}H_{30}O$. Calculated, %: C 82.38; H 11.52. IIb: Found, %: C 82.19; H 11.77. Calculated, %: C 82.38; H 11.52. Both products are individual according to gas-liquid chromatography data on two phases.

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Note: Figure translations are in progress. See original paper for figures.