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Abstract

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A NEW ROUTE TO THE STEREOSPECIFIC CYCLIZATION OF ISOPRENOIDS

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Using the example of the *cis*-6,7- and *trans*-6,7-stereoisomers of farnesylacetone (Ia and Ib, respectively), we have for the first time demonstrated the feasibility of stereospecific cyclization of isoprenoids (ˆ1). In the present work the cyclization of α- and β-monocyclofarnesylacetones (IIa and IIb, respectively) was studied. We found that in the case of IIa or IIb, as also in the case of Ia or Ib, the reaction is structurally nonselective. However, in the mixture formed it is always possible to identify a tricyclic oxide product (IIIa or IIIb), the content of which can reach 70% (i.e., approximately twice as much as in the cyclization of Ia or Ib). In pure form it can be isolated by the previously described procedure (ˆ1) in up to 40% yield. By means of IR and NMR spectra, as well as gas–liquid chromatography on two phases, it was possible to show that the tricyclic oxides obtained from IIa and IIb (IIIa and IIIb, respectively) are different; moreover, IIIb is identical with the product previously obtained from Ib sclareol oxide with a trans-anti-trans ring fusion, while IIIa is identical with its *cis*-syn-*trans* isomer obtained from Ia (ˆ1). From these data it follows that the cyclization of α- and β-monocyclofarnesylacetones proceeds stereospecifically,* with derivatives of *cis*-decalin (IIIa) being formed from the α-isomer (IIa), and derivatives of *trans*-decalin from the β-isomer (IIb). It is interesting that the cyclization of α- and β-monocyclofarnesyl ethers proceeds nonstereospecifically, with formation only of derivatives of the *trans*-decalin series, which may be explained by the reduced nucleophilicity of the $3',4'$-double bond.

The result obtained by us shows that the stereochemistry of ring fusion in decalin derivatives formed upon cyclization can be determined not only by the configuration of the 6,7-double bond in the original acyclic 2,6,10-triene, but also by the α- or β-position of the double bond in the ring of the corresponding monocyclic analog; this had previously been observed only for the formation of hexahydrochromene systems (ˆ2).

The regularity established by us opens up fundamentally new possibilities for the stereospecific synthesis of polycyclic compounds.

Along with the isomeric oxides III (a or b), in the cyclization of IIa and IIb there is always formed an appreciable amount of a bicyclic product (IV), sharply different from III in gas–liquid chromatography and in R_f on alumina and silica gel.** It is characteristic that this bicycloproduct is not an intermediate in the formation of the tricyclic oxides, since it is not converted into the latter either with time or under more severe reaction conditions. From IIa and IIb different bicycloproducts are formed (IVa and IVb, respectively); however, IVa is capable of being converted into IVb under more severe conditions. Thus, under the conditions of experiment No. 1 (see table), in the cyclization of IIa the resulting mixture IV contains 55% IVa and 45% IVb, while under the conditions of experiment No. 2, 17% IVa and 52% IVb. The isomerization IVa → IVb can also be observed when the temperature of the experiment is raised or when an additional amount of sulfuric acid is added. The cis- or trans-$3', 4'$-isomers II give one and the same substance IVa. All this makes it possible to propose for IVa and IVb the structures shown in the scheme, which are also confirmed by a number of transformations and by IR-spectral data.

(Scheme: compounds labeled α (IIa), (IIIa), (IVa); β (IIb), (IIIb), (IVb), (IVc), (IVa), (IVb); reagents and conditions shown include $1M\ H_2/PtO_2$, SiO_2, 150°, $POCl_3/C_5H_5N$; annotations: "94% $C{=}O$ groups" and "5% $C{=}O$ groups.")

In addition to III and IV, the mixture of cyclization products contains other substances, the nature of which has not yet been elucidated, but their content, as a rule, does not exceed 10-15%. From the data in Table 1 it is easy to see that, for the formation of III, the most favorable conditions are severe ones—minimum solvent and maximum sulfuric acid. Conversely, the largest amount of the bicyclic product IV (content up to 90%) is formed under comparatively mild conditions (a large amount of solvent, a slight excess of acid). It should be noted that under all conditions the stereospecificity of the reaction forming III is retained.

Table 1*

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* The degree of stereospecificity reaches 95% in the cyclization of IIb and 88% for the cyclization of IIa.

** During chromatography on silica gel (neutral), IV is quantitatively converted into a hydration product, which readily eliminates water upon distillation or in the chromatograph vaporizer with formation of the starting IV.

Series No.	Amount of H_2SO_4, mol per mol of ketone	Amount of $C_3H_7NO_2$, ml per 1 g of ketone	Time, min	Oxide content during cyclization, %: Ia	Oxide content during cyclization, %: Ib	Oxide content during cyclization, %: IIa	Oxide content during cyclization, %: IIb	Ratio III:IV in the mixture during cyclization: Ia	Ratio III:IV in the mixture during cyclization: Ib	Ratio III:IV in the mixture during cyclization: IIa	Ratio III:IV in the mixture during cyclization: IIb
1	10 : 1	300 : 1	30	17	23	7	4	1 : 4	1 : 2,3	1 : 10	1 : 95
2	10 : 1	100 : 1	10	24	34	20	3	1 : 2	1 : 1	4 : 3	1 : 30
3	40 : 1	100 : 1	10	36	41	40	9	1,3 : 1	2,3 : 1	1 : 1	1 : 9
4	40 : 1	10 : 1	10	42	45	60	50	2,6 : 1	2,6 : 1	8 : 1	1,2 : 1

* All experiments at −70°.

Comparison of the chromatograms of the reaction mixtures (Fig. 1) obtained in the cyclization of Ia, b and IIa, b made it possible to clarify somewhat the question of the structural direction of cyclization of I. It turned out that, upon cyclization of both Ia and Ib, together with III (a and b) a bicyclic product is also formed, identified as IVb by comparison with an authentic sample by GLC on two phases, and also by R_f on silica gel and alumina. For the case of cyclization of Ia (Fig. 2), the entire process of formation of IVb can be traced as a sequence of three reactions: a) closure of the pyran ring (IVb), b) closure of the cyclohexene system with formation of IVa, and c) isomerization of the latter into IVb. The ease with which reactions (b) and (c) proceed does not permit the process to be stopped at any one of the stages. Evidently, the formation of IVb during the cyclization of Ib proceeds analogously, with the only difference that, owing to the trans-configuration of the 6,7-double bond, stage (b) immediately leads to IVb (3). It is also evident from the data of Table 1 that the formation of tricyclic products from acyclic compounds (Ia, b) proceeds more readily than from monocyclic compounds (IIa, b) (see series 1 or 2), and, consequently, the latter cannot be intermediates in the cyclization of the former. This also follows from the fact that, under the mildest conditions of cyclization of I, it is not possible to observe the formation of products IIa or IIb.

Fig. 1. Chromatograms of the experiments of series 3 of Table 1, obtained on Apiezon M

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Fig. 2. Chromatogram of an experiment on the cyclization of Ia under the conditions of series 1 with sampling over time

Figure 2: Fig. 2. Chromatogram of an experiment on the cyclization of Ia under the conditions of series 1 with sampling over time

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Experimental Part

The starting ketones were obtained from the corresponding dihydro-α- and dihydro-β-ionones by the standard procedure and were purified through semicarbazones. The pure trans-3′,4′-stereoisomer of α-monocyclofarnesylacetone (IIa) obtained in this way had the following constants: b.p. 125–127° at 1 mm, n_D^{20} 1.4884. The semicarbazone has m.p. 115–116°.

Found, %: C 71.22, 71.02; H 10.50, 10.51
$C_{19}H_{33}ON_3$. Calculated, %: C 71.43; H 10.41

Similarly, for the trans-3′,4′-isomer of β-monocyclofarnesylacetone: b.p. 125–127° at 1 mm, n_D^{20} 1.4895. The semicarbazone has m.p. 125–126°.

Found, %:	C 71.58, 71.60;	H 10.61, 10.65
$C_{19}H_{33}ON_3$. Calculated, %:	C 71.43;	H 10.41

All experiments on selecting the conditions were carried out according to the standard procedure described previously ([1]), and their results are summarized in Table 1. The conditions for analysis by GLC were the same as in the preceding communication. Typical preparative experiments are described below.

Cyclization of α-monocyclofarnesylacetone (IIa). To a solution of 40 ml of sulfuric acid (100%) in 40 ml of nitropropane (abs.) there was added, with stirring at −70°, a cooled solution of 5.0 g of IIa in 10 ml of nitropropane, at such a rate that the temperature did not exceed −65° (5-7 min). After 5 min the mixture was decomposed by pouring it into stirred ice water. After the usual work-up, 4.5 g of product was obtained which, according to GLC data, contains 60% IIIa, 20% IVb, and 20% of a substance of undetermined structure. IIIa was isolated from this mixture by chromatography on neutral silica gel, followed by purification via the oxime ketone semicarbazone with m.p. 187-188.5° (does not give a depression in admixture with a sample obtained in the cyclization of

Ia). In this way individual IIIa was obtained in about 40% yield as a colorless liquid which in the refrigerator turns into colorless crystals with m.p. 37-39°. According to the IR and NMR spectra it is identical to the oxide obtained in the cyclization of Ia (^{1}).

Cyclization of β-monocyclofarnesylacetone (IIb).
a) Under analogous conditions, from 2.0 g of IIb there was obtained 1.65 g of a mixture containing 55% IIIb and 35% IVb. IIIb was isolated by the usual procedure. The IIIb obtained in 30% yield is identical to the oxide obtained in the cyclization of Ib (^{1}) according to the IR and NMR spectra, and also according to the melting point of the oxime ketone semicarbazone.

b) To a solution of 2.0 g of IIb in 20 ml of nitropropane (abs.) there was added, with stirring at −70°, a cooled solution of 2.0 ml of sulfuric acid (100%) in 2.0 ml of nitropropane, at such a rate that the temperature did not exceed −55° (5 min). After stirring for 1 h at −50 to −40°, the mixture was decomposed by pouring it into stirred ice water. After the usual work-up, 1.6 g of product IVb was obtained with b.p. 95-96° at 0.3 mm, n_D^{20} 1.4963. The semicarbazone has m.p. 90-92°.

Found, %:	N 12.35, 12.30
$C_{19}H_{35}O_2N_3$. Calculated, %:	N 12.45

Oximination of the reaction product indicates a CO-group content of 94%. Upon hydrogenation of the product over platinum oxide (0.2 M) in ethyl acetate, after reduction of the catalyst, 1 M of hydrogen is absorbed. Oximination of the hydrogenation product shows the presence of 5% CO-groups; the IR spectrum shows the absence of $-CH=C-O-$ and OH groups. Chromatography of IVb on silica gel (^{1}) leads to a hydroxyl-containing product which, after dehydration with phosphorus oxychloride in pyridine (^{4}) and hydrogenation over platinum oxide in ethyl acetate (1 M of hydrogen), contains 85% CO-groups and proves identical by GLC with the hydrogenation product of IIb (1 M of hydrogen).

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